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Review

Future Directions for the Early Detection of Recurrent Breast Cancer

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Abstract

The main goal of follow-up care after breast cancer treatment is the early detection of disease recurrence. In this review, we emphasize the multidisciplinary approach to this continuity of care from surgery, medical oncology, and radiology. Challenges within each setting are briefly addressed as a means of discussion for the future directions of an effective and efficient surveillance plan of post-treatment breast cancer care.

Key words: Breast cancer; recurrence; adjuvant; surveillance; follow-up.

Introduction

Breast cancer is the most common malignancy in women with post-operative recurrence and metastases acting as the leading cause of breast-cancer associated mortality [1]. The number of patients in post-treatment surveillance programs is increasing secondary to the survival benefit of screening mammography and adjuvant therapies [2]. After curative primary treatment, approximately 15% of breast cancer survivors will develop a second breast malignancy within ten years [3]. This risk is further compounded by personal characteristics such as age and family history.

Despite the fact that randomized trials of intensive surveillance testing such as more frequent clinical examinations, biannual chest x-rays, and bones scans have shown no mortality benefit [4-7], there has been a continued rise in financial cost and resource utilization devoted to developing more effective follow-up strategies to detect early recurrences [8]. In this paper, we will explore some of the new technologies being studied to improve breast cancer surveillance after primary treatment.

Current surveillance guidelines recommend mammography and clinical physical examinations [9, 10]. Unfortunately, this strategy may be less than ideal for a heterogeneous population. This review also explores a risk stratification strategy to allocate costlier yet more sensitive surveillance strategies. Future directions in breast cancer follow-up are examined within the settings of clinical, laboratory, and radiologic assessment. Emphasis is placed on detection of loco-regional or contralateral recurrence as detection of distant recurrence is classified as incurable without a correlated survival benefit [10, 11].

Clinical Assessment

Follow-up care after primary breast cancer treatment includes physical and psychological rehabilitation, assessment of treatment efficacy, and detection of recurrent or metachronous cancers. Current

National Comprehensive Cancer Network (NCCN) guidelines recommend a history and physical examination every 4-6 months for 5 years, then every 12 months [10]. The American Society of Clinical Oncology (ASCO) [9, 11, 12] recommends a careful history and physical examination every 3–6 months for the first three years, every 6–12 months for the 4th and 5th year and annually thereafter by a physician skilled in cancer surveillance and breast examinations.

Historically, most recurrences have been detected by the patient or by a clinician's physical exam [13]. The self-breast examination (SBE) and clinical breast examination (CBE) remain cost-effective methods intended to detect regional or contra-lateral breast cancer recurrence [14]. The value of clinical examination in detecting locoregional relapse is uncertain [15] although consistently valued by those producing current guidelines [9, 16]. A lack of survival advantage from CBE-detected recurrence has been suggested [17] in addition to the already significant limitations of the breast exam to include breast heterogeneity, examiner inexperience, and a lack of high specificity resulting in unnecessary biopsies [18].

The future of the CBE requires standardization to enhance sensitivity and specificity and minimize false positives. Ultimately, the development of better skills training and performance standards can enhance reliability of the CBE with multiple tools in development to achieve this goal. Two applications currently in practice include the use of silicone breast models for research and training and in-office breast ultrasound (US). Research of Mammacare® silicone breast models (Mammatech Corp., Gainesville, Fl, USA), a method for standardizing examinations of patients with various breast characteristics, has revealed the effects of tumor size and breast firmness on CBE precision [19-23]. Clinician training with these silicones breast models has also been shown to improve sensitivity [24]. In-office US may also be a useful adjunct to the physical exam although larger studies examining operator variability are needed [25-28]. The in-office US may clarify abnormal findings to eliminate biopsy of benign lesions. However, in-office breast US is not currently used for screening of the asymptomatic breast due to the interpretation skills required, poor visualization in patients with dense or nodular breasts, and the inability to reliably detect microcalcifications [27, 29, 30].

