Cancer Treatment and Research
Steven T. Rosen, M.D., Series Editor
Robert H. Lurie Comprehensive Cancer Center
Northwestern University Medical School

Advances in Breast Cancer Management

Second Edition

edited by
William J. Gradishar
William C. Wood

Springer

ADVANCES IN BREAST CANCER MANAGEMENT, SECOND EDITION

Cancer Treatment and Research

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Gradishar, W.J., Wood, W.C. (eds): *Advances in Breast Cancer Management, Second Edition*. 2008. ISBN 978-0-387-73160-5

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Advances in Breast Cancer Management, Second Edition

ISBN-13: 978-0-387-73160-5 e-ISBN-13: 978-0-387-73161-2

Library of Congress Control Number: 2007931730

Printed on acid-free paper.

9 8 7 6 5 4 3 2 1

springer.com

PREFACE

During the last five years significant advances have been made in our understanding of the biology of breast cancer. As a result of linking observations made in the laboratory to new treatment strategies, the outcome of breast cancer patients with both early and late stage disease has continued to improve.

Advances in Breast Cancer Management, Second Edition will highlight many of the important advances that have improved our understanding of the biology and therapeutics of breast cancer.

The initial discussion by Dr. Pasche will focus on the evolving understanding of the genetics of breast cancer. In addition to the well known genetic mutations BRCA1 and BRCA2, other mutations have recently been identified. Strategies for surveillance of high-risk populations and prevention strategies under evaluation are highlighted. The underlying molecular pathways that control malignant cell growth are being better characterized through laboratory investigation and as a result, numerous novel therapeutics that target these pathways are already in the clinic. Drs. Doyle and Miller will discuss the rationale for development of some of the agents farthest along in clinical development.

Though novel therapeutic agents or "targeted therapy" hold significant promise, standard treatment modalities including chemotherapy, endocrine therapy, surgery and radiation therapy will remain important for management of breast cancer patients. The decision to offer patients with early stage breast cancer systemic adjuvant therapy has been made based largely on clinical parameters including tumor size and nodal status. Clinicians have long recognized that this method of evaluating risk of recurrence for an individual patient is imprecise. Much research over the last several years has focused on developing molecular profiles of individual tumors that correlate with long-term outcome. Drs. Dinh, Cardoso, Sotiriou

and Piccart-Gebhart will discuss the development of this strategy and the results from the first commercially available assays.

During the last five years, the aromatase inhibitors have been investigated extensively as an alternative to tamoxifen or as a class of agents contributing to the effects of tamoxifen in postmenopausal woman with hormone receptor positive breast cancer. A review of the data from pivotal trials will be put in context by Drs. Zalnak and O'Regan. Similarly, adjuvant chemotherapy has been refined in recent years to include taxanes and trastuzamab in select patients. Dr. Ravdin will highlight the findings from the most recent (2005) Oxford Overview of randomized clinical trials involving chemotherapy and tamoxifen. Drs. McArthur and Hudis will provide a critical analysis as to how recent data related to the incorporation of taxanes and trastuzamab in adjuvant therapy programs refines clinical decision-making.

Local therapy in the form of radiation and surgery are critical components in the management of breast cancer patients. As systemic therapy is more frequently administered in the preoperative setting, implications for breast conservation and management of the axilla are critical. Dr. Newman will review the recent data that is relevant to this topic. Drs. Hazard and Hanson will place in context the role of sentinal lymph node biopsy and the controversies that remain regarding its use in various situations. Dr. Recht will review the emerging data related to new techniques of breast irradiation and how these potentially more "patient friendly" approaches compare to standard breast irradiation. Finally Drs. Reeder and Vogel will provide an overview of data from the most recent chemoprevention trials in women at elevated risk of developing breast cancer and will consider the ongoing research to identify those individuals most likely to benefit from prevention strategies.

