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TOPIC HIGHLIGHT

WJCO 5th Anniversary Special Issues (2): Breast cancer

Pathogenesis, prevention, diagnosis and treatment of breast cancer

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Core tip: This is a review of past and current literature/landmark trials in the etio-pathogenesis, diagnosis and management of breast cancer. We have attempted to cover this vast topic in review form and hope that it will serve as a reference for clinicians who treat patients with breast cancer.

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Abstract

Breast cancer is the most common cancer affecting women worldwide. Prediction models stratify a woman's risk for developing cancer and can guide screening recommendations based on the presence of known and quantifiable hormonal, environmental, personal, or genetic risk factors. Mammography remains the mainstay breast cancer screening and detection but magnetic resonance imaging and ultrasound have become useful diagnostic adjuncts in select patient populations. The management of breast cancer has seen much refinement with increased specialization and collaboration with multidisciplinary teams that include surgeons, oncologists, radiation oncologists, nurses, geneticist, reconstructive surgeons and patients. Evidence supports a less invasive surgical approach to the staging and management of the axilla in select patients. In the era of patient/tumor specific management, the advent of molecular and genomic profiling is a paradigm shift in the treatment of a biologically heterogenous disease.

INTRODUCTION

Breast cancer is the most common cancer and also the leading cause of cancer mortality in women worldwide. Approximately 1.38 million new breast cancer cases were diagnosed in 2008 with almost half of all breast cancer cases and nearly 60% of deaths occurring in lower income countries[1]. There is a large variation in breast cancer survival rates around the world, with an estimated 5-year survival of 80% in high income countries to below 40% for low income countries[2].

Low and middle income countries face resource and infrastructure constraints that challenge the goal of improving breast cancer outcomes by early detection, diagnosis and treatment[3]. In high income countries like the United States, approximately 232340 women will be diagnosed and 39620 will die of breast cancer in 2013[4]. For an American woman, the lifetime risk of developing breast cancer is 12.38% or 1 in 8[4]. The significant decrease in breast cancer-related mortality in the United

States from 1975 to 2000 is attributed to continued improvement in both screening mammography and treatment[5,6]. According to the World Health Organization, improving breast cancer outcome and survival by early detection remains the cornerstone of breast cancer control.

RISK FACTORS ANDRISK PREDICTION

Age, reproductive factors, personal or family history of breast disease, genetic pre-disposition and environmental factors have been associated with an increased risk for the development of female breast cancer.

Age

The risk of developing breast cancer increases with age. By using the Surveillance, Epidemiology, and End Results (SEER) database, the probability of a woman in the United states developing breast cancer is a lifetime risk of 1 in 8; 1 in 202 from birth to age 39 years of age, 1 in 26 from 40-59 years, and 1 in 28 from 60-69 years[4].

Personal history

A personal history of breast cancer is also a significant risk factor for the development of a second ipsilateral or contralateral breast cancer. In fact, the most common cancer amongst breast cancer survivors is a metachronous contralateral breast cancer[7]. Factors associated with an increased risk of a second breast cancer include an initial diagnosis of DCIS, stage IIB, hormone receptor negative cancers, and young age[8].

Breast pathology

Proliferative breast disease is associated with an increased risk of breast cancer. Proliferative breast lesions without atypia, including usual ductal hyperplasia, intraductal papillomas, sclerosing adenosis and fibroadenomas confer only a small increased risk of breast cancer development, approximately 1.5-2 times that of the general population[9]. Atypical hyperplasia including both ductal and lobular, usually incidentally found on screening mammography, confers a substantial increased risk of breast cancer. Women with atypia have an approximately 4.3 times greater risk of developing cancer compared to the general population[9,10].

Family history

A woman's risk of breast cancer is increased if she has a family history of the disease. In the Nurses' Health Study follow-up, women with a mother diagnosed before age 50 had an adjusted relative risk of 1.69 and women with a mother diagnosed at 50 or older had a relative risk of 1.37 compared to women without a family history of breast cancer. A history of a sister with breast cancer also demonstrated an increased relative risk of 1.66 if the diagnosis was made prior to age 50 and a relative risk of 1.52 if diagnosed after age 50 compared to patients without a family history[11]. The highest risk is associated with increasing number of first degree relatives diagnosed with breast cancer at a young age (under age 50). Compared with women who had no affected relative, women who had one, two or three or more affected first degree relatives had risk ratios of 1.80, 2.93 and 3.90, respectively[12].

Genetic predisposition

Approximately 20%-25% of breast cancer patients have a positive family history but only 5%-10% of breast cancer cases demonstrate an autosomal dominant inheritance[13,14]. Genetic predisposition alleles have been described in terms of clinical significance[15]. High-risk predisposition alleles conferring a 40%-85% lifetime risk of developing breast cancer include BRCA1 and BRCA2 mutations, mutations in TP53 gene resulting in Li-Fraumeni syndrome, PTEN resulting in Cowden syndrome, STK11 causing Peutz-Jegher's syndrome, Neurofibromatosis (NF1) and (CDH-1) E-Cadherin[16]. Half of the breast cancer predisposition syndromes are associated with mutations in BRCA1 and BRCA2. Women with BRCA1 or BRCA2 deleterious mutations have a significantly higher risk of developing breast cancer. Lifetime breast cancer risk ranges from 65% to 81% for BRCA1 mutation carriers and 45% to 85% for BRCA2 carriers[17-19]. Moderate risk genes including homozygous ataxia-telangiectasia (ATM) mutations[20], somatic mutations in tumor suppressor gene CHEK2, and BRCA1 and BRCA2 modifier genes BRIP1[21] and PALB2[22] confer a 20%-40% lifetime risk of breast cancer. Numerous low-risk common alleles have been identified largely through genome-wide association studies[15] and the clinical application in the presence of these mutations is yet to be determined.

