Recent Studies and Advances in Breast Cancer

Chapter 1

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1. Introduction

Breast cancer is the most common cancer affecting women, accounting for approximately 30% of all new cancer diagnoses in the United States. It is estimated that 1 in 8 women will develop breast cancer in their lifetime. In the United States in 2017, an estimated 255,180 new cases of breast cancer and 63,410 cases of carcinoma in situ of the female breast will be diagnosed. However, Due to Major advances in breast cancer diagnosis, management, and treatment, breast cancer has been surpassed by lung cancer (as of 2013) as the most deadly female cancer. In 2017, 41,070 of the expected new cases, will die of breast cancer, which calculates out to an 84% survival rate. While the overall incidence of breast cancer has slightly increased since 2004, the death rate for female breast cancer dropped 38% from 1989 to 2014, further validating our improvements in breast cancer treatment. This means that of the expected 600,920 deaths related to cancer, only 6.8% will be attributable to breast cancer. Men are affected by breast cancer as well. An estimated 2,470 cases of male breast cancer will be diagnosed in 2017, making up 0.3 percent of all new cancer diagnoses, with 460 estimated deaths. This results in an approximately 19 percent mortality rate. In comparison, prostate, lung/bronchus, and colorectal cancer make up the top three cancers in men, accounting for nearly 42% of new cancer diagnoses. However, the combined mortality of colorectal and prostate cancer comes in at 17 percent, making male breast cancer more deadly if diagnosed [1].

Despite tremendous improvements, breast cancer remains one of the top killers of women before the age of 40. In fact, cancer is the second leading cause of death in women of all

ages, behind heart disease [1]. However, with recent advancements in diagnosis, management, and treatment, the future remains bright for most with newly diagnosed breast cancer.

Over the last 40 years, large randomized clinical trials conducted by National Surgical Adjuvant Breast and Bowel Project (NSABP) have made major contributions in making breast surgical procedures less invasive, improving patient outcome in early-stage breast cancer, establishing standard of care in surgical management and the use of adjuvant hormonal therapy and chemotherapy [2].

2. Screening

Women at Average Risk

In 2015, American cancer Society (ACS) updated their breast cancer screening guidelines for average risk women. This was a major departure from their previous recommendations back in 2003. The updated guidelines are as follows [3]:

1 Women at average risk for breast cancer should undergo regular screening mammography starting at age 45.

2 Women ages 45 to 54 years should undergo annual screening.

3 Women 55 years and older should get biennial screening or have the opportunity to continue annual screening.

4 Women should have the opportunity to begin annual screening between the ages of 40 and 44 years.

5 Women should continue screening mammography as long as their overall health is good and their life expectancy is 10 years or longer.

6 The ACS does not recommend clinical breast examination at any age.

The American college of radiology (ACR) recommendations are as follows:

Average-Risk Women: <15% lifetime risk of breast cancer [4, 5].

1 Annual screening mammography or tomosynthesis starting at age 40.

2 Ultrasound may be considered.

3 The ACR does not recommend stopping screening on the basis of age and it should be tailored to individual situations such as life expectancy exceeding 5 to 7 years, comorbidities, intention to seek and ability to tolerate treatment if cancer is diagnosed.

High-Risk Women: Women with BRCA or other known genetic predisposition and their untested first-degree relatives, women with history of chest irradiation between 10 to 30 years of age, women with 20% or greater lifetime risk of breast cancer [5].

1 Annual mammography or tomosynthesis starting 8 years after radiation therapy but not before age 25.

2 Annual screening in women with an inherited cancer predisposition, beginning 10 years earlier than the affected relative at the time of diagnosis but not before age 30.

3 Screening MRI is recommended in addition to screening mammography or tomosynthesis

4 Screening US is indicated in high-risk patients who cannot tolerate MRI

The ACS recommends screening MRI in high-risk women, and ACR and the Society of Breast Imaging endorse those recommendations.

3. Major Changes in the American Joint Committee on Cancer (AJCC) Eighth Edition Cancer Staging (Implemented as of January 1, 2018)

The anatomic TNM system for staging provides classification categories for the primary tumor (T), regional lymph nodes (N), and distant metastasis (M), which are combined to determine the stage of the tumor. Historically the TNM staging have been associated with outcome measures, including OS and DFS but are somewhat problematic when applied to individual patients with different biologic subtypes of cancers expressing different biomarkers. Some of the major changes are listed below;

1 There are two stage groups;

The anatomic stage group is based solely on TNM staging so that stage can be assigned in regions of the world where the biomarkers cannot be routinely obtained.

The prognostic stage group includes the anatomic TNM plus tumor grade, and the status of the biomarkers ER, PR, and Her-2. It is preferred for patient care and should be used for reporting of all cancer patients in the United States.

2 All invasive carcinomas should be assessed for ER, PR, and Her2 status, whenever possible.

3 Lobular carcinoma in situ (LCIS) is removed as a pathologic tumor in situ (pTis) as it is a benign entity and is removed from TNM staging.

4 For patients with hormone receptor (HR)-positive, Her2 negative and lymph node-

negative tumors, a 21 gene (Oncotype Dx) recurrence score less than 11, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0M0. The tumor is staged using the AJCC prognostic stage group table as stage I (Oncotype Dx is the only multigene panel included in the prognostic stage group table of the eighth edition, because it is supported by level I evidence).

5 For patients with HR-positive, Her2 -negative, and lymph node-negative tumors, a Mammaprint low-risk score, a 12-gene (EndoPredict) low-risk score, a PAM50 (Prosignia) risk-of-recurrence score in the low range, or a Breast Cancer Index (BCI) in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0M0 (level II evidence) [6].