CONTENTS

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1. RECENT ADVANCES IN BREAST CANCER GENETICS

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INTRODUCTION

Breast cancer is the second most common cancer among women and the second leading cause of cancer death in the US. In 2006, more than 214,000 new breast cancer cases were diagnosed. It is estimated that close to 50,000 women died of the same disease in 2006.[13] Breast cancer develops in about 12% of women who live to age 90. A positive family history is reported by 15–20% of women with breast cancer. Studies of twins suggest that heritable factors accounts for 25 to 30% of all breast cancers.[20] However, less than 7% of all breast cancers are associated with known inherited high penetrance gene mutations. The first two major susceptibility genes for breast cancer, *BRCA1* and *BRCA2*, were identified in 1994 and 1995, respectively.[23,39] Other tumor susceptibility genes such as *TP53* are known to increase breast cancer risk to an even greater level than *BRCA1* and *BRCA2*. Nonetheless, deleterious mutations of *TP53* are rare and therefore accounts for a much smaller proportion of breast cancer cases.[19] We will review recent developments in the search for additional breast cancer susceptibility genes, recommendations for genetic counseling referral as well as follow-up of *BRCA*- gene mutation carriers.

HIGH PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES

Functional Role of *BRCA1* and *BRCA2* Genes

Mutations and genomic rearrangements within the *BRCA1* and *BRCA2* genes have been clearly associated with breast cancer. These two genes are the best known of a small group of genes that have been associated with the disease (Table 1).

Table 1. Breast cancer susceptibility genes

Gene	Associated syndrome	Gene location	Gene frequency	Penetrance
BRCA1	Hereditary breast and ovarian cancer	17q21	Rare	Very high
BRCA2	Hereditary breast and ovarian cancer	13q12.3	Rare	High
TP53	Li-Fraumeni	17p13.1	Very rare	Very high
PTEN	Cowden	10q23.3	Very rare	High
ATM	Ataxia-telangiectasia	11q22-q23	Common	Low to moderate
STK11	Peutz-Jeghers	19p13.3	Very rare	High
*TGFBR1*6A*	None to date	9q22	Very common	Low to moderate
TGFB1 L10P	None to date	19q13.1	Very common	Low
*CHEK2*1100delC*	None to date	22q12.1	Rare	Moderate
CASP8 D302H	None to date	2q33-q34	Common	Low

The exact function of the *BRCA1* and *BRCA2* genes is still unknown, more than a decade following their discovery. Mice that lack one copy of either the *Brca1* or the *Brca2* genes do not exhibit any strong tumor predisposition and mice that lack two copies of the *Brca1* gene die in utero.[9] These traits have limited in vivo analysis of these genes. The BRCA1 protein may not have one specific function, but its interaction with a variety of other proteins is essential for regulating DNA repair, transcription, and cell cycle progression.[8] Some functional clues have emerged from in vitro studies of the *BRCA2* gene. After double strand DNA breaks, BRCA2 induces the translocation of the protein RAD51 into the nucleus and directs RAD51 to the site of the breaks for homologous recombination-directed repair.[40]

Since deleterious mutations alter their function, *BRCA* genes appear to serve as tumor suppressor genes. The inherited mutation represents the first "hit" of Knudson's two-hit model of tumorigenesis. *BRCA*-gene mutations interfere with the DNA repair function of the normal gene, thus resulting in the accumulation of chromosomal abnormalities, and an increased susceptibility to develop malignancy. If the second allele of the gene becomes mutated, this leads to the development of cancer.

Clinical Significance of BRCA1 and BRCA2 Genes

These two genes are believed to account for the largest proportion of familial breast cancer cases. Current estimates suggest that 20–25% of familial breast cancer cases are caused by mutations or genomic rearrangements within these genes. Nevertheless, the frequency of these mutations is relatively rare, occurring in approximately 0.1–0.5% of the general population. This means that the population attributable risk of *BRCA1* and *BRCA2* ranges from a minimum of 3% to a maximum of 7%. Deleterious mutations among individuals of Ashkenazi Jewish descent are 10-fold more common than in the general population. Approximately 2% of