ENDOGENOUS HORMONE EXPOSURE AND REPRODUCTIVE FACTORS

The cycles of endogenous estrogen levels throughout a woman's lifetime have implications for the development of or the protection against breast cancer.

Early menarche

Early age at menarche is a risk factor among both pre- and postmenopausal women for developing breast cancer. Delay in menarche by two years is associated with corresponding risk reduction of 10%[23].Within the European Prospective Investigation into Cancer and Nutrition cohort, women who had early menarche (≤ 13 years) demonstrated a nearly twofold increase in risk of hormone receptor positive tumors[24].

Parity and age at first full term pregnancy

Nulliparous women are at an increased risk for the development of breast cancer compared to parous women. Young age at first birth has an overall protective effect, whereas relatively advanced age at first birth confers a relative risk of breast cancer greater than that of a nulliparous woman. Compared to nulliparous women the

cumulative incidence of breast cancer in women experiencing their first birth at age 20, 25, and 35 years was 20% lower, 10% lower and 5% higher, respectively[25].

Breast feeding

Evidence suggests that breast feeding has a protective effect against the development of breast cancer. Breast feeding may delay return of regular ovulatory cycles and decrease endogenous sex hormone levels. It has been estimated that there is a 4.3% reduction for every one-year of breast feeding[26].

Testosterone

High endogenous sex hormone levels increase the risk of breast cancer in both premenopausal and postmenopausal women. High levels of circulating testosterone in postmenopausal women have been linked to increased risk of developing breast cancer [relative risk (RR), 2.86-3.28][27].

Age at menopause

Later onset of menopause has also been associated with increased breast cancer risk. Every year delay in the onset of menopause confers a 3% increase in risk and every five year delay in the onset of menopause confers a 17% increase in risk of breast cancer[23,28].

EXOGENOUS HORMONE EXPOSURE

Evidence suggests a relationship between the use of hormone replacement therapy (HRT) and breast cancer risk. Breast cancers related to HRT use are usually hormone receptor positive. When compared with patients who do not use HRT, breast cancer risk is higher in HRT users[29]. An international meta-analysis examining the risk of breast cancer with HRT found that in women who did not use HRT, RR increased by a factor of 1.028 for each year older at menopause, comparable to the relative risk of 1.023 per year in women who use HRT or for those who ceased to use HRT up to four years previously[30].

In the Woman's Health Initiative randomized control trial, combined estrogen plus progestin in postmenopausal women with an intact uterus significantly increased the risk of breast cancer, delayed breast cancer detection and diagnosis, and significantly increased breast cancer mortality. The study was terminated early because of increased mortality in the combined estrogen plus progestin group. By contrast, the use of estrogen alone by postmenopausal women without a uterus did not interfere with breast cancer detection and statistically significantly decreased the risk of breast cancer[31]. Data from the Nurses' Health Study, however, suggest that women who use unopposed postmenopausal estrogen increase their risk of breast cancer by 23% at age 70[32].

Timing and duration of HRT seem to be important factors associated with breast cancer risk as well. Breast cancer risk from exogenous hormone exposure is inversely associated with time from menopause. Women initiating hormone therapy closer to menopause have a higher breast cancer risk[33]. Long term (> 5 years) combined HRT use has been associated with the highest risk whereas short-term use of combined estrogen-progestin therapy does not appear to confer a significantly increased risk (RR = 1.023 per year)[30].

LIFESTYLE FACTORS

Modifiable risk factors including the excessive use of alcohol, obesity and physical inactivity account for 21% of all breast cancer deaths worldwide[34].

Alcohol consumption

Alcohol consumption has been associated with increased breast cancer risk that is statistically significant at levels as low as 5.0 to 9.9 g per day, equivalent to 3 to 6 drinks per week (RR = 1.15; 95%CI: 1.06-1.24; 333 cases/100000 person-years). Binge drinking, but not frequency of drinking, was associated with breast cancer risk after controlling for cumulative alcohol intake. Alcohol intake both earlier and later in adult life was independently associated with risk[35].

Physical activity

Consistent physical activity has been shown to reduce the risk of breast cancer in a dose dependent manner, with modest activity conferring a 2% decrease in risk and vigorous activity a 5% decrease in risk[36].

Obesity

Obesity, specifically in postmenopausal women, has also been shown to increase a woman's risk of breast cancer. In the EPIC multicenter prospective cohort study, postmenopausal women who did not use HRT had elevated breast cancer risk with increasing weight, body mass index (BMI) and hip circumference[29]. In this cohort, multivariate relative risk was 1.28 for overweight women (BMI 25.0-29.9) and obese women (BMI > 30.0) compared to women in the normal weight range. Lean women on HRT are incongruously at an increased risk of breast cancer (RR = 2.04) compared to their overweight (1.93) and obese (1.39) counterparts[29].

Insulin resistance and hyperinsulinemia have been studied as a risk factor for the comorbidities associated with obesity including cardiovascular disease and diabetes. Insulin has anabolic effects on cellular metabolism and insulin receptor overexpression has been demonstrated in human cancer cells[37]. Hyperinsulinemia has been shown to be an independent risk factor for breast cancer in non-diabetic postmenopausal women and may help to explain the relationship between obesity and breast cancer[38].

Radiation

Radiation exposure from various sources including medical treatment and nuclear explosion increases the risk of breast cancer. Radiation to the chest wall for treatment of childhood cancer increases the risk of breast cancer

linearly with chest radiation dose[39]. Survivors of childhood cancers who received therapeutic radiation are at a dose dependent risk for the development of breast cancer, and those treated for Hodgkin's disease are at highest risk (RR = 7)[40]. Radiation effects on the development of female breast cancer have also been demonstrated in Japan post nuclear attack on Hiroshima and Nagaskai[41] and positively correlate with age younger than 35 years at time of exposure. The incidence of breast cancer has also increased in areas of Belarus and Ukraine. A significant two fold increase was seen in the most contaminated areas around Chernobyl following the nuclear accident and manifest in women who were younger at the time of the exposure[42].