4. High Risk Lesions

The most common high-risk lesions are atypical ductal hyperplasia (ADH), a typical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS). Multiple studies have shown a 4-5 fold increase in the relative risk of breast cancer over the general population. LCIS has also proven to have significant pre-malignant potential, with up to an 8-fold increase in breast cancer risk [7]. While none of these lesions are classified as breast cancer, they do require high risk screening, with potential chemoprevention.

5. Ductal Carcinoma in Situ (DCIS)

Ductal carcinoma in situ (DCIS) is malignant proliferation of ductal cells within the ducto-lobular unit, confined to the basement membrane. The incidence of DCIS has increased significantly from less than 5% of breast cancers up to 20% to 30% following the advent of screening mammography. Ductal carcinoma in situ is treated as a malignancy because of the increased risk of developing invasive ductal carcinoma. Based on available data 14 to 53% of DCIS progress to invasive carcinoma within 10 years or more, if left untreated. Treatment for DCIS may include lumpectomy (the preferred surgery with local recurrence of 25% within 10 years, 50% of which is invasive [8]) with or without radiation, unilateral mastectomy (with low recurrence rate of 1%-5% after 10 years which tends to be invasive [8]), and even bilateral mastectomies. For hormone receptor positive DCIS, tamoxifen may be added to the treatment schedule [9-16].

In the NSABP B-17, the lumpectomy plus RT group showed a 52% risk reduction in invasive LR(I-LR) and 47% reduction in DCIS-LR compared with lumpectomy only (LO) group. The (NSABP) B-24 showed that women treated with lumpectomy and RT and Tamoxifen had a 32% reduction in I-LR but a non-statistically significant reduction of 16% in DCIS-LR compared with patients treated with RT plus placebo, as well as a 53% risk reduction in contralateral breast cancers. Comparing across trials, RT plus Tamoxifen showed a relative

risk reduction of I-LR by about 70% compared with the LO group. Radiation therapy reduced the I-LR at 15 years from 19.4% in LO to 8.9% in the B17 RT group and to 10% in the B-24 RT plus placebo group. The NSABP DCIS trials showed an overall survival of greater than 85% and breast cancer mortality rate of 4.7% in all treatment groups at 15 years [15]. The NSABP B-35/NRG Oncology showed that the aromatase inhibitor, Anastrozole, resulted in further improvement in breast cancer-free interval as compared to Tamoxifen, in younger post-menopausal patients, <60 years of age, as well as reduction of contralateral invasive breast cancer [17].

Patients undergoing lumpectomy with RT had similar survival compared with mastectomy [12]. Although multiple trials have demonstrated a decrease in the risk of recurrence by adding radiation and Tamoxifen after surgical excision, improvement in the rates of distant metastasis and overall survival (OS) have not been shown in any randomized clinical trial [8,11,13,14, 15,18]. The breast cancer-specific mortality after diagnosis of DCIS is estimated to be 1.1% at 10 years and 3.3% at 20 years [19]. The European Organisation for Research and Treatment of Cancer (EORTC) 10853 was another study on breast conservation surgery (BCS) with or without radiation in DCIS and demonstrated DCIS LR reduction from 14% to 7% in 10 years and from 16% to 8% in 15 years with addition of RT. The reduction was from 13% to 8% of invasive LR in 10 years and from 16% to 10% in 15 years with addition of RT [13,14]. Their study revealed that women 40 years and younger, those with clinically detected DCIS and with margins that were not free were at a high risk for LR which was consistent with NSABP B-17 & B-24 data [13,14,15]. Well-differentiated DCIS had a lower risk of DCIS LR but not of invasive LR [13,14].

The Swedish DCIS (SweDCIS) trial was also a study reporting on the effect of RT after BCS. After 20 years of follow up the LR reduction was 12%, with a relative risk reduction of 37.5% with addition of RT [18]. In the United Kingdom/ Australia and New Zealand (UK/ANZ) DCIS trial, patients were assigned to RT, Tamoxifen, or both, after BCS, the LR reduction was 59% at a median follow up time of 12.7 years with addition of RT [14,15,16]. A meta-analysis of all 4 randomized trials (including the EORTC 10853 trial) revealed a LR reduction of 0.46 and all trials showed a comparable reduction in invasive and noninvasive recurrences [14,15]. Contrary to the NSABP trials the UK/ANZ DCIS trial in their first report analysis, no significant reduction in new breast events was noted with Tamoxifen; however, the update on their long-term follow up revealed that the reduction in new breast events was significant. No effect was noted in ipsilateral invasive new breast events and the largest effect was on contralateral new breast events but it did reduce DCIS-LR [15,16]. A pure DCIS LR did not effect survival significantly whereas I-LR had a significantly worse survival compared with those without I-LR. The breast cancer-related death was 7.3% at 5 years and 10.4% at 10 years with I-LR compared to 2.7% at 10 years with DCIS-LR [14,15].

Multiple clinical trials tried assessing the safety of close surveillance as an alternative to surgery in the "low-risk" DCIS, including the LOw-RISk DCIS (LORIS) trial, the Low Risk Dcis (LORD) trial, Comparison of Operative to Monitoring and Endocrine Therapy (COMET) trial, and the proposed trial; Low And inteRmediate RIsK ductal carcinoma IN situ study (LARRIKIN). However the phenotypic and genotypic heterogeneity of DCIS lesions creates a great challenge in risk stratification and hence in management decision making. Although the current management of DCIS may be considered over treatment, at least in some cases, the exact criteria to characterize low-risk patients are still not fully clear. Current trials for management of low-risk DCIS by surveillance are welcomed and will potentially generate evidence-based data [10]. The Radiation Therapy Oncology Group (RTOG) 9804 was a prospective randomized trial for good-risk DCIS comparing radiotherapy with observation. This study concluded that although lower risk DCIS may have a low rate of local failure (LF) in the first 5 years, the rate continues to increase over time and addition of RT significantly decreased the LF rate [20].