In addition to silicone breast models and in-office US, other tools include tactile sensing technologies, electrical impedance scanning (EIS), and diffuse optical spectroscopy (DOS). Specific tactile sensing instruments include the piezoelectric finger (PEF) [31], the SureTouch Visual Mapping System (Medical Tactile, Inc.) [32, 33], and the Robotic Tactile Breast Mass Identifier (Robo-Tac-BMI) [34] where capacitive sensors utilized to standardize quantitative information are intended to improve a physician's examination [34]. Although an early study demonstrates Robo-Tac-BMI's enhanced ability to detect cancer by sensing the elasticity of breast tissues, further testing of this technology is needed [31]. EIS utilizes differences between the electrical properties of malignant and normal breast cancer tissue. However, EIS requires the ability of the clinician to deliver a consistent and reproducible examination [35]. Further research is needed to ascertain the actual sensitivity of EIS [36, 37]. DOS bases utility on the theory that malignant tissue reflects light of different intensities, although this technique is still in the earliest stages of research [38]. Overall, future research employing examination of asymptomatic patients with novel tools and technologies requires standardized research and reporting methods by multicenter trials prior to implementation in practice.

The future of clinical assessment may simply be the modification of performance standards compounded with better skills training. However, research funding is increasingly being dedicated to devising novel adjuncts to the clinical examination in order to address the challenging issue of over-diagnosis. With health care dollars limited and the need for services expanding, resources should be spent prudently. Although new approaches and technologies have great potential to dramatically change current standard of care, additional training and evaluation to ensure standardization of use and examination reproducibility in clinical practice is pivotal [39].

Laboratory Assessment

Guidelines for routine follow-up in asymptomatic patients do not recommend the use of complete blood counts, chemistry panels, and tumor markers [9]. The future of laboratory workup to detect relapse may instead exist in defining individual risk assessment. Given the heterogeneity of the disease, the challenge has become to personalize cancer care to best formulate an efficient treatment plan for each individual patient. Aside from deciding which women will benefit from cytotoxic chemotherapy, this treatment plan may also include defining the frequency and duration of follow up care. It is becoming increasingly recognized that a certain proportion of patients are at risk for late recurrence of disease beyond 5 years and in some cases beyond 10 years, which has led to the study of longer durations of adjuvant hormonal therapy. Current methods for defining risk of recurrence include lymph node status, tumor size, tumor grade, estrogen receptor (ER) posi-

tivity, and human epidermal growth factor receptor 2 (HER2) positivity in addition to patient factors such as age and comorbidities.

The emergence of non-clinical risk factors including the study of genetic heterogeneity in breast cancer may help to better predict disease behavior and patterns of recurrence. In 2000, Perou *et al* [40] described molecular portraits of breast cancer by analyzing gene expression patterns using fluorescently labeled complimentary DNA (cDNA) prepared from messenger RNA (mRNA) that had been isolated from cultured cell lines. The final result is a matrix that displays gene transcript levels below the mean, equal to the mean, or above the mean. Based on this data, we now have the ability to make biological interpretations regarding disease behavior based on these unique molecular portraits. In the human breast there are luminal epithelial cells and basal epithelial cells, each type expressing different genes [40]. Based on gene expression clusters, breast cancer can be classified into at least 4 biologic subtypes [41, 42]. These are listed in Table 1.

At the 12th International Breast Cancer Conference in March 2011, the topic of defining breast cancer subtypes was addressed [43]. As gene arrays can be costly and time consuming because of the need to send tissue to specialized laboratories, clinicopathological criteria were developed. One development was the use of immunohistochemical (IHC) stains to define risk of recurrence. An IHC profile was developed using ER and progesterone receptor (PgR) expression, the detection or overexpression of the HER2 oncogene and Ki-67 labeling index or an alternate method of measure of proliferation such as tumor grade. The definitions for each profile are listed alongside the genetic characteristics in Table 1. Though experts acknowledge that breast cancer is made up of several subtypes, the consequences and utility of classifying the disease into these subtypes is unclear.