PREDICTION MODELS

Prediction models are used to better stratify a person's risk for developing cancer based on the presence of known and quantifiable risk factors. There is great value in identifying high risk individuals to better tailor timing of screening modalities or prompt referral to a geneticist for counseling and testing. The concordance statistic or "c-statistic" quantifies the ability to distinguish patients who will develop cancer from those who will not. A c-statistic of 0.5 indicates that the prediction model is no better at discriminating patients who are at risk from those who are not than flipping a coin.

Gail model

The most well-known and widely used screening tool is the Breast Cancer Risk Assessment Tool (BCRAT) or the Gail model, developed by Dr Mitchell Gail[43,44] at the National Cancer Institute (NCI). The initial model used age, age at menarche, age at first live birth, number of previous biopsies, and number of first degree relatives with breast cancer, modified to include history of atypical ductal hyperplasia, lobular carcinoma *in situ*, and predicts a women's 5-year and lifetime risk of developing invasive breast cancer. It was developed with data from the Breast Cancer Detection Demonstration Project (BCDDP) and included white and black women over age 35 only. Screening tools rely on incidence of disease and the Gail model is updated as necessary and is easily accessed at www.cancer.gov/bcrisktool. The NCI's BCRAT is widely available to clinicians and is best used for women without a strong family history. The c-statistic for the Gail model has reported to be between 0.55-0.67[45]. The Gail model may under-predict women with a strong familial predisposition.

Models that emphasize family history

A commonly used risk prediction model with an emphasis on family history, including maternal and paternal family history and age of onset is the Claus model, engineered by Dr. Elizabeth Claus. The model, which predicted an autosomal dominant gene that led to an increased risk for developing breast cancer, was published the same year as the BRCA1 gene was cloned[46]. This model used data from the Cancer and Steroid Hormone study to assess breast cancer risk in women with a family history of breast cancer[47]. The c-statistic for the Claus model is approximately 0.56[48].

Mendelian models outperform epidemiologic models, owing to the high penetrance of BRCA gene mutations. BRCAPRO is a computer model developed by the University of Texas Southwestern Medical Center and Duke University that incorporates six unique predictive models to assess a woman's risk of developing breast cancer or carrying a deleterious BRCA gene mutation[49,50]. The c-statistic for BRCAPRO is 0.76-0.92[51,52] but when compared to experienced risk counselors, sensitivity for identifying BRCA gene mutation carriers were similar[53].

The Tyrer-Cuzick model incorporates personal, familial and genetic risk factors in a comprehensive way to compare a woman's personal risk of developing breast cancer in 10 years with that of the population[54]. The model accounts for BRCA genes, low penetrance genes, family history and personal risk factors such as age, age at menarche, age at first birth, menopausal state, body mass index and use of hormonal therapy. This model is considered to be one of the most accurate models in predicting a woman's risk for cancer with a c-statistic of 0.762, but may overestimate risk in patients with atypia[55,56].

Most risk factors for breast cancer are fairly weak, ubiquitous or not yet known, making the prediction models that examine epidemiological risk factors inherently difficult. Advances in genomic sequencing, biomarker identification and genetic testing may improve the accuracy of these quantitative risk prediction models in the future.

SCREENING

Breast self- and clinical breast examination

Utility of the breast self-examination (BSE) is controversial as the benefit in terms of decreased mortality has not been demonstrated[57]. Most clinicians encourage women to perform monthly BSE to become familiar with their normal anatomy and empower them with regards to their own healthcare[58]. The 2013 NCCN guidelines recommend annual clinical breast examination (CBE) for women of average risk > 40 years of age as well as BSE to develop and exhibit breast self-awareness[59].

Mammography

One of the most important advances in the treatment of breast cancer is early detection of non-palpable masses. In the 1960's, the first randomized control trials comparing periodic mammography screening *vs* clinical examination demonstrated a decreased mortality by approximately one third in the experimental group. However there is still controversy regarding mortality from breast cancer in the subset of women aged 40-49 years[60-62]. Contemporary randomized control trials have demonstrated the benefits from screening mammography in women aged 40 to 70

years[63-65]. A 2013 Cochrane Review suggests that mortality is an outcome biased toward screening, routine mammography leads to undue stress and uncertainty in the face of false-positive results with increase in total numbers of lumpectomies and mastectomies but no decrease in mortality[66]. Controversy surrounding mammography is related to the inherent lead time and length time biases in screening for disease. Lead time bias is an overestimation of survival among screen detected cases compared to clinically detected cases when true survival time actually remains unchanged. Length bias is an overestimation of survival time among screening-detected cases, which is caused by those slowly progressing cases that may never be clinically relevant. The 2013 NCCN guidelines recommends annual screening mammography in women ⩾ 40 years of average risk and annual mammography at age 25 or individualized based on onset of cancer in proband in patients who are high risk by prediction models, known history or genetic predisposition syndrome as well as the counseling and education of risks and benefits related to participating in cancer screening[59].

Magnetic resonance imaging

Mammography remains the gold standard for breast imaging but magnetic resonance imaging(MRI) has become an important modality in the detection, assessment, staging, and management of breast cancer in selected patients. Screening MRI is more sensitive but less specific for the detection of cancer in high risk women. The sensitivity of MRI is 0.77-0.79 compared to mammographic sensitivity of 0.33-0.39. Specificity of MRI is 0.86-0.89 compared to mammographic specificity of 0.95[67,68]. In a systematic review, MRI and mammography demonstrated a combined sensitivity and specificity of 0.94 and 0.77, respectively[67]. The 2013 NCCN guidelines recommend patients who have increased (> 20%) lifetime risk of developing breast cancer undergo annual mammography and MRI starting at age 25 or an age tailored to the risk of the patient on an individual basis. MRI is valuable in the screening of select high risk patients, patients in whom breast augmentation prevents effective screening mammography, or in patients with equivocal findings on other imaging modalities.