Williams et al reported on review of five DCIS clinical trials; DCIS I, IBIS II (DCIS), IRESSA trial, ERISAC and Lapatinib DCIS. Although similar subtypes in invasive tumors have been identified in DCIS using IHC, its prognostic significance is unknown at this time. They reported that high grade DCIS is more likely to recur and that high Ki67 expression (>14%) was a predictor for invasive recurrence in DCIS. Their findings were consistent with the data reported by Kerlikowske et al. showing that patients with ER- negative DCIS express high Ki67 of >10% and Her-2-positive were at greater risk of local recurrence. Although currently Her-2 status is not routinely assessed in pure DCIS in clinical practice, the authors suggest that clinicians should consider routine measurement of Her-2 status for DCIS as well [8].

6. Invasive Breast Cancer

The most commonly identified invasive breast cancers include infiltrating ductal carcinoma (75-80%), infiltrating lobular carcinoma (5-10%), medullary (5-7%), mucinous (3%), and tubular (1-2%). Other less common forms include inflammatory breast cancer and Paget's disease of the nipple. There are 4 molecular phenotypes: Luminal A (ER+/PR+ & Her-2-), Luminal B (ER+/PR+ & Her 2+), Her2 type (ER-/PR- & Her 2+) and triple negative (ER-/PR-/Her2-) [8]. Treatment for invasive breast cancer is highly variable, and may include lumpectomy, simple mastectomy, skin and nipple sparing mastectomy, modified radical mastectomy (clinically positive lymph nodes), radical mastectomy (largely historical), neo-adjuvant or adjuvant chemotherapy, radiation, anti-hormonal therapy or a combination. Treatment largely depends on type of invasive cancer and staging according to the American Joint Committee on Cancer (AJCC), based on the tumor size (T), node status (N), and presence or absence of metastasis (M), the TNM staging system [9].

In 1971, The NSABP conducted the B-04 randomized clinical trial, with the 25-year findings that showed that there was no significant difference in survival between women treated with Halsted radical mastectomy and those treated with less invasive surgery [20]. The 20 year follow up of the NSABP B-06 trial demonstrated no significant differences in OS, disease free survival (DFS), or distant DFS between patients who underwent total mastectomy and those with lumpectomy with or without RT. However it showed a significant decrease in LR in the group who underwent lumpectomy followed by RT as compared to LO [2,20,21,22].

A meta-analysis updating previous data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) of 17 randomized trials showed that radiotherapy after breast conservation surgery for invasive cancer decrease the risk of recurrence by 50% as well as moderately reducing the risk of death from breast cancer by about a sixth [23].

NSABP B-21 trial demonstrated that in node negative patients with small invasive tumors, combination of RT and Tamoxifen resulted in superior local disease control than either modality alone. The NSABP B-14 trial demonstrated a significant benefit in DFS and OS in node negative, ER-positive patients, as well as a significant decrease in contralateral breast cancer (CBC) with 5 years of adjuvant Tamoxifen as compared to 5 years of placebo [2]. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial revealed that 5 years of Anastrozole (Arimidex) significantly improved DFS, reduced distant metastases and CBCs as compared to Tamoxifen with fewer noncompliance and side-effects, making it the preferred initial treatment for postmenopausal women with hormone-receptor-positive early breast cancer [24-29].

In both DCIS and small invasive cancers, tumor size and grade are significant predictors of mortality. For both, the ER-positive cancers have a lower annual mortality initially and then the relationship between ER status and annual death reverses. For both DCIS and invasive cancer, women diagnosed before age 40 years have relatively poor survival and black women do worse than white women [19].

In this chapter, we would like to focus on a few of the new and exciting advancements in the field of breast cancer.

7. Genetics

One of the more exciting areas of research has focused on the role of genetics in breast cancer. It is estimated that only 5-10% of breast cancers are hereditary [31]. BRCA-1 and BRCA-2 are two of the most common and well-known genes and may be identified in approximately 80% of all cases of breast cancer [32]. What about the 20% of cases that are BRCA negative? In recent years, a number of different genes have been associated with a high risk for developing breast cancer – TP53, PTEN, STK11, CDH1, ATM, CHEK2, PALB2 and

BRIP1. These genes will not be discussed in detail in this chapter, but some do merit a brief discussion on their impact on recent advancements in breast cancer.

7.1 BRCA

BRCA-1 was discovered in 1990, followed by BRCA-2 in 1995 and mutations in either gene are associated with breast and ovarian cancer syndrome. BRCA-1 is a tumor suppressor gene involved with cell cycle checkpoint control, genomic stability, and DNA repair and damage response. BRCA-2 plays an important role in homologous recombination. Both BRCA-1/2 interact with various proteins, including PALB2, discussed below. BRCA-1 mutations confers an estimated risk of up to 87% for developing breast cancer by the age of 70 as well as up to 68% risk of developing ovarian cancer. BRCA-2 has been associated with a slightly lower risk at 84%, however, it has been associated with 4-6% of all male breast cancer cases. Treatment options for BRCA+ breast cancer patients include surgical, anti-cancer medications and radiation and often consists of a combination of these options. Surgical treatments can include bilateral mastectomy and salpingo-oophorectomy which can be prophylactic in the absence of cancer, both of which have shown to decrease breast and ovarian cancer risk. Anti-cancer medications include etoposide, bleomycin– both of which cause double stand breaks – or platinum based drugs, such as cisplatin or carboplatin – which affect inter-strand cross linking. BRCA mutations tend to show resistance to vinca alkaloids and taxanes – anti-microtubule agents – thus limiting their effectiveness [31, 32, 33, 34]. In addition, perhaps Tamoxifen should be recommended to BRCA carriers who decide not to undergo prophylactic surgery.