Ashkenazi Jews carry a deleterious *BRCA1* or *BRCA2* mutation.[35] Therefore, the breast cancer population attributable risk of *BRCA1* and *BRCA2* deleterious mutations among Ashkenazi Jews is probably as high as 15–30%.[1,10,24,37] Several studies have shown that 90% of deleterious mutation within the *BRCA1* or *BRCA2* genes among of Ashkenazi Jews are one of the following three mutations: *BRCA1* 185deAG, *BRCA1* 5382insC, or *BRCA2* 6174delT. It is therefore recommended to proceed with genetic testing of the three common Ashkenazi mutations among all Ashkenazi Jewish women who develop breast cancer. Additional sequencing of the remainder of the *BRCA* genes should be conducted whenever other features evocative of the hereditary breast and ovarian cancer syndrome are present.

A recent analysis of 22 studies involving 8,139 index case patients unselected for family history shows that carrying a deleterious *BRCA1* or *BRCA2* mutation confers an estimated lifetime risk for developing breast cancer of 65% (95% CI = 44–78%) and 45% (95% CI = 31–56%), respectively (Antoniou et al., 2003). Importantly, breast cancer risk does not appear to be increased before adulthood. By the age of 40, carrying a deleterious *BRCA1* mutation confers a 20% chance of developing breast cancer, and the risk increases with age, with the maximum lifetime risk being 82% by age 80.[17] Mutations in *BRCA1* are strongly associated with ovarian and fallopian tube cancer.[2] The risk for ovarian cancer for *BRCA1* mutation carriers is 17% by age 40. It increases to 39% by age 70 and 54% by age 80.[2] The risks are smaller for *BRCA2* mutation carriers. Hence, current data suggest that *BRCA1* penetrance with respect to both breast and ovarian/fallopian tube cancer is higher than that of *BRCA2*.

Identification of Additional *BRCA1* and *BRCA2* Mutation Carriers

Mutations constitute only one possible mechanism of gene inactivation. Genomic rearrangements and epigenetic modifications such as promoter methylation are additional mechanisms that may lead to gene inactivation. Genomic rearrangements within the *BRCA1* and *BRCA2* genes had not been thoroughly assessed until recently. In a recent study of women with a diagnosis of invasive breast cancer at any age, a strong family history of breast cancer (defined as a family with a minimum of 4 cases of female or male breast cancer, and/or ovarian cancer), and who had no evidence of mutations within the *BRCA1* and *BRCA2* as assessed by sequencing of the full coding region of each gene, 35 of the 300 probands (11.6%) carried genomic rearrangements within these genes. These mutations were more frequent among individuals under 40 years old.[36] The same study showed that five percent of the families had a mutation in *CHEK2* and 1% had a mutation in *TP53*.

These provocative results suggest that genomic rearrangements within the *BRCA1* and *BRCA2* genes should be assessed in young probands with a strong family history of breast cancer, especially if the family history also includes male breast cancer and/or ovarian cancer. It is our hope that commercial testing options will expand in the near future so that genomic rearrangement analysis of the BRCA1 and BRCA2 genes and testing for *CHEK2* and *TP53* become

more widely available. Another exciting development in the field comes from the discovery that a single nucleotide polymorphism (SNP) within the MDM2 gene promoter (SNP 309) accelerates the age of onset of Li-Fraumeni associated cancers, including breast cancers.[5] Additional studies are needed to define the true clinical significance of these findings for women with breast cancer.

Current Recommendations for Genetic Counseling and Genetic Testing Referral for Breast Cancer