Ultrasound

There are several studies supporting the use of adjunctive screening ultrasound in high risk patients with dense breast tissue, which imparts a substantial but accepted number of false positives[69]. No randomized controlled trials have been conducted to evaluate the impact of screening ultrasonography on breast cancer mortality rates. Whole breast ultrasound may allow the clinician to screen for breast cancers not detected by traditional mammography, especially in dense breasts where mammographic sensitivity is lower[70]. Single center studies have shown that the incremental detection of breast cancer by ultrasound following screening mammogram offers only marginal added benefit in women of average risk[71].

DIAGNOSIS

History and physical examination

The clinical history is directed at assessing cancer risk and establishing the presence or absence of symptoms indicative of breast disease. It should include age at menarche, menopausal status, previous pregnancies and use of oral contraceptives or post-menopausal hormone replacements. A personal history of breast cancer and age at diagnosis, as well as a history of other cancers treated with radiation. In addition, a family history of breast cancer and/or ovarian cancer in a first- degree relative should be established. Any significant prior breast history should be elucidated including previous breast biopsies. After the estimated risk for breast cancer has been determined (see above), the patient should be assessed for specific symptoms like breast pain, nipple discharge, malaise, bony pain and weight loss.

Physical examination should include a careful visual inspection with the patient sitting upright. Nipple changes, asymmetry and obvious masses should be noted. The skin must be inspected for changes such as; dimpling, erythema, peaud' orange (associated with local advanced or inflammatory breast cancer). After careful inspection and with the patient in the sitting position the cervical, supraclavicular and axillary lymph node basins are palpated for adenopathy. When palpable the size, number and mobility should be ascertained. Palpation of the breast parenchyma itself is performed with the patient supine and the ipsilateral arm placed over the head. The subareolar (central quadrant) and each quadrant of both breasts is palpated systematically. Masses are noted with respect to their size, shape, location, consistency and mobility.

DIAGNOSTIC IMAGING

The initial choice of imaging should be individualized to each patient based on the age and characteristics of the lesions. Diagnostic imaging and image-guided needle biopsies play a central role in the diagnosis, treatment planning, and staging of patients with breast cancer.

Mammography

Mammography remains the mainstay in breast cancer detection[72]. Diagnostic mammograms are performed in women who have a palpable mass or other symptom of breast disease, a history of breast cancer within the preceding 5 years, or have been recalled for additional imaging from an abnormal screening mammogram. Diagnostic mammograms include special views such as focal compression of one area of the breast tissue or magnification images. The breast imaging reporting and database system (BI-RADS) is the standardized method for reporting of mammographic findings[73]. Carcinomas present as masses, asymmetries, and calcifications (Table 1). By definition, a mass is a space-occupying lesion seen in

Table 1 Breast imaging reporting and database system[73]

Category	Assessment	Follow up
0	Need additional imaging evaluation	Additional imaging needed before a category can be assigned
1	Negative	Continue annual screening mammograms (women older than 40 yr)
2	Benign	Continue annual screening mammograms (women older than 40 yr)
3	Probably benign	Initial short term follow-up (usually six month) mammogram (< 2% chance of malignancy)
4	Suspicious abnormality	Biopsy should be considered (2%-95% chance of malignancy)
5	Highly suggestive of malignancy	Requires biopsy (> 95% chance of malignancy)
6	Known cancer	Biopsy-proven malignancy

two different planes. This is distinguished from a density, which is seen only in a single plane. The shape of masses is described as round, oval, lobular, or irregular, while the margins are identified as circumscribed (with well-defined margins), indistinct, and spiculated (with densities radiating from the margins). Calcifications associated with benign disease are generally larger than those seen with malignancy and typically are coarse (round, lucent centered, or "layering" on medial lateral or lateral medial images). Clustered amorphous, indistinct, pleomorphic (or heterogeneous), or fine, linear, or branching calcifications are more typical of carcinomas.

MRI

Breast MRI has become an integral part of breast cancer diagnosis and management in selected patients. Current indications for breast MRI include evaluation of patients in whom mammographic evaluation is limited by augmentation (including silicone and saline implants and silicone injections), determining the extent of disease at the time of initial diagnosis of breast cancer (including identification of invasion of the pectoralis major, serratus anterior, and intercostal muscles), evaluation of inconclusive findings on clinical examination, mammography, and/or ultrasonography, screening of the contralateral breast in selected patients with newly diagnosed breast carcinoma, and asymptomatic screening of patients at very high risk of breast carcinoma (in conjunction with routine mammography). Other uses of breast MRI include evaluation of response to neoadjuvant chemotherapy with imaging before, during, and/or after treatment, and identification of residual disease in patients with positive margins after lumpectomy.

Ultrasound

The current indications for breast ultrasonography include palpable findings (including as the initial imaging test of palpable findings in patients who are younger than 30 years, pregnant, or lactating), abnormalities or suspected abnormalities on mammography or MRI, problems with breast implants, suspected underlying mass in the setting of microcalcifications or architectural distortion on mammography, supplemental screening in women at high risk for breast cancer who are not candidates for or do not have easy access to MRI, and suspected axillary lymphadenopathy. Real-time imaging is also possible with ultrasonography, making it ideal for interventional procedures. Breast ultrasound imaging should be performed with a high-resolution real-time linear array transducer with a center frequency of at least 10 MHz, using the highest frequency with which adequate penetration of the tissue is feasible.