There are a number of genetic assays that assist in predicting recurrence risk. These include Oncotype DX™, MammaPrint®, PAM50™ and others. Oncotype DX (Genomic Health, Inc., CA) uses reverse transcription polymerase chain reaction (RT-PCR) to measure expression of 21 genes and calculate a recurrence score from 0-100 that correlates with the risk of distant relapse within 10 years. At present, the test has only been validated in node-negative, ER positive tumors [44, 45]. In addition, though a higher recurrence score predicts worse prognosis, it also correlates with a better response to chemotherapy [46]. MammaPrint® (Agendia, Irvine, Ca and Amsterdam, The Netherlands) is a 70-gene microarray primarily detecting expression of genes responsible for proliferation, invasion, and angiogenesis. At present, it is intended for use in younger women (age 61 or under) with node-negative breast cancer that is <5cm and either estrogen receptor positive or negative [44]. This test categorizes tumors into one of two groups: low-risk and high risk, each corresponding to either a lower or higher chance of developing distant metastases at 10 years [47]. It has been studied in women who had not received any endocrine therapy or cytotoxic chemotherapy as well as in patients with 1-3 positive nodes who received appropriate therapy and may be better at predicting recurrence than clinical models used to predict recurrence [48]. It was designed mainly as a tool to identify patients most likely to benefit from chemotherapy. The PAM50/Breast Bioclassifier™ (University Genomics, Inc.) is an assay that uses quantitative RT-PCR of 50 genes to classify breast cancers into the subtypes discussed above (see Table 1). It can provide prognostic information on any breast cancer subtype regardless of hormone receptor status.

Table 1: Four biologic subtypes of breast cancer based on gene expression. FISH: fluorescence in situ hybridization.

	Genetic characteristics	IHC Profile	Clinical characteristics
Luminal A	High expression of ESR1 (ER), PGR (PR) as well as genes associated with ER activation.	ER and/or PgR positive	Lower grade tumors
		HER2 negative	Best outcomes
	Expression of keratins 8 and 18	Ki-67 low (<14%)	May relapse beyond 5 years
Luminal B	Shares gene expression rates similar to both luminal A and basal-like subtypes.	ER and/or PgR positive	Higher grade tumors
		HER2 negative or amplified or over-expressed	Worse outcomes Less responsive to endocrine therapy
		Ki-67 high	May relapse beyond 5 years
Basal-like	Higher expression of keratin 5, keratin 6, *c-kit* and other genes.	ER and PgR absent	"triple negative"
	Lower expression of fibronectin 1 and mucin 1.	HER2 negative	Poor prognosis
	Higher expression of genes related to cell growth and transcription which indicate higher proliferation rates.		If disease relapses, it usually occurs within first 5 years
Her2 enriched	Express ERBB2 (HER2) as well as higher expression rates of MDR1, *S100* calcium binding protein P, fatty acid synthase, fibronectin 1, syndecan 1.	ER and PgR absent HER2 amplified or over-expressed	1/3 of these will NOT be HER2 over-expressed or amplified, but will have defining gene expression profile
	Lower expression of *c-kit* and *c-myc*.		If disease relapses, it usually occurs within first 5 years

Voduc *et al* studied tumor samples from women with nonmetastatic breast cancer and classified them by IHC profile. Investigators then analyzed the incidence of local and regional recurrence. This study found that luminal A tumors had the lowest risk of local and regional relapse at 5 and 10 years and that HER2 enriched and basal-like tumors had the highest rates of relapse. An interesting finding in this study is that luminal B tumors (the second most common subtype behind luminal A) had an unexpectedly high rate of locoregional relapse [49]. The same year, Kennecke *et al* published a study examining the metastatic potential of breast cancer subtypes [50]. This study also used immunohistochemistry to classify tumors into subtypes. Of those patients with relapse, Basal-like and HER2 tumors almost always relapsed within the first 5 years whereas luminal subtypes experienced continued relapses between 5 and 15 years. Brain metastases were more often seen in HER2-enriched and basal-like subytpes whereas bone was the predominant metastatic site in luminal A, luminal B, and luminal HER2 subgroups.

Presently, genetic assays are employed to assist clinicians in counseling patients on whether the benefits of cytotoxic chemotherapy outweigh the risks. The future of such assays and biological classifications is open to a wide range of possibilities. An alternative to expensive genetic testing is to use IHC profiles to classify tumors into biologic subtypes, though this, too, has limitations such as inter-rater reliability.

Circulating tumor cells

Although advances are constantly being made, further research is needed to find the most efficient and accurate tools that will assist patients and their providers in formulating individualized treatment plans that maximize benefit while minimizing harm. Circulating tumor cells (CTC) hold promise as a sensitive and specific surrogate to provide crucial information on prognosis and treatment efficacy. The early dissemination of tumor cells from heterogeneous breast tumor, a complex and multi-factorial process [51], is often undetectable by current high-resolution imaging technologies. Only recently have clinical researchers been able to accurately and reproducibly detect occult tumor cells secondary to advances in isolation, enrichment, and detection methods [52].