7.2 PALB2

Just like BRCA-2, PALB2 is associated with homologous recombination, a step in the DNA-damage response. PALB2 interacts with both BRCA-1/2, forming a BRCA complex, and acting as a bridge between BRCA-1 and BRCA-2. With monoallelic mutations, individuals are at increased risk for developing not only breast cancer, but pancreatic and ovarian cancers as well. In cases of hereditary breast cancer, PALB2 is implicated in up to almost 4% of cases. The difficulties with this mutation arise, in part, to its relatively new discovery in relation to breast cancer. As noted above, successful treatment strategies are well described for BRCA mutations. Data is still lacking for the optimal treatment of PALB2 positive breast cancers [31, 32]. However, the risk for breast cancer can be as high as 58% to age 70 with two or more close family members with breast cancer at age 50 or younger.

7.3 CHEK-2

CHEK-2 is a tumor suppressor gene associated with a 2-fold increase in breast cancer risk. It consists of three functional domains and its activity is increased following DNA damage.

It is closely associated with ataxia-telangiectasia mutation (ATM) kinase, BRCA-1 and p53, all of which have been shown to increase the risk of breast cancer. CHEK2 is activated by ATM in response to double-stand DNA breaks, and phosphorylates p53 resulting in cell-cycle arrest. It was first associated with increased breast cancer risk in 1998-1999 when researchers discovered three CHEK2 germline mutations among four classical Li-Fraumeni and 18 Li-Fraumeni-like families [35, 36, 37, 38].

8. Genomic testing

To further improve breast cancer treatment and prevent over treatment, such as the case with cancers genetically not responsive to chemotherapy, calls for genetic testing of cancer cells became very popular after the turn of the century. Gene assays work by analyzing RNA extracted from tumor tissue, giving clinicians insight into estrogen and progesterone receptor status, as well as HER-2 status, among others. Many women with early-stage breast cancer are treated with adjuvant systemic therapy that can include chemotherapy, HER-2 directed therapy, hormone therapy, or a combination of systemic therapies. Treatment decisions are largely based on tumor characteristics, such as HER-2 status, lymph node status, and tumor grade, as well as characteristics of individual patients, such as age and menopause status [39, 40]. Thus, as multiple expression-based assays analyze an array of biomarkers, this allows clinicians to tailor treatment to patients individually, and guide treatment decisions.

Two such tests, Oncotype Dx, a 21-gene assay, and MammaPrint, a 70-gene assay, have both gained significant popularity. Today, Oncotype Dx is the preferred genetic test of the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). However, studies have shown that Oncotype Dx and MammaPrint are less useful to predict late recurrences after 5 years [34,41,42,43,44,45,46]. The Breast Cancer Index (BCI) has been shown to be superior at predicting late recurrences after 5 years.

8.1 Oncotype Dx

8.1.1 Invasive Breast Cancer

Oncotype Dx uses a reverse transcriptase PCR on the extracted RNA, giving information on 16 cancer related genes (with an additional five reference genes). Each gene is assigned a weighted expression resulting in a recurrence score which is divided into three categories. Low risk is a recurrence score less than 18, moderate risk between 18 and 30, and high risk greater than 31. However, this test can only be used for hormone-receptor positive, Her-2 negative and node negative early breast cancer [47]. The clinical trial RxPONDER (Rx for Positive Node, Endocrine Responsive Breast Cancer) showed that node positive patients with a low to intermediate recurrence score could benefit from chemotherapy. Oncotype Dx has been validated by multiple clinical trials, including TAILORx, the Trial Assigning Individualized

Options for Treatment. In this study, in patients with a very low recurrence score of less than 11, OS reached 98%, rate of invasive disease-free survival was 93.8%, with 5-year freedom from distant recurrence at 99.3%, without addition of chemotherapy. Thus, TAILORx found that low-risk patients with hormone-receptor positive, HER-2 negative, axillary node-negative breast cancer had very low recurrence rates with endocrine therapy alone [27, 38, 39, 40, 41, 42, 43, 44].

8.1.2 DCIS

The 12-gene Oncotype Dx DCIS score is calculated from seven cancer-related genes and five reference genes and is scaled from zero to 100. A prospective-retrospective study was performed by doing DCIS score for patients with DCIS who underwent BC without radiation in the Eastern Cooperative Oncology Group (ECOG) E5194 study. The DCIS score predicted the 10-year LR risk and provided information for recurrence risk independent of traditional clinical and pathologic factors. The risk of LR was more than twofold higher for the 30% of patients with an intermediate or high DCIS score compared with the 70% of patients with a low DCIS score. The DCIS score can help clinical decision making by identifying patients with a lower DCIS score for whom breast conservation surgery alone maybe adequate [45].