PROGNOSTIC INDICATORS

Estrogen receptor and progesterone receptor status

Estrogen receptor (ER) and progesterone receptor (PR) represent weak prognostic factors for patients with breast cancer, but these receptors are the strongest predictive factors for response to endocrine therapy. ER and PR assays should be performed on all invasive breast cancers[74]. Both ER and PR are assessed by immunohistochemistry (IHC) on paraffin sections. IHC allows assessment of the expression specifically in either invasive or *in situ* cancer. Positive interpretation requires at least 1% of tumor cells showing positive nuclear staining of any intensity. Receptor negative is reported if less than 1% of tumor cells show staining of any intensity[75]. The cutoff to define positivity is 1% because patients with even 1% ER/PR-positive tumors may benefit from hormonal therapy. About 70% of all breast cancers are ER-positive and 60% to 65% of all breast cancers are PR-positive. For the patients with a "weak positive' result an Allred score helps differentiate positive from negative receptor status. The Allred score categorizes the percentage of cells (scored from 0 to 5) with the intensity (scored from 0 to 3) and adds these two scores to give a numerical score from 0 to 8[76]. A score of 0-2 was regarded as negative and 3-8 as positive

HER2 protein expression and gene amplification

HER-2/neu is a proto-oncogene that encodes for a transmembrane tyrosine kinase growth receptor, and it is involved in several regulatory pathways in breast, involving proliferation, survival, cell motility, and invasion. HER2 is usually assessed by IHC. Fluorescence *in situ* hybridization (FISH) assay of HER2 expression is usually performed when the evaluation by IHC is equivocal. HER2 is a prognostic factor for outcome in both node-negative and node-positive patients and is a predictive factor for response to certain therapies that target the HER-2/neu receptor such as trastuzumab (Herceptin), a monoclonal antibody targeted to the HER2 protein, and other newer anti-HER2 agents.

Overexpression/amplification is reported in 10% to 34% of invasive breast cancers. Gene over expression and amplification and surface membrane protein expression are concordant in more than 90% of cases[77,78].

Commercially available gene assays

OncotypeDX (Genomic Health, Inc, Redwood City, California) is a reverse transcription polymerase chain reaction-based assay that can be performed on paraffin sections. It is based on analysis of the expression of 21 genes and provides a "recurrence score" that correlates with outcome. Although it was initially used to assess prognosis in ER-positive, node-negative patients[79], data have indicated that it is an equally valuable prognostic indicator in ER-positive, node-positive patients.

Another molecular profiling product is the Amsterdam 70-gene profile, Mammaprint (Agendia, Amsterdam, Netherlands), in which a microarray analysis of gene expression is used on breast cancer tissue. It is used to determine the prognosis of patients with breast cancer and can be used for all tumors, including node-positive, *HER- 2 neu*-positive, and ER/PR-negative disease[80].

MANAGEMENT

After a breast cancer has been diagnosed, the patient is clinically staged using the American Joint Commission on Cancer (AJCC) guidelines (Tables 2 and 3).

Several landmark trials with decades of follow-up form the foundation of contemporary breast surgery. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial compared radical mastectomy (RM) to total mastectomy (TM) with or without radiation therapy in a prospective randomized fashion. In the TM arm, axillary dissection was performed only if lymph nodes were positive. The investigators reported no difference in either group with regard to disease-free survival, relapse-free survival, distant-disease-free survival, or overall survival, confirming no advantage to RM. The NSABP B-06 trial prospectively randomized women with tumors less than 4 cm to mastectomy, lumpectomy, or lumpectomy with radiation. All women had an ALND regardless of treatment assignment or nodal status; negative margins, defined as no tumor at ink, were required. The 20-year follow-up data were published in 2002; the investigators found no difference in disease-free, distant-disease-free, or overall survival between any of the treatment arms[81,82]. The data did demonstrate, however, a significant reduction in local recurrence (LR) after lumpectomy with the addition of radiation therapy (39.2% *vs* 14.3%, $P < 0.001$). The National Institutes of Health (NIH) issued a Consensus Conference statement in 1990 recommending BCT as the preferred surgical treatment of women with early stage breast cancer[83].

Contraindications to BCT exist and are classified as absolute or relative. Absolute contraindications include multicentric disease (tumors in more than one quadrant of the breast), diffuse malignant-appearing calcifications, inflammatory breast cancer, prior radiation to the chest or breast or inability to receive radiation, persistent positive margins despite appropriate attempts for breast-conserving surgery, and the need for radiation during pregnancy. Skin dimpling, nipple and areolar retraction, and tumor location are not contraindications to BCT, yet these should be considered in the preoperative assessment, specifically with respect to the ability to achieve negative margins.

Achieving negative surgical margins is a hallmark of successful BCT because this is associated with a lower rate of LR. However, what constitutes a negative margin remains a matter of considerable debate. The NSABP has long defined a negative margin as "no tumor at ink" regardless of the proximity of the nearest tumor cell. Historically, other series have argued that margins of more than 1 mm, more than 2 mm, more than 5 mm, or even more than 10 mm provide better local control. A recent meta-analysis reviewed 21 studies and 14571 patients undergoing BCT[84]. Data demonstrate a significant increase in LR for positive margins with an odds ratio (OR) of 2.42 ($P < 0.001$) compared with negative margins. Direct comparison between different margin widths found no statistically significant improvement in local control. Although a weak trend was identified suggesting declining LR with increasing margin distance, this trend disappeared after adjustments for radiation boost treatment and endocrine therapy.