The current practical application of CTC monitoring is within the metastatic setting [53]. Independent of other known prognostic factors, CTC burden has been shown to predict treatment efficacy, progression-free, and overall survival in patients with metastatic breast cancer prior to and at any point after initiation of systemic therapy [53-55]. The CellSearch system (Veridex, Warren, NJ) has gained Food and Drug Administration (FDA) approval for targeted CTC detection in patients with metastatic breast and prostate cancer [56, 57].

Outside the metastatic setting, new research is emerging regarding the relevance of peripheral blood CTCs in high-risk, disease-free patients, who have completed primary curative therapy. Detection of CTCs in 10-60% of patients with non-metastatic breast cancer has been reported via various detection assays including density-gradient separation and subsequent cytokeratin immunostaining [58-60], cytokeratin-19 mRNA amplification [61-63], HER2 immunostaining [64], and the CellSearch method [65-67]. Here, the quantitative response of CTC (increasing, decreasing, or marginal change) before, during, and after adjuvant chemotherapy has shown significant correlation with relapse-free survival non-metastatic breast cancer patients [68]. Studies are also revealing the prognostic importance of CTC quantification in patients with non-metastatic breast cancer prior to neoadjuvant or adjuvant therapies. The presence of one or more circulating tumor cells is shown to predict early recurrence and decreased survival in chemo-naive patients with non-metastatic breast cancer [69]. Quantifying CTC in this manner may allow for an effective monitoring surrogate [70] that results in new therapeutic and surveillance concepts beyond the metastatic setting [51].

In contrast to mammography and clinical examination, routine laboratory evaluation is not currently recommended in the asymptomatic patient. However, the utility of laboratory testing may be to define risk assessment given the heterogeneity of breast cancer. As research continues, these biologic technologies hold promise in development of a highly personalized approach in cancer care.

Radiology Assessment

Mammography is proven to detect breast cancer at an early stage and reduce mortality when combined with the appropriate treatment [71, 72]. However, mammography has limitations to include decreased sensitivity in women with dense breasts and undesirable false positive rates [71, 73]. Concerns related to radiation risk from mammography may also decrease patient compliance even though the overall radiation dose is low. Future methods of breast cancer screening and detection must demonstrate increased sensitivity and specificity while being non-invasive, low cost, and have a low radiation burden. Future models will incorporate appropriate patient risk assessment models to develop a tailored imaging strategy for each patient to maximize sensitivity and specificity while minimizing cost and radiation risk. The following is a discussion of some potential imaging

modalities that may improve early detection of recurrent disease.

Digital Breast Tomosynthesis

Overlapping normal breast parenchyma is a frequent cause of false-positives in standard digital mammography. Digital breast tomosynthesis (DBT) acquires images in the same orientation as conventional digital mammography but can display images in a three-dimensional manner reducing the likelihood of breast tissue superimposition. Several clinical studies have confirmed DBT's ability to improve screening performance for asymptomatic women with increased cancer detection rates while lowering screening recall rates [74, 75]. Furthermore, several small studies have suggested that two-view DBT may prove to be an alternative to obtaining additional mammographic views in the diagnostic or symptomatic setting [76, 77]. The performance of DBT in both screening and diagnostic settings suggests it will improve the accuracy of surveillance in women with a personal history of breast cancer; however, appropriate clinical trials are necessary to evaluate this indication.

Low-dose Mammography

The risk of radiation induced cancer from mammography is exceedingly small compared to the proven mortality reduction of routine screening [78]. Nevertheless, concern remains about the radiation risks of mammography amongst patients and referring providers. To allay these concerns, without hindering the ability of detect cancer, low dose mammography units are utilized throughout Europe and the FDA recently approved a low-dose photon counting mammography unit in the United States. These units deliver half the absorbed dose of radiation to the breasts as a standard mammography machine [79]. Venturini and colleagues recently evaluated the efficacy of low-dose mammography with adjunct screening using either ultrasound or magnetic resonance imaging (MRI) in Europe. This resulted in a higher than expected cancer detection rate with good diagnostic performance and a low average glandular radiation dose to the breast [80]. A similar study evaluating a tailored imaging algorithm with low-dose mammography in the United States is a potential area of further investigation.