8.2 MammaPrint

MammaPrint is a gene-expression panel that contains 70 genes related to risk of metastasis. RNA is isolated from fresh frozen tumor tissue to obtain complementary DNA. It was first developed by the Netherlands Cancer Institute group. The RASTER trial was the first phase III clinical trial to investigate MammaPrint. In this study, MammaPrint was also compared to Adjuvant! Online. Patients were followed for roughly 5 years, which showed distant recurrence-free interval to be 98.4% in gene signature low risk Adjuvant! Online high risk patients. 76% of patients had not received adjuvant chemotherapy [44]. Another study, the MINDACT, was designed to validate MammaPrint's clinical usefulness in selecting patients for adjuvant chemotherapy. 6693 women classified with early-stage breast cancer were enrolled, with their genomic risk calculated using MammaPrint and their clinical risk using Adjuvant! Online. Those deemed low genomic and clinical risk did not receive chemotherapy. Results of 1550 women deemed high clinical risk and low genomic risk at 5 years revealed 94.7% survival without distant metastasis among those not receiving chemotherapy. Based on these findings, it was determined that those not receiving chemotherapy were 1.5 percentage points lower than the rate with chemotherapy. Thus, approximately 46% of women at high clinical risk may not require chemotherapy [27,37].

8.3 Prosigna (PAM50)

2/3 of breast cancers will express ER or PR positive tumors, making them candidates for

hormone therapy [46]. Recent advances in gene analyses have shown more complex molecular portraits [47]. In 2000, Perou et al first described the four intrinsic subtypes of breast cancer: luminal A, luminal B, HER2-enriched, and basal like [48,49]. In 2009, a gene expression-based test was introduced that provides an intrinsic subtype diagnosis, known as prediction analysis of microarray 50, or PAM50. It measures the expression of 50 genes and has reported a 93% accuracy in identifying the various intrinsic sybtypes [48]. The use of PAM50 has been validated in multiple studies.

8.4 EndoPredict

The EndoPredict assay (EP), is a RNA-based test based on gene expression data in combination with two clinicopathological risk parameters, namely tumor and nodal status [50, 51]. It was developed to assess the risk of distant metastasis in patients with ER+/HER2- primary breast cancer.

It measures the expression of eight cancer-related genes of interest (three proliferative and five ER-signaling/differentiation-associated) genes, along with three reference genes [50, 51]. These are used to calculate a molecular risk score (EP score) which together with nodal status and tumor size are used to give a molecular-clinicopathological hybrid score (EPclin score). Patients are then stratified into low- or high-risk for distant recurrence [50]. EndoPredict has been validated by multiple studies and has proven effective in helping to determine risk of distant metastases.

8.5 Breast Cancer Index

The Breast Cancer Index (BCI) was first developed using data from the Stockholm trial, a study that combined two gene expression assays, HOXB13:IL17BR (H:I), and molecular grade index (MGI), which, together, was termed the Breast Cancer Index. It is shown to be an independent prognostic factor for ER+ and node-negative patients. It is prognostic for early and late distant recurrences as well as predictive of extended aromatase inhibitor benefit [27]. MGI is a gene expression assay, comprised of five genes related to tumor progression and histological grade. MGI is also highly prognostic in patients with ER+ breast cancer. In the Stockholm trial, 2738 patients from 1976-1990 were selected based on low risk, ER+, node-negative status with or without treatment with tamoxifen for 2 or 5 years. The results of this study demonstrated improved disease free survival in patients treated with tamoxifen [27, 40, 41]. In a more recent study by the same group, data from the Stockholm trial was obtained using tumor blocks of some 800 patients, both tamoxifen treated and untreated. The BCI was used to evaluate distant recurrence and death. This study found that tamoxifen treated patients categorized as low risk had <3% 10 year distant recurrence risk.

Data from the ATAC trial was also used to validate BCI. [24-26].

9. Nipple Sparing Mastectomy

Aesthetic outcome is a major consideration for many women when discussing surgical options for breast cancer. Mastectomy can be a very daunting, and sometimes intimidating part of the recovery process, leaving major emotional and physical scars. Methods to improve breast surgery aesthetic outcomes have come a long way since the introduction of the radical mastectomy, a mutilating procedure with no survival benefit to patients. While improving aesthetics is important, an emphasis has been maintained on preserving oncologic outcomes. Various studies have shown no significant difference in local recurrence when comparing modified radical mastectomy and skin sparing mastectomy (SSM) [53-58]. Skin Sparing mastectomy, especially in the setting of immediate breast reconstruction, has improved patient satisfaction, however removal of the nipple areolar complex (NAC) can be emotionally disturbing for the patient [55]. Nipple sparing mastectomy (NSM) has become a popular surgical option for many women. Although the procedure can be technically challenging, aesthetic results are significantly superior to the traditional simple mastectomy.

In a NSM, the procedure preserves the NAC and skin. Oftentimes, an incision is made in the inframammary fold or axilla, helping to improve aesthetic outcome. While not all patients will begood candidates for NSM, those undergoing prophylactic mastectomy should be strongly considered [53-55]. The oncologic outcomes and complication rates with NSM compared to other techniques are still under debate when treating patients with breast cancer. However, rates of locoregional and distant recurrence have been shown in multiple studies to be acceptably low after NSMin patients with breast cancer [53-57]. In fact, in some studies, results have demonstrated zero recurrences involving the retained NAC. While much research is still underway, there has been promising results to date, especially in BRCA positive patients. In one study, 548 risk-reducing NSMs were performed at 9 different institutions. Bilateral prophylactic NSMs were performed in 202 patients (58.4%), and 144 patients (41.6%) underwent a unilateral risk-reducing NSM secondary to cancer in the contralateral breast. Overall, 201 patients with BRCA1 mutations and 145 with BRCA2 mutations were included. With median and mean follow-up of 34 and 56 months, respectively, no ipsilateral breast cancers occurred after prophylactic NSM. Breast cancer did not develop in any patients undergoing bilateral risk-reducing NSMs [56].