Identification of candidates for genetic counseling and genetic testing remains a central priority as only a small fraction of the estimated carriers has been identified to date. Individuals fulfilling one or more of the following criteria should be referred to a cancer genetics professional for evaluation: 1) invasive breast cancer or ductal carcinoma in situ diagnosed by age 50 or younger, 2) two primary breast cancers or breast cancer and ovarian cancer in a single individual, 3) two primary breast cancers or breast cancer and ovarian cancer in any close relative from the same side of the family (paternal or maternal), 4) clustering of breast cancer with male breast cancer, thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, dermatologic manifestations or leukemia/lymphoma on the same side of the family, 5) member of a family with a known mutation in a breast cancer susceptibility gene, 6) breast or ovarian cancer at any age in patient of Ashkenazi Jewish descent, 7) member of a family with a known mutation in a breast cancer susceptibility gene, 8) any male breast cancer, 9) one or more cases of ovarian cases on the same side of the family. These broad inclusions criteria represent the consensus reached by the members of the National Comprehensive Cancer Network Genetic/Familial Breast and Ovarian Cancer High-Risk Assessment Panel (Table 2).[7] These criteria include clinical features of the rare Li-Fraumeni and Cowden syndromes in addition to the better known hereditary breast and ovarian cancer syndrome.

Table 2. Inclusion criteria for breast and/or ovarian genetic assessment

The presence of one or more of the following criteria warrants referral to a cancer genetics professional:
- Breast cancer onset before the age of 50
- Two breast cancer primaries or breast and ovarian cancer in a single individual
- Two breast cancer primaries or breast and ovarian cancers in close relatives from the same side of family (maternal or paternal)
- Clustering of breast cancer with male breast cancer, thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, dermatologic manifestations, or leukemia/ lymphoma on the same side of the family.
- Member of the family with a known dictation in a breast cancer susceptibility gene such as *BRCA1, BRCA2, TP53, PTEN*
- Women of Ashkenazi Jewish descent with breast or ovarian cancer at any age
- Any male breast cancer
- One or more ovarian cancer on the same side of family.

Furthermore, there are several tools to estimate an individual woman's breast cancer risk, and the risk that she carries a deleterious mutation within the *BRCA1* or *BRCA2* genes. BRCAPRO is one of the most commonly used software that incorporates several predictive models for inherited or familial breast cancer: the Claus model,[6] the Couch model,[38] the Shattuck-Eidens model,[34] the Frank model,[11,22] and a new Bayesian probability model. This software was developed by investigators at the University of Texas Southwestern Medical Center at Dallas and Duke University and is available free of charge at http://www3.utsouthwestern.edu/cancergene. This program is particularly useful to calculate a woman's risk of developing breast and/or ovarian cancer and the probability of carrying a mutation within the *BRCA1* or *BRCA2* genes. It has been validated in several studies and appears to predict breast cancer risk equally well in Caucasian and African American women.[4,22]

It is important to remember that the autosomal dominant pattern of transmission of the *BRCA1* and *BRCA2* genes means that these genes are transmitted equally well by fathers and mothers. A small family size or transmission through males may mask recognition of the hereditary breast and ovarian cancer syndrome. Hence, in small families or whenever there is a predominance of males in the family, less stringent criteria may be used for referral.

Role of Low Penetrance Breast Cancer Susceptibility Genes

There is growing genetic evidence that high penetrance germline mutations in genes such as *BRCA1* and *BRCA2* account for a small proportion of familial risk of breast cancer, and much of the remaining variation in genetic risk is likely to be caused by combinations of more common, lower penetrance variants.[29]

We were the first to identify *TGFBR1**6A, a common variant of the *TGFBR1* gene. This variant has a deletion of three GCG triplets coding for alanine within a nine alanine (9A) repeat sequence of *TGFBR1* exon 1, which results in a six alanine repeat (6A) sequence.[27] We have shown that in normal epithelial cells TGFBR1*6A transmits TGF-β growth inhibitory signals less effectively than TGFBR1 and is able to switch growth inhibitory signals into growth stimulatory signals in breast cancer cells.[26,28] Epidemiologically, the *TGFBR1**6A allele is a candidate tumor susceptibility allele that has been associated with an increased incidence of several types of cancer.[3,15] A recent meta-analysis of 17 case-control studies that included 6,968 patients with a diagnosis of cancer and 6,145 healthy controls showed that *TGFBR1**6A carriers have a significantly increased risk of breast, colon, ovarian, and prostate cancer as compared with noncarriers.[41] Overall, breast cancer risk is more than twofold higher among *TGFBR1**6A homozygotes (O.R. 2.69, 95% CI 1.54-4.68) than among *TGFBR1**6A heterozygotes (O.R. 1.23, 95% CI 1.06-1.43), which is indicative of a strong allelic dosing effect. More than one in seven healthy individuals and one in six patients with cancer is a *TGFBR1**6A carrier. This establishes *TGFBR1**6A as one of the most common and potentially clinically relevant high-frequency, low-penetrance candidate breast cancer susceptibility