Contrast Enhanced Mammography

Contrast enhanced mammography is a technology recently FDA-approved in the US as an adjunct to standard mammography. In this technique an iodine-based contrast agent is injected intravenously and mammographic images obtained using either temporal contrast or dual energy techniques. Early studies demonstrate improved reader sensitivity and improved reader performance with the addition of contrast enhanced mammography to standard mammography and ultrasound in a diagnostic setting [81]. Other early studies show improved accuracy for the detection of breast cancer when compared with standard mammography. Limitations of this technique include the use of intravenous iodinated contrast and a slightly increased radiation dose compared to standard mammography. Contrast-enhanced mammography is similar to breast MRI in that it relies on tumor angiogenesis to detect cancer. Therefore, in theory it may perform similar to breast MRI in other settings such as high risk screening, as a means for early detection of breast cancer recurrence or monitoring response to neoadjuvant chemotherapy [81].

Automated Whole-Breast Ultrasound

Sonography is a widely available and inexpensive tool that does not require ionizing radiation or contrast injection. Studies demonstrate that hand-held sonography increases cancer detection rate in high risk populations, to include women with a personal history or breast cancer, but at the cost of increased recall examinations, biopsies, and recommendations for short term follow-ups [82]. Automated whole-breast ultrasound system is a new technology that performs two-dimensional ultrasound of both breasts utilizing robotic guidance of a standard ultrasound probe. This technique is hypothesized to provide a consistent high-quality study which eliminates user variability and decreases the time required for each examination. Currently automated whole-breast ultrasound used in conjunction with mammography has a similar cancer detection rate to hand-held ultrasound of 3.6 per 1000 with an acceptable positive predictive value for recommended biopsies of 38% [82]. Disadvantages of automated whole breast ultrasound include a limited ability to scan the posterior regions of large breasts, the time commitment required to review a large number of images by radiologists, and the need to recall patients for evaluation of indeterminate findings [82].

Diffusion Weighted MRI of the Breast

Diffusion weighted imaging is a magnetic resonance imaging technique that characterizes the mobility of water molecules; it is a currently established technique in neuroimaging that is rapid and does not require the administration of intravenous contrast. It shows potential as an adjunct tool with contrast enhanced breast MRI to reduce false positive findings and unnecessary biopsies. A meta-analysis demonstrated improved specificity of diffusion weighted

breast imaging compared with dynamic contrast enhanced breast MR for differentiation of benign and malignant masses [83]. The American College of Radiology Imaging Network (ACRIN) is initiating a study to evaluate this indication for diffusion weighted imaging of the breast [84].

Diffusion weighted imaging may also play a role in evaluating patients' response to neoadjuvant chemotherapy. It shows similar accuracy to contrast enhanced MR for monitoring neoadjuvant chemotherapy; this may be of use for patients with impaired renal function [84]. The utility of diffusion weighted imaging for predicting response prior to initiation of chemotherapy is unclear at this time. Richard et al. demonstrated that pretreatment apparent diffusion coefficients (ADCs) from diffusion imaging could predict responders and non-responders to therapy when accounting for tumor subtypes (i.e. triple negative, HER2-enriched, luminal A, or luminal B) while other investigators showed no difference in pre-therapy ADC values for responders versus non-responders [79, 85-87]. Currently an ACRIN multi-institutional protocol is evaluating if changes in ADC values after each treatment cycle is predictive of pathologic complete response.

Diffusion weighted imaging may eventually be utilized as a non-contrast adjunct screening modality, particularly in patients with contraindications to intravenous contrast. This indication shows promise but is in the early stages of clinical investigation [84].

Magnetic Resonance Spectroscopy of the Breast

Magnetic resonance (MR) spectroscopy is a non-invasive and non-ionizing method of measuring chemical composition from a region in the body. By using choline-containing compounds as a biomarker of malignancy, spectroscopy can distinguish between benign and malignant lesions [88]. Multiple studies demonstrate improved specificity for distinguishing benign from malignant lesions when using MR spectroscopy in conjunction with contrast enhanced breast MR [88]. Early studies also show MR spectroscopy may play a role in assessing early response to neoadjuvant chemotherapy [89]. A multi-instititutional ACRIN study assessing the role of MRI in neoadjuvant chemotherapy is evaluating the effectiveness of MR spectroscopy after one cycle of chemotherapy.