Nipple-sparing mastectomy provides the patient with multiple options for reconstruction however multiple factors must be taken into consideration, including breast size/ptosis, body habitus, patient comorbidities, age, radiation therapy, mastectomy, flap quality, and others. Reconstruction can be challenging to provide optimum results; however, with careful selection of patients and in the hands of a well-trained surgeon, NSM provides aesthetic and emotionally satisfying results [59].

10. Nodal Evaluation

Although axillary lymph node dissection (ALND) is a reliable method of identifying nodal metastases and maintains regional control, it can potentially carry unacceptable risk of seroma, infection,paresthesias, lymphedema, axillary web syndrome and decreased arm and shoulder function [60, 61, 62]. Sentinel lymph node biopsy (SLNB) in breast cancer was first reported in 1994 by Giuliano et al. [62] and was shown to accurately identify the axillary lymph nodes draining the tumor with less morbidity than ALND [60, 62] and subsequently became the standard of care in patients with clinically node negative axilla [60, 61, 62, 63, 64].

10.1 ACOSOG Z0011 trial and IBCSG 23-01 trial

With better understanding the tumor biology and realizing that many factors, patient and tumor-related, influences the decision to use systemic therapy with lymph node status being one but not necessarily mandating chemotherapy use and therefore putting into question whether ALND is necessary in certain cases. The American College of Surgeons oncology Group (ACOSOG) designed and initiated the multicenter Z0011 randomized trial. The inclusion criteria included women with T1-T2 invasive breast cancer, no palpable adenopathy, and 1-2 sentinel lymph nodes (SLNs) containing metastasis identified by frozen section, touch preparation, or hematoxylin and eosin (H & E) staining on permanent section. Women with 3 or more positive SLNs, matted nodes, or gross extranodal disease, prior neoadjuvant hormonal or chemotherapy were excluded. All patients underwent partial

mastectomy and tangential whole breast radiation. The 5-year overall survival (OS) was 91.8% with ALND and 92.5% with SLNB alone; 5-year disease free survival (DFS) was 82.2% with ALND and 83.9% with SLNB alone [62].

A similar study, The International Breast Cancer Study Group Trial 23-01 (IBCSG 23-01 trial) was a multicenter randomized trial comparing no ALND with ALND in breast cancer patients with SLN micrometastases. The findings were consistent with those of ACOSOG Z0011 trial finding no differences between the arms for any end point [65]. Therefore, in patients with limited SLN metastasis undergoing breast conservation, whole breast radiation and systemic adjuvant therapy, the use of SLNB compared with ALND does not result in decreased survival and ALND may no longer be justified for these women [61, 62, 65]. Unlike the ACOSOG Z0011 trial 9% of the IBCSG 23-01 patients underwent mastectomy suggesting that ALND may not be necessary in these patients if the invasive component of the cancer is small [65].

10.2 EORTC 10981-22023 AMAROS

In 2001, the European Organisation for Research and Treatment of Cancer (EORTC) initiated the 10981-22023 After Mapping of the Axilla, Radiotherapy or Surgery (AMAROS), a multicenter randomized trial in patients with T1-T2 invasive breast cancer with clinically negative axilla without prior systemic treatment or radiotherapy. The patients were randomized to ALND or axillary radiotherapy in case of a positive SLN. There were no significant differences in DFS and OS between the 2 treatment arms. The 5-year DFS was 86.9% in the ALND group and 82.7% in the axillary radiotherapy group. The 5-year overall survival was 93.3% in the ALND group and 92.5% in the axillary radiotherapy group. The axillary radiotherapy resulted in significantly less morbidity [60, 61].

11. Axillary Nodal Evaluation in DCIS

Ductal carcinoma in situ (DCIS) accounts for 20% of breast cancers affecting approximately 65,000 women per year with several fold increase in diagnoses over time due to widespread use of screening mammography [12, 66]. The National Comprehensive Cancer Network (NCCN) does not recommend axillary lymph node evaluation in breast conserving therapy (BCT) cases. Because invasive cancer can be found at the time of surgery in a small percentage of patients, the NCCN and ASCO recommend to strongly consider SLNB with mastectomy or excision in an anatomical location that further compromise a SLNB in the future due to lymphatic disruption, a mass forming DCIS or large volume DCIS (NCCN guidelines reference, www.asco.org/guidelines/snbbreast). A study by Mitchell et al. revealed that the compliance with the NCCN and ASCO guidelines was varied based on patient age, tumor size, geographic location, and practice type [66].

12. Axillary Micrometastases and Isolated Tumor Cells

The use of SLNB and the more detailed pathologic evaluation resulted in emergence of isolated tumor cells (ITCs) [size =<0.2 mm, AJCC staging system 7th edition as < 200 cells) and micrometastases (size > 0.2 mm and =< 2 mm), found in 10-15% of patients undergoing SLNB [63, 64]. In the sixth edition of AJCC staging system, T1N1miM0 and T1N1M0 were both categorized as stage IIA, however in the seventh and eighth editions, T1N1miM0 was categorized as stage IB [45, 64]. In a study by Mittendorf et al, it was reported that the recurrence-free survival (RFS), disease-specific survival (DSS), and OS are not different between patients with Stage I A and stage IB. Therefore they have the same prognosis, with biologic factors, including grade, ER and Her-2 status better stratified patients with respect to their prognosis than presence of micrometastasis in the lymph nodes [64, 67].