allele. The lifelong breast cancer risk incurred by *TGFBR1*6A homozygotes is ~35% compared to 13% for noncarriers; *TGFBR1*6A population attributable risk (PAR) for breast cancer is 4.9 % (2.7–7.2%). This is almost identical to the PAR for *BRCA1* and *BRCA2* combined (3–7%).

In contrast, increased TGF-β circulating levels have been associated with a decreased propensity to develop mammary tumors in animal models.[31] Similarly, increased TGF-β signaling has been shown to prevent the development of mammary tumors in animal models. A common variant within the human TGF-β1 (*TGFB1*) gene is represented by the substitutions of Leucine to Proline (T → C) at the 10th amino acid position (T29C). Studies have shown that the T → C substitution results in higher extracellular TGFB1 secretion and higher TGFB1 circulating levels have been observed in humans that carry this allele. We were the first to propose that various combinations of two naturally-occurring and functionally relevant polymorphisms of the TGF-β signaling pathway may predict breast cancer risk. This proof of concept shows that women with high constitutive TGF-β signaling have a 70% lower risk of breast cancer than women with low TGF-β signaling.[14] This suggests that functional interactions within the TGF-β signaling pathway may act as significant modifiers of breast cancer risk and make contributions to a large portion of a yet unidentified fraction of familial and sporadic breast cancers.

Surveillance of *BRCA*-Mutation Positive Women

Women in their fourth and fifth decade of life who carry deleterious mutations within the *BRCA1* gene have approximately a 30-fold higher risk of breast cancer than women without mutations. For *BRCA2* mutation carriers there is a 10- to 16-fold higher risk.[2] This has led a fraction of female carriers to elect prophylactic mastectomy, a procedure that has been shown to reduce breast cancer risk by 90% or more.[12,21,32] However, many women cannot accept the psychological and physical trauma associated with this procedure and a recent study suggests that less than 15% of *BRCA*-mutation carriers undergo prophylactic bilateral mastectomy to reduce breast cancer risk.[30] Additional interventions that reduce breast cancer risk among carriers of deleterious mutation within the *BRCA1* and *BRCA2* genes are therefore sorely needed. Both prophylactic salpingo-oophorectomy and tamoxifen have been investigated as breast cancer risk reducing strategies in *BRCA*-mutation carriers. While adjuvant therapy with tamoxifen seems to reduce contralateral breast cancer risk in affected *BRCA*-mutation carriers,[22,25] its effectiveness as primary prevention in unaffected women has not been investigated. Two separate groups have shown that prophylactic salpingo-oophorectomy significantly reduce breast cancer risk among premenopausal women with mutations within the *BRCA1* and *BRCA2* genes.[16,33] However, despite the use of these breast cancer risk reduction strategies, breast cancer risk remains a major source of concern for female *BRCA*-mutation carriers who opt against prophylactic mastectomy. Two recent studies of *BRCA*-mutation carriers have highlighted the crucial role of breast MRI as an effective breast cancer screening method. In a study by Kriege et al.[18] performed

in the Netherlands, 1909 women at a 15% or more lifetime breast cancer risk (including 358 *BRCA*-mutation carriers) were screened annually with concurrent mammography and MRI. Of the 45 cancers diagnosed in this cohort, 22 (49%) were identify by MRI alone, with an overall sensitivity of 71% for MRI versus 40% for mammography.[18] In a study by Warner et al performed in Canada, 236 *BRCA*-mutation positive women underwent annual multimodality screening with clinical breast exam, mammography, screening ultrasound, and breast MRI, all performed on the same day. An interval clinical breast exam was performed 6 months later. On the 22 cancers diagnosed, 77% were detected by MRI, and 30% were identified by MRI alone. MRI identified a greater proportion of breast cancers than either mammography (36%) or ultrasound (33%). In these two studies, receiving operating characteristic curves, which reflect both sensitivity and specificity, confirm a greater diagnostic accuracy for MRI as compared with mammography. Consequently, annual mammogram and breast MRI screening are currently recommended starting at age 25 for all female carriers of a deleterious *BRCA* gene mutation.[7]