Diffuse Optical Imaging

Diffuse optical imaging of the breast employs near infrared light to produce images and resolve spectroscopic information about the composition of tissues. It is a non-ionizing, low-cost, and non-invasive means to evaluate breast tissue without breast compression. Furthermore, it can measure physiologic properties of tissue such as hemoglobin concentration, blood oxygen saturation, and water/fat content [90]. Current investigations focus on the ability of diffuse optical imaging to identify and characterize breast masses as benign or malignant, detect cancer in dense breast tissue, and assess response to neoadjuvant therapy [91].

Molecular Imaging

Despite extensive research and development of novel molecular imaging agents, none are expected to be entering clinical use in the near future specifically for the role of surveillance of patients with a history of breast cancer. For the foreseeable future, fluorodeoxyglucose (FDG) positron-emission computed tomography (PET-CT) will continue to be instrumental in the imaging of evaluation of patient's with clinical or laboratory findings suspicious for recurrent disease. It's accuracy in this setting is well documented with the largest study to date demonstrating a sensitivity of 94% and specificity of 85% for an accuracy of 92%. Compared with a conventional workup, the researchers found PET-CT's increased accuracy resulted in a change in management of more than half of the patients [92].

One unique exception to the utility of FDG PET-CT is in the scenario where recurrence is suspected, but the differential diagnosis includes the possibility of an active infectious or inflammatory process, something that can frequently be seen in association with ongoing cancer therapy. Activated granulocytes and macrophages have markedly increased metabolism and thus FDG uptake is increased, mimicking malignancy. In contrast, F-18 Fluorothymidine (FLT) is a PET radiolabeled biomarker for cell proliferation whose uptake is a direct reflection of thymidine kinase 1 (TK1) activity. TK1 is over-expressed in multiplying cells such as malignant breast tumors and their metastatic lesions. Thus, unlike FDG, FLT has the advantage of not accumulating in inflammation [93]. Therefore, FLT may offer a specific means of differentiating residual/recurrent disease from infection or bland inflammation.

Once recurrence is identified, the future focus of molecular imaging is to providing a non-invasive, whole-body means of characterizing the biologic nature of an individual's tumor burden in order to better select targeted therapies. Tumor phenotypes (receptor functional status) can shift over time, and thus recurrent breast cancer may have a different ER, PgR, and HER2 statuses than the patient's original primary tumor prompting the need for reassessment. While biopsy is often a simple means for re-assessing a solitary site of recurrent disease, tissue sampling of mul-

tiple lesions is often not practical and some sites may be inaccessible. Additionally, tissue sampling of boney breast cancer metastases can be complicated by epitope loss related to decalcification, reducing the accuracy of histological analysis [93]. Fortunately, novel PET tracers are showing the ability to image the presence and thus may, in the future, be of critical value in determining which patients may benefit from various endocrine therapies (Table 2).

The estrogen receptor has been the focus of many investigations and fluoroestradiol (FES) seems to show the most promise. FES is a PET labeled estrogen analog that binds to estrogen receptors with high affinity and specificity. Several studies have demonstrated its tissue uptake correlates accurately with tumor ER expression when compared IHC [94]. Subsequently, FES-PET positivity has shown the ability to provide information similar to tissue ER expression, predicting which patients may benefit from endocrine therapy (Table 3).

About half of ER positive breast cancers are also positive for the expression of PgR. Tumors that are both ER and PgR positive are more likely to respond to endocrine therapy in comparison to tumors that are ER positive, but PgR negative. Thus, knowledge of the PgR status is valuable for the optimal selection of therapy in patients with recurrent breast cancer. A compound still in preclinical trials, called fluoro furanyl norprogesterone (FFNP), has shown high affinity and selectivity for PgR [95]. In a small-animal study, Fowler and colleagues demonstrated its ability to identify early response to endocrine therapy prior to measurable changes in tumor size [96]. It is hoped that future studies may demonstrate the value of FFNP-PET in predicting the response to endocrine therapy.