13. Postmastectomy Radiotherapy

The need for ALND and postmastectomy radiotherapy (PMRT) in settings of micrometastases is uncertain while the use of PMRT is widely accepted with four or more positive lymph nodes [63]. Current guidelines (ASCO, ASTRO, and SSO focused guideline update) recommend consideration of PMRT in patients with T1-2 breast cancer with macrometastases in one to three axillary nodes who undergo ALND, reducing risk of locoregional recurrence (LRR), any recurrence, and breast cancer mortality [63,68]. Furthermore, the panel recommends including the internal mammary nodes and the supraclavicular-axillary apical nodes in the radiation field in addition to the chest wall or reconstructed breast when PMRT is used in patients with T1-2 tumors with one to three involved axillary lymph nodes [68]. Some clinicians do not proceed to ALND with one or two involved sentinel nodes in mastectomy cases mainly by extrapolating the data from trials with breast conservation surgery and whole-breast radiation or breast plus axillary radiation whereas others feel ALND should still be performed. The consensus panel recommends PMRT only if there is already justification for its use when ALND is omitted and states that ALND should be performed when there is no clear evidence for PMRT [68].

A recent study by Mamtani et al, reported a LRR of 2.8% at 6 years in patients with T1-T2N0i+/N1mi breast cancer treated with mastectomy without PMRT, with no axillary failures to date. The tumor biology, rather than nodal disease, appearing to be the primary driver of LRR. Therefore, in patients with early stage breast cancer with micrometastases or ITCs undergoing mastectomy, especially in cases of a single positive lymph node, great locoregional control can be achieved without PMRT or nodal radiotherapy [63].

The consensus panel recommends administration of PMRT in patients with involvement of axillary node persisting after neoadjuvant systemic therapy (NAST) [incomplete pathological response]. Data suggest a low risk of LRR in clinically node negative patients who receive NAST or those with complete pathologic response in the lymph nodes with NAST. However currently there is not enough evidence to recommend for or against PMRT in these groups. The panel recommends enrolling these patients in clinical trials addressing this question [68].

14. Margin Status

14.1 Invasive Breast Cancer

Multiple randomized trials with long-term follow up have shown that survival after breast-conserving surgery (BCS) followed by whole-breast radiation therapy (WBRT), is equivalent to mastectomy for stage I and II breast cancer treatment [23,69]. However, there has always been controversy regarding appropriate margin width for invasive breast cancer in BCS. In view of dramatic changes in breast cancer management in the last 30 years, the

SSO and ASTRO developed a multidisciplinary expert panel, Margins Panel (MP), in 2013 to examine the association of margin width in BCS with WBRT in stages I and II invasive breast cancer and ipsilateral breast tumor recurrence (IBTR) rates . The MP defined a positive margin as ink on invasive cancer or DCIS, with at least two-fold increase in IBTR, which is not nullified with the use of radiation boost, systemic therapy, or favorable biology. The consensus was that negative margins, defined as no ink on tumor, minimize the risk of IBTR and therefore wider negative margins is not indicated, this holds true for invasive lobular carcinoma (ILC) as well. The panel felt that classic lobular carcinoma in situ (LCIS) at the margin is not an indication for re-excision however the significance of pleomorphic LCIS at the margin is uncertain [70]. Based on insufficient outcome data for pleomorphic LCIS and florid LCIS, the NCCN does not make specific recommendations and leaves the decision as to whether pursue negative margins up to the clinician [71].

14.2 DCIS

Although breast cancer mortality in women with DCIS is low, regardless of whether BCS or mastectomy is performed, higher rates of IBTR is associated with BCS [72]. Approximately half of all IBTRs are invasive, with an associated risk of breast cancer mortality. Optimal margin width for DCIS has always been a topic of debate for several decades [72,73]. Due to the lack of consensus on what is considered an adequate negative margin, a meta-analysis was performed by Marinovich et al. in 2016, indicating that a 2 mm negative margin is adequate in women with DCIS undergoing BCS with WBRT [74]. Subsequently the SSO, ASTRO and ASCO convened a multidisciplinary MP to assess IBTR in association with margin width in DCIS and a consensus guideline was developed. A positive margin was defined as ink on DCIS, with a significant increase in IBTR, which is not nullified by WBRT use.While the MP felt that negative margins of at least 2 mm are associated with reduced risk of IBTR in patients undergoing BCS with WBRT, clinical judgement must be used in deciding whether patients with smaller margin width need re-excision [72].

A recent study from MD Anderson Cancer Center suggests that patients with close margins (<2mm) who forego radiation therapy (RT) should undergo re-excision to obtain margins of 2 mm or greater. In patients undergoing RT, re-excision does not offer additional benefit in the 10-year LRR rate in patients with close margins compared with those with free margins. In cases of close margins, a postsurgical mammography is recommended to ensure that malignant-appearing calcifications have been completely excised. However multicenter, prospective studies with additional follow up are needed to ensure the findings of this study remains applicable [73]. There is no evidence supporting greater than 2 mm negative margins. Regardless of the margin width, excision without WBRT, is associated with significantly higher rates of IBTR than if followed by WBRT [72].

14.3 DCIS in the Presence of Invasive Breast Cancer

Ductal carcinoma in situ with microinvasion (no invasive focus > 1 mm in size), should be considered as DCIS when considering the optimal margin width. However, for an invasive cancer with a DCIS component, the MP recommends that the invasive cancer guideline is applicable, even when the close margin contains DCIS [72].