CONCLUSIONS

More than a decade following the discovery of the first high penetrance breast cancer susceptibility genes identification of additional *BRCA*-gene mutation carriers remains a major priority. Broad inclusion criteria as well as analysis of genomic rearrangements are likely to facilitate this goal. Low penetrance breast cancer susceptibility genes are emerging as significant contributors to breast cancer risk. Inclusion of these genes into genetic counseling and genetic testing is currently being studied. Future strategies aimed at identifying women at high risk of breast cancer are likely to include a combination of high, moderate and low penetrance breast cancer susceptibility genes.

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2. SENTINEL LYMPHADENECTOMY IN BREAST CANCER

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INTRODUCTION

An estimated 178,480 people in the United States will be diagnosed with and 40,460 will die from breast cancer in 2007.[1] With the institution of screening mammography guidelines between 1980 and 1987, there was a doubling in the incidence of small breast cancers (≤ 2 cm) with a concomitant decrease by 27% in the incidence of larger breast cancers (≥ 3 cm)[2]. As a greater percentage of breast cancers are being diagnosed at an earlier stage, the medical community has been challenged to develop diagnostic and treatment modalities that maximize benefit from therapy while reducing the morbidity associated with treatment. The management of breast cancer has changed dramatically in the last two decades with improvements in systemic therapy and advances in surgical techniques.

The single greatest predictor of overall survival for women diagnosed with operable breast cancer is the presence or absence of lymph node metastasis. Traditionally, axillary staging was performed with Level I and II axillary lymph node dissection (ALND). This identified women with poorer prognosis and greater risk of recurrence while helping direct their adjuvant therapy. Unfortunately, ALND for axillary staging in breast cancer carries a relatively high risk of secondary lymphedema as well as other morbidities such as parethesias and limited arm mobility. The concept of the sentinel lymph node (SLN) is based on the knowledge that there is an orderly progression of lymph drainage from the tumor via the lymphatic system to the dominant lymph basin of the affected area. Sentinel lymph node biopsy (SLNB) was established by Morton et al and was found to be an accurate technique in identifying nodal metastasis in malignant melanoma. The authors were able to

avoid the associated morbidities of complete lymphadenectomy for early stage extremity melanoma[3]. In breast cancer, tumor cells shed from the primary breast lesion progress along the lymphatic channels to the first draining lymph nodes in the axilla. By mapping the lymphatic drainage of the breast, the sentinel node can be identified, removed and evaluated for evidence of metastatic disease. As the number of tumors detected by imaging modalities alone increases, patients are being diagnosed with early stage breast cancer and therefore have a lower probability of axillary metastasis. The development of a less invasive method to evaluate the axilla and thereby reduce the risk of the morbidities associated with ALND was a logical next step in the treatment of breast cancer.

The use of SLNB in breast cancer was first published by Krag et al in a small pilot study in 1993. Twenty-two women underwent lymphatic mapping with intraparenchymal injection radionucleotide labeled sulfur colloid and the sentinel node was localized in 18 patients (82%). Seven patients were found to have axillary disease and in three (43%) the SLN was the only node involved[4]. This study was quickly followed by the work of Giuliano et al in a much larger trial. Unlike Krag, Giuliano's group used isosulfan blue dye injected into the parenchyma surrounding the breast mass and, after messaging the breast for 5 minutes to stimulate lymphatic uptake, blue lymphatic channels were traced to the sentinel node(s). In the first published group of 174 patients with predominantly T1-2 tumors, 114 sentinel nodes were successfully identified resulting in an identification rate (IR) of 65.5%. All the SLNB were followed by completion ALND and 5 false negative SLN were noted. The result was a false negative rate of 4.3% and an overall accuracy rate of 95.6%. In addition, the authors noted an increase in success rate with increase in experience. The initial IR was 58.6% but as more procedures were performed the IR increased to 72.4%[5]. An update from the same group at the John Wayne Cancer Institute of 107 patients was published several years later. In this study, the IR was 93.5%, no false negatives biopsies were observed and the SLN was 100% predictive of the axillary status. Of the 42 women with node positive disease, the sentinel node represented the only involved lymph node in 28 (67%) patients. Based on the strength of these results, the authors proposed eliminating ALND in patients with negative SLN and early stage breast cancer[6].