Neo-adjuvant chemotherapy increases eligibility for breast-conserving surgery, especially in patients presenting with locally advanced breast cancer or in borderline cases whereby the tumor-to-breast size ratio will not allow for excision and acceptable cosmetic results. NSABP B-1840 established the efficacy of neo-adjuvant therapy randomizing women with early stage breast cancer to 4 cycles of neo-adjuvant or adjuvant doxorubicin plus cyclophosphamide. An updated analysis with more than 16 years of follow-up demonstrates no difference in overall survival, disease-free survival, or event-free survival between the two arms[85]. Women receiving neo- adjuvant therapy had a higher rate of pathologic negative axillary lymph nodes at surgery and a higher rate of BCT.

Radiation therapy plays a crucial role in successful BCT and has long been recognized to reduce LR risk by approximately 50%. The 2005 Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) overview analyses demonstrated the influence of local control on long-term survival[86]. With regard to BCT, the EBCTCG collectively analyzed data from 10 trials of 7300 women and found the risk of LR at 5 years to be significantly reduced from 26% after lumpectomy alone to 7% after lumpectomy with radiation therapy, an absolute reduction of 19%. The EBCTCG recently updated this data in 2011, expanding their analysis to 17 randomized trials of 10801 women undergoing breast-conserving surgery with and without radiotherapy. This meta-analysis again confirmed that radiation therapy resulted in an overall absolute reduction in LR of 15.7% at 10 years compared with those

Table 2 American Joint Commission on Cancer guidelines–tumor node metastasis classification

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (LCIS)	Lobular carcinoma *in situ*
Tis (Paget's)	Paget's disease of the nipple
T1	Tumor ≤ 20 mm in greatest dimension
T1mi	Tumor ≤ 1 mm in greatest dimension
T1a	Tumor > 1 mm but ≤ 5 mm in greatest dimension
T1b	Tumor > 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumor > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension
T3	Tumor > 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed (for example, previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level Ⅰ, Ⅱ axillary lymph node(s)
N2	Metastases in ipsilateral level Ⅰ, Ⅱ axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases Metastases in ipsilateral level Ⅰ, Ⅱ axillary lymph nodes fixed to one another (matted) or to other structures
N2a	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N2b	
N3	Metastases in ipsilateralinfraclavicular (level Ⅲ axillary) lymph node(s) with or without level Ⅰ, Ⅱ axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level Ⅰ, Ⅱ axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateralinfraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)
Distant metastases (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i +)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

not receiving radiation (19.3% *vs* 35.0%, $P < 0.00001$, two-tailed); this translated into an absolute reduction in breast cancer death of 3.8% at 15 years[87].

LR after BCT can be described as: (1) a true recurrence, one within the primary tumor bed; (2) a marginal miss, one within the same quadrant just outside of the tumor bed; and (3) an elsewhere recurrence, one in a separate quadrant of the breast. Generally, true recurrences and marginal misses account for 46% to 91% of all LRs and tend to occur earlier than elsewhere recurrences[88]. The EBCTCG demonstrates that more than 75% of all recurrences occur within 5 years[86]. Risk factors for LR include positive margins, young age, ER-negative receptor status, larger tumor size, positive nodes, and lymphovascular invasion[89,90]. Systemic therapy, especially targeted therapy, reduces the risk of LR. For example, the adjuvant trastuzumab trials demonstrate that patients receiving trastuzumab had a 50% reduction in LR[91]. Similarly, Mamounas and colleagues evaluated LR in estrogen receptor-positive patients enrolled in NSABP B-14 and NSABP B-20 according to the 21-gene recurrence score assay (Oncotype DX, Genomic Health, Redwood City, California, United States)[92]. At 10 years, tamoxifen significantly reduced the risk of LR in the low-risk group from 10.8% to 4.3% ($P < 0.001$). The addition of chemotherapy further reduced LR to 1.6% in that group ($P = 5.028$).

LOCOREGIONAL TREATMENT OF CLINICAL STAGE Ⅰ, ⅡA, OR ⅡB DISEASE OR T3, N1, M0

Lumpectomy with surgical axillary staging

Negative axillary nodes: Radiation therapy to whole breast with or without boost (by photons, brachytherapy,

Table 3 Clinical staging-American Joint Commission on Cancer guidelines

Stage 0	Tis	N0	M0
Stage Ⅰ A	T1	N0	M0
Stage Ⅰ B	T0	N1mi	M0
	T1	N1mi	M0
Stage Ⅱ A	T0	N1	M0
	T1	N1	M0
	T2	N0	Mo
Stage Ⅱ B	T2	N1	M0
	T3	N0	M0
Stage Ⅲ A	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage Ⅲ B	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage Ⅲ C	Any T	N3	M0
Stage Ⅳ	Any T	Any N	M1

or electron beam) to tumor bed or consideration of partial breast irradiation (PBI) in selected patients. Radiation therapy should follow chemotherapy when chemotherapy is indicated.

One-three positive axillary nodes: Radiation therapy to whole breast with or without boost (by photons, brachytherapy, or electron beam) to tumor bed following chemotherapy when chemotherapy is indicated. Strongly consider radiation therapy to infraclavicular region and supraclavicular area. Strongly consider radiation therapy to internal mammary nodes. Radiation therapy should follow chemotherapy when chemotherapy is indicated.

> Four positive axillary nodes: Radiation therapy to whole breast with or without boost (by photons, brachytherapy, or electron beam) to tumor bed, infraclavicular region and supraclavicular area. Strongly consider radiation therapy to internal mammary nodes. Radiation therapy should follow chemotherapy when chemotherapy is indicated.

Total mastectomy with surgical axillary staging ± reconstruction

No radiation therapy: Negative axillary nodes and tumor ≤ 5 cm and margins ≥ 1 mm.

Consider postchemotherapy radiation therapy to chest wall: Negative axillary nodes and tumor ≤ 5 cm and close margins (< 1 mm).

Strongly consider radiation therapy to internal mammary nodes: Negative axillary nodes and tumor > 5 cm ormargins positive: Consider radiation therapy to chest wall ± infraclavicular.