15. Localization in Breast Surgery

Since the development of screening mammography in the 1970s, there have been a significant increase in detection of nonpalpable abnormalities requiring biopsies. Mammographic and later ultrasound guided Wire localization (WL) developed to aid in surgical excisionin BCS for carcinoma, atypia or in cases where image-guided core needle biopsy is not feasible. Although WL is reliable, well tolerated and cost effective, some of its disadvantages are coordination between surgery and radiology, resulting in delayed operating room (OR) start, patient discomfort, risk of the wire displacement, potential wire transection intraoperatively and the localization route often dictates the incision. Alternative techniques were therefore developed [75-82].

15.1 Radioactive Seed Localization (RSL)

Iodine-125 impregnated radioactive seed was first described in 2001 by Gray et al [83]. It has become popular and is the preferred technique in many hospitals around the world. The seed can be placed up to 5 days before surgery with minimal radiation exposure to patients and staff with more focal localization. It rarely migrates after insertion and it can be used simultaneously with SLNB using Technitium-99m [75,76,77,78,80,83]. However it, too, has its own disadvantages related to use of radioactive material and the nuclear regulatory issues [75,78,80]. There is conflicting data on whether this technique is associated with reduced rates of positive margins, smaller volume of excision, shorter operating times and improved ease of use compared to WL [76,77,78,79,83].

15.2 Radioactive Occult Lesion Localization (ROLL)

Several centers in the United Kingdom (UK) have experience in using ROLL which involves injection of Technetium-99m nanocolloid into the tumor and subsequent excision using a gamma probe. Some of its limitations are possibly larger excision volumes due to dispersion of the Technitium-99 into the surrounding tissues, its short half-life of 6 hours and difficulty to accurately check the localization due to being mammographically occult [79].

15.3 SAVI SCOUT

The US food and Drug Administration (FDA) cleared the first nonradioactive nonwire

localizer in 2014, the SAVI SCOUT radar localization system from Cianna Medical Inc, which is a radar reflector activated with infrared light. It can be placed up to 30 days before surgery with acceptable margin positivity and re-excision rates [80, 81]. Its most significant limitation is the potential of disabling the reflector with direct contact with electrocautery. Although it has been modified since, the possibilitystill remains. Other limitations are risk of transection of the SAVI SCOUT antenna, inability to reposition after reflector deployment, possible reflector migration specially in the setting of a hematoma, and recommended maximal detection depth of 4 to 5 cm [75,80, 81]. In detecting the reflector, the hand piece has to be moved slowly to allow the system time to detect the reflector [80].

15.4 Intraoperative Ultrasound (IOUS)

The IOUS technique has shown lower re-excision rate than WL however, the lesion, hematoma, or biopsy marker has to be sonographically visible. It requires training, competence in interpreting images and it may not be available to all surgeons. In addition, there are technical issues such as removing the retractors and dimming the lights in the operating room while scanning with the probe to localize the lesion for excision [80].

15.5 Magseed

Magseed system from Endomagnetics was cleared by FDA in 2016 and can be placed up to 30 days before surgery. Its major flaw is that ferromagnetic instruments interfere with the signal requiring special surgical instruments. Electrocautery and other metallic equipment in the OR can also interfere with the signal requiring recalibration of the probe [75].

16. Human Epidermal Growth Factor Receptor 2 (Her-2/neu) Positive Breast Cancer

Overexpression of Her-2 is found in approximately 15-20% of patients with invasive breast cancer and is associated with aggressive behavior, lower response to traditional therapies, shorter time relapse, increased incidence of metastasis with brain being a common site and decreased survival [84-86]. Evaluation of Her-2/neu expression in breast cancer, along with ER/PR, is necessary in assessing prognosis and therapeutic options. Routine testing of these 3 markers are mandated by ASCO/College of American Pathologists (CAP) guidelines in every new, recurrent, invasive and metastatic breast carcinoma [82].

Adjuvant chemotherapy combined with Trastuzumab, an anti-Her-2 monoclonal antibody, has significantly improved outcomes in patients with Her-2 positive early breast cancer, reducing the risk of disease recurrence and death. Its use has been extended to both adjuvant and neoadjuvant settings for a total of 1 year in early breast cancer resulting in improved survival and increased PCR rates and it is considered the standard of care [84-86].

Pertuzumab is a humanized monoclonal antibody, complementing the mechanisms of

action of Trastuzumab by binding to different domains [87]. In neoadjuvant setting, the addition of Pertuzumab to Trastuzumab plus Docetaxel for 12 weeks in the randomized, multicenter, open-label NeoSphere trial increased the PCR rate significantly from 29.0% to 45.8% without substantial differences in tolerability, and thus it is considered a standard of care [88,89]. The NeoSphere trial revealed that patients that achieved PCR had longer progression free survival compared with patients who did not, therefore suggesting that PCR could be an early indicator of long-term outcome in early stage Her-2 positive breast cancer [89].

A recent study by Gunter et al. reported that addition of Pertuzumab to chemotherapy and Trastuzumab in adjuvant setting significantly improved the rates of invasive-disease-free survival in patients with Her-2 positive early breast cancer. This effect was most detectable in patients with higher risks of relapse due to lymph node involvement or hormone-receptor negativity [89]. This study reported positive results consistent with those of the neoadjuvant NeoSphere trial, although the chemotherapy regimen used was not the same in the two trials [87]. A study by Von Minckwitz et al. reported Pertuzumab significantly improved the rates of invasive-disease–free survival among patients with HER2-positive, operable breast cancer when it was added to trastuzumab and chemotherapy [87]. Pertuzumab was associated with a higher rate of adverse effects mainly low grade diarrhea [87,89]

Although many advances in the field of breast cancer has been discussed in this chapter, many other topics were not discussed as they are out of the scope of this chapter.

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