Observing the success of sentinel node mapping with radionucleotide (Krag) and isosulfan blue (Giuliano) independently, Albertini and colleagues reported the results of 62 patients undergoing lymphatic mapping using both modalities. Peritumoral injections of blue dye and radiocolloid identified the sentinel node in patients presenting with clinically negative axilla. All patients had follow up ALND. No false negative SLN were observed in the 57 successfully identified SLN (IR 92%). They observed 12 patients did not have blue dye uptake in the sentinel node leading the authors to conclude the addition of radiocolloid increased the success rate from 73% to 92%. Much like the results of Giuliano, metastasis were identified in 18 (32%) patients and the sentinel node was the only involved node in 12 (67%) of patients[7]. Two other early studies by Veronesi and O'Hea reported similar, encouraging results. O'Hea et al reported a 93% success rate in 59 patients under-

going lymphatic mapping with peritumoral injection of blue dye and radiocolloid. They noted 3 false negatives, an overall accuracy of 95% but noted the procedure appeared to be more accurate for smaller tumors. Nodal disease was identified in 28% of the patients and in 41%, this was the only involved lymph node[8]. Veronesi et al reported a 98% success rate using subdermal injection of radiocolloid in 163 patients with T1-3 primary breast tumors. There were 4 false negative cases and lymphatic metastases were confined to the SLN in 39.5% of the patients. The authors concluded the concept of the sentinel lymph node was biologically correct and supported the use of SLNB in staging the axilla in patients diagnosed with operable breast cancer[9].

These single institutional cohort studies were followed by four multicenter validation trials. The first, by Krag et al, reported the results of 443 patients who underwent lymphatic mapping with peritumoral radiocolloid SLNB and subsequent ALND. The participating surgeons were trained by surgeons at the pilot institution experienced in SLNB. The overall identification rate was 93%. The overall false negative rate was 11% but ranged between 0% and 28.6% depending on the surgeon. The procedure was 97% accurate in predicting the axillary status, the negative predictive value was 96%, the specificity was 100% and the sensitivity was 89%. Interestingly, the authors noted that all the false negative occurrences were in patients with tumors in the lateral aspect of the breast. They concluded SLNB could accurately predict the axillary nodal status but there was considerable patient variability and surgeon variability that must be taken into account[10]. The second multi-institution study was somewhat different in that it looked at the success rates for surgeons as they were learning the procedure. McMasters et al reports the results of 806 SLNB done by 99 surgeons of whom 83 had not performed more than 10 SLNB prior to participation in the study. Recommendations were given regarding blue dye and radionucleotide lymphatic mapping but the decision on how to perform the lymphatic mapping was at the discretion of the operating surgeon. All SLNB were followed by ALND. The overall success rate and false negative rate for the single-agent technique was 86% and 11.8%, respectively. When two-agents were employed, the IR was 90%. In addition, the dual-agent false negative rate was 5.8%, a difference that was statistically significant. In regard to patient characteristics, the authors noted women > 50y had lower identification rates and lesions in the upper outer quadrant had higher false negative rates. Interestingly, a statistically significant difference in IR and false negative rate was not observed between surgeons who performed < 10 SLNB or ≥ 10 SLNB prior to participation in the study. This may be due to the fact that only 16 of the 99 surgeons composed the later group. McMasters et al demonstrated the SLNB procedure could be performed accurately with low false negative rates in a variety of clinical settings provided radionucleotide and blue dye were used for localization. Therefore, SLNB was deemed a reasonable alternative to ALND in clinically node negative patients[11]. The third study, the Department of Defense Breast Lymphatic Mapping Trial, reported the results of SLNB from 41 academic and community hospitals. An overall 86% identification