One-three positive axillary nodes: Strongly consider postchemotherapy radiation therapy to chest wall + infraclavicular and supraclavicular areas; if radiation therapy is given, strongly consider internal mammary node radiation therapy.

≥ Four positive axillary nodes: Postchemotherapy radiation therapy to chest wall + infraclavicular and supraclavicular areas. Strongly consider radiation therapy to internal mammary nodes.

MASTECTOMY

Approximately 30% to 40% of breast cancer patients in the United States are candidates for mastectomy, either because they are not eligible for BCT or the patients choose mastectomy.

The types of mastectomy available are: TM or simple mastectomy: removal of the breast, overlying skin, and the nipple and areolar complex; SSM or skin-sparing: same as TM or simple mastectomy but sparing as much skin as possible and the infra-mammary fold for immediate or delayed reconstruction; MRM or modified radical mastectomy: same as TM but within continuity axillary lymph node dissection.

NSM: SSM technique also saving the areola and/or nipple; RM or radical mastectomy which includes removal of the pectoralis muscles and level Ⅲ axillary nodes. Mastectomy is usually done in conjunction with sentinel node biopsy. Prophylactic mastectomy (PM) is a term that applies to mastectomy when there is no cancer in the breast.

MANAGEMENT OF THE AXILLA

The status of the axillary lymph nodes is one of the most important factors impacting overall prognosis and treatment decision-making for breast cancer. Complete axillary lymph node dissection (ALND), or removal of level Ⅰ and Ⅱ axillary nodes was the standard surgical approach to invasive breast cancer until recently. Now this operation is reserved for patients with clinically positive lymph nodes confirmed on needle biopsy at initial evaluation, or when a clinically negative axilla is evaluated by ultrasound, found to have a suspicious node and this is confirmed by needle biopsy. In patients with a clinically and radiologically negative axilla, a sentinel lymph node (SLN) biopsy can be performed safely at the time of mastectomy or lumpectomy, sparing patients the morbidity associated with ALND.

The sentinel node is based on the concept that breast cancers drain to a single node or nodes, the sentinel nodes, before draining to more distal nodes. One of the earliest randomized trials examining the use of SLN biopsy in breast cancer was reported by Veronesi *et al*[93] in 2003. They randomized 516 patients with breast cancer with tumors less than 2 cm in diameter to receive a SLN biopsy followed by routine ALND or SLN biopsy followed by an ALND only if the SLN contained metas-

tases. After 10 years of follow-up, no differences were observed between the groups for local axillary recurrence (0% in the SLN biopsy group *vs* 2% in the ALND group) or disease-free survival (89.9% *vs* 88.8%)[94].

Recent research has questioned whether all patients with a positive SLN require a completion ALND. In patients with clinically node-negative disease, the SLN is the only involved node in 60% to 70% of patients, which raises the question as to whether ALND offers additional therapeutic benefit for all patients[95].

This question was addressed prospectively in the ASOCOG Z0011 trial[96]. Patients with T1 and T2 tumors undergoing lumpectomy who were found to have metastatic disease in the SLNs were randomized to undergo either ALND or no further treatment of the axilla. All patients were required to have negative margins in the breast excision, and went on to have whole-breast irradiation. Adjuvant treatment was per the primary team, with 96% receiving chemotherapy and 47% endocrine therapy. The trial closed early because of low accrual and events rates, reaching only 47% of its accrual goals (891 patients enrolled). Median follow-up for the evaluable patients was 6.3 years. At 5 years, the local recurrence rate was 1.6% in the SLN biopsy group compared with 3.1% in the ALND arm. There was also no difference in 5-year disease-free survival (89.9% *vs* 88.8%). The authors concluded that for select patients with node-positive breast cancer and low-volume axillary disease, a SLN biopsy alone does not result in inferior survival or inadequate local control.

ADJUVANT THERAPY

A multidisciplinary approach to the treatment of breast cancer has been fundamental for the recent advances in the management of this disease. A meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which included randomized clinical trials conducted since adjuvant therapies became widely used in the 1990s, reported a decrease in annual relative risk of relapse and mortality of 23% and 17% respectively[97]. The purpose of adjuvant systemic therapy is to improve the disease-free survival (DFS) and overall survival (OS) rates associated with treatment of BC by local therapies (surgery and/or radiation) alone. The high rates of recurrence are probably related to the presence of micrometastatic disease in 10%-30% of LN-negative and in 35%-90% of LN-positive patients at the time of diagnosis[98,99]. Adjuvant chemotherapy helps eradicate residual local or distant residual microscopic metastatic disease. The addition of taxanes (paclitaxel anddocetaxel) to the standard anthracycline based chemotherapy has been studied extensively and has shown a significant reduction of 17% in the risk of recurrence[100,101]. A meta-analysis demonstrated that taxane-based regimens provide both DFS and OS benefit with an absolute 5-year risk reduction of 5% for DFS and 3% for OS when compared with standard anthracycline regimens irrespective of ER status, LN status, and age. Additionally, the improvements in DFS and OS were similar for both paclitaxel and docetaxel[102].

Current guidelines for adjuvant hormonal and chemotherapy after surgical treatment for invasive breast cancer vary depending on hormone receptor positivity or negativity and expression of HER-2/neu. Applicable practice guidelines are reproduced from the NCCN Breast Cancer Practice Guidelines below[103].

Hormone receptor-positive

Her2-positive disease: pT1, pT2, or pT3; and pN0 or pN1mi (≤ 2 mm axillary node metastasis)**:** (1) Tumory ≤ 0.5 cm or microinvasive (pN0, consider adjuvant endocrine therapy; pN1mi, adjuvant endocrine therapy or adjuvant chemotherapy with trastuzumab followed by endocrine therapy); (2) Tumor 0.6-1.0 cm, adjuvant endocrine therapy ± adjuvant chemotherapy with trastuzumab; (3) Tumor > 1 cm, adjuvant endocrine therapy + adjuvant chemotherapy with trastuzumab; and (4) Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes), adjuvant endocrine therapy + adjuvant chemotherapy with trastuzumab.