Overexpression of the HER2 neu receptor is seen in nearly a third of breast cancers and plays a role in cell growth/survival. Like the steroid receptors, ER and PgR, therapies have been targeted against it and thus tissue expression of HER2 is routinely assessed in clinical practice. Several single photon and positron-emitting radionuclides are under investigation for the in vivo evaluation of HER2 expression. One compound, the positron emitting 89Zr-trastuzumab (the same monoclonal antibody that comprises Herceptin) has been studied in 14 patients with metastatic breast cancer and was successful in identifying the majority of known lesions as well as some occult sites of disease [97]. Further trials will be necessary to assess the utility of this radiotracer in management of recurrent breast cancer.

Table 2: Novel PET tracers showing promise for use in patients with recurrent breast cancer.

Radiotracer	Mechanism
F18-fluorothymidine (FLT)	Marker for cell proliferation, uptake reflects TK1 activity
F18- fluoroestradiol (FES)	Distrobution & intensity of uptake mimics +ER lesions as assessed by IHC
F-18 furanyl norprogesterone (FFNP)	Shows high affinity & selectivity for PgR as confirmed by IHC/FISH
89Zr-trastuzumab	Initial studies show ability to identify sites of HER2 pos disease

Table 3: Studies demonstrating ability of FES-PET to predict response to endocrine therapies in patients with breast cancer.

Lead Author	Number	Methods	Results
Mortimer 2001[98]	40 women with +ER breast cancer	-Baseline FES-PET with SUVs measured -Underwent tamoxifen tx -21 (52%) clinical responders -19 (48%) disease progression	-Significant association between pre-tx FES-PET uptake and response -SUV 4.3+/-2.4 in responders -SUV 1.8 +/-1.3 in nonresponders
Linden 2006[99]	47 women with +ER tumors	-Baseline FES-PET with SUV>=1.5 considered +ER -Compared with response following 6 months of hormonal therapy -23% responders	-Significant association between FDS uptake and response -0% with SUV <1.5 were responders -34% with SUV>=1.5 responded to tx
Dehdashti 2008[100]	51 women with advanced +ER breast cancer	-Baseline FES-PET with SUV>=2 considered +ER -Tx with aromatase inhibitor or fulvestrant -17 responders & 34 non-responders	-Higher tumor FES SUV noted in responders (3.5 +/- 2.5) compared with non-responders (2.1+/-1.8)
Peterson 2012[101]	19 women with de novo metastatic breast cancer from +ER primary	-Baseline evaluation with FES and FDG-PET prior to endocrine therapy -102 tumor sites identified by FDG-PET with -84 visible on FES-PET (areas of high physiology FES uptake such as the liver resulted in decreased sensitivity) -Compared to clinical response in 15 women -40% progressive disease -33% stable disease -27% partial response	-Only 1 of 9 women who experienced a partial response or had stable disease had an area of qualitatively absent FES-PET uptake -All 6 women with progressive disease had a site of qualitatively FES-PET negative disease

Future of Imaging Modalities

The imaging setting provides numerous although costly advanced techniques. Similar to the clinical and laboratory setting, identification of the appropriate population in addition to treatment and survival benefit need to be identified prior to common application of these new technologies. In the future, optimal breast imaging paradigms for screening or detection of recurrence may rely on one or more of these future imaging modalities. However, the literature and clinical experience of most practitioners suggests the optimal strategy will employ a highly personalized approach based upon risk stratification guiding appropriate selection of screening technologies.

Conclusion

As the prevalence of breast cancer rises, a dramatic increase in the number of breast cancer survivors will place clinical and financial demands on the long-term surveillance system [2]. Despite these challenges, evidence is mounting to suggest that disease relapse may be curable if diagnosed and treated early. We have explored several novel methods of clinical examination, laboratory testing, and advanced imaging which so far have failed to elicit a survival benefit. One difficulty has been trying to utilize newer technologies in a "one size fits all" prescription. This has led to an increase in resource utilization and expensive workups of false positive tests. Moving forward, developing testing models relevant to a risk stratification system for individualized care may help better elicit the clinical benefit of early detection. Clinicians should continue to be aware of the risk/benefit ratio of available options with future guidelines designed for optimal disease management that avoid both over- and under-evaluation of a patient's disease status.

Competing Interests

The authors have declared that no competing interest exists.

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