Her2-negative disease: pT1, pT2, or pT3; and pN0 or pN1mi (2 mm axillary node metastasis)**:** (1) Tumor ≤ 0.5 cm or microinvasive (pN0, consider adjuvant endocrine therapy; pN1mi, adjuvant endocrine therapy or adjuvant chemotherapy with trastuzumab followed by endocrine therapy); (2) Tumor > 0.5 cm, consider 21-gene RT-PCR assay (not don, adjuvant endocrine therapy ± adjuvant chemotherapy; low recurrence score (< 18); adjuvant endocrine therapy; intermediate recurrence score (18-30), adjuvant endocrine therapy ± adjuvant chemotherapy; high recurrence score (≥ 31), adjuvant endocrine therapy + adjuvant chemotherapy; node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes), adjuvant endocrine therapy + adjuvant chemotherapy).

Hormone receptor-negative

Her2-positive disease: pT1, pT2, or pT3; and pN0 or pN1mi (≤ 2 mm axillary node metastasis)**:** (1) Tumory ≤ 0.5 cm or microinvasive (pN0, no adjuvant therapy; pN1mi, consider adjuvant therapy with trastuzumab); (2) Tumor 0.6-1.0 cm, consider adjuvant chemotherapy with trastuzumab; and (3) Tumor > 1 cm, adjuvant chemotherapy with trastuzumab.

Her2-negative disease: pT1, pT2, or pT3; and pN0 or pN1mi (≤ 2 mm axillary node metastasis): (1) Tumor ≤ 0.5 cm or microinvasive (pN0, no adjuvant therapy; pN1mi, consider adjuvant chemotherapy); (2) Tumor 0.6-1.0 cm-Consider adjuvant chemotherapy; (3) Tumor > 1 cm-Adjuvant chemotherapy; and (4) Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes), adjuvant chemotherapy.

More recently, the development of genomic profil-

ing techniques has identified gene expression patterns in breast tumors with distinct molecular profiles, pathologic features, and clinical outcomes[104,105]. Expression patterns have defined 4 different subtypes: luminal A and B (estrogen-sensitive BC), HER2-enriched, and basal-like tumors (negative ER/PR and negative HER2). Luminal A tumors are classified by positive ER/PR, negative HER2, and low Ki-67, whereas luminal B tumors characteristically have positive ER/PR, negative HER2, and high Ki-67[106,107]. The additive prognostic value of Ki-67, a cell proliferation marker, to steroid and HER2 receptors is accepted, as many significant genes in gene expression profiles are proliferation related. Ki-67 marks the difference between luminal A and B tumors; however, Ki-67 is not yet routinely available and standard cutoffs are not well defined.

Adjuvant hormone therapy is considered standard in all patients with endocrine-sensitive tumors defined by the expression of ER and PR by IHC. Approximately 70% of BCs have positive expression of the ER and are considered hormone sensitive. Treatment with tamoxifen for 5 years reduces the risk of recurrence by 41% and BC mortality by 34%[97].

In postmenopausal women, an Aromatase Inhibitor may be substituted because of the proven efficacy and the low risk of for development of endometrial cancer with this drug. The arimidex, tamoxifen, alone or in combination (ATAC) trial, is a pivotal trial in adjuvant hormone therapy[108]. The ATAC trial compared the adjuvant use of anastrozole plus tamoxifen either alone in postmenopausal women with early-stage BC. At 10 years, anastrozole as initial therapy showed increased DFS (HR 0.86, P = 5.003), time to local and distant recurrence (HR 0.79, P = 5.0002; HR 0.85, P = 5.02, respectively), and reduced indices of contralateral BC (HR 0.62, P = 5.003) compared with tamoxifen. However, there was no significant difference in overall mortality between the 2 groups[109].

Approximately 15% to 20% of all BCs present with amplification of the HER2 gene[110]. HER2 over-expression is reported to be an independent predictor of poor prognosis. This can be addressed by the incorporation of anti-HER2 therapy with trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, which in the adjuvant setting has shown significant improvement in clinical outcomes from adjuvant chemotherapy plus trastuzumab compared with chemotherapy alone. Based on results from randomized clinical trials, a trastuzumab-containing regimen for up to 1 year is now considered standard for all patients with HER2-positive tumors larger than 1 cm[111,112].

There are rapid advances being made with respect to systemic therapy targeting specific molecular targets like phosphatidylinositol 3-kinase vascular endothelial growth factor receptor, epidermal growth factor receptor and poly polymerase.

SURVEILLANCE AND FOLLOW-UP

A systematic review of the relevant published literature performed by de Bock *et al*[113] identified that 40% of recurrent cancers are diagnosed in asymptomatic patients during routine visits. This data stresses the importance of follow up and surveillance. Clinical evaluation including history and physical exam is recommended every four to six months for five years, then every twelve months with annual mammography. Women on tamoxifen should undergo annual gynecologic assessment if the uterus is present. Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter. Patients should also be instructed to augment modifiable risk factors such as decreasing alcohol consumption, increasing physical activity and decreasing BMI.

CONCLUSION

There is a greater refinement in breast cancer care with increased specialization and collaboration amongst surgeons, oncologists, radiation oncologists, nurses, geneticist, reconstructive surgeons and patients. The effectiveness and benefits of a multidisciplinary approach to the treatment of breast cancer has been empirically demonstrated[114,115]. In the future, there will be great value in genomic sequencing and proto-identification of women at risk for developing breast cancer.

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