rate was noted but an IR of 92% was observed in the university-based practices and the IR was 85% in the community hospitals. The overall false negative rate was 4% and the overall accuracy of the SLNB predicting the axillary status was 99%[12]. Finally, Tafra et al published the results of another multi-institutional study in which both academic and private practice surgeons performed SLNB on 529 patients. The overall success rate was 87%, the false negative rate was 13% and the SLNB accurately predicted the axilla in 96% of the patients[13].

To date, there are only two completed and published randomized controlled trials that compared SLNB and ALND. Veronesi and colleagues, with the approval of the European Institute of Oncology and the support from the Italian Association for Cancer Research, randomized 516 patients with primary breast cancer ≥ 2 cm to undergo either SLNB followed by ALND (ALND group) or SLNB with ALND reserved for patients with positive SLN (SLNB group). Two hundred fifty-seven women were randomized to the ALND group and 259 patients were randomized to the SLNB group. Patient demographics and tumor characteristics were similar between the two groups. The accuracy of the procedure was 96.9%, the sensitivity was 91.2%, the specificity was 100%, the negative predictive value was 95.4% and the false negative rate was 8.8% as determined from the ALND group. Metastasis were found in 83 patients (32%) in the ALND group of which 29 were micrometastasis and in 24 of 29 (83%) patients, the SLN was the only node involved. In the SLNB group, lymph node metastasis were identified in 92 patients (35%) of which 31 where micrometastatic and in 26 of 31 (84%), the SLN was the only involved node. At a median follow up of 46 months, there were 25 breast cancer related events, 15 in the ALND group and 10 in the SLNB group. Assuming a similar 8.8% false negative rate for the SLNB group as was witnessed in the ALND group, the authors estimated 8 patients of the 167 negative SLN had the potential to harbor occult metastatic disease. However, none of the breast cancer related events observed were axillary metastasis. Thus, the authors concluded patients with negative SLN did not require ALND as part of the local management of their disease[14].

The ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) trial is a multi-institution, randomized trial involving 13 breast cancer treatment facilities in the United Kingdom. The trial was composed of two phases, the validation phase in which participating surgeons were required to perform 40 SLNB followed by axillary clearance or axillary sampling (a minimum of four axillary nodes are palpated and removed to stage the axilla) and achieve an IR of 90% or greater with no more than 2 false negative results. Clarke et al published, on behalf of the trial, the learning curves of 13 participating surgeons. The overall IR was better when both blue dye and radiocolloid were used to localize the SLN (96.5% versus 76.8% with blue dye alone versus 83.7% with radiocolloid alone). No significant learning curve was observed although 2 of the 19 failed localizations and 2 of the 10 false negative SLN were the first submissions of the participating surgeons. The authors concluded the learning curve was very short when the standardized training program was completed[15]. In the second phase of the study,

1031 patients were randomized to undergo SLNB followed by standard axillary treatment (axillary clearance or sampling at the surgeons discretion) or SLNB with axillary clearance performed when the SLNB was positive or for radiation therapy to the axilla in lieu of axillary clearance. The study was terminated early because of a significant difference in morbidity was documented between the two procedures and the difficulty in patient accrual that resulted. Of the 515 patients assigned to the SLNB group, 121 had positive SLN with 83 undergoing subsequent axillary clearance and 33 receiving radiation therapy. In the standard axillary treatment arm, 373 had axillary clearance and 123 had axillary sampling. Patients who underwent SLNB reported a better quality of life, less arm swelling and less sensory impairment in comparison to those undergoing standard axillary treatment. At 12 months after surgery, there were 3 axillary recurrences in the standard axillary treatment arm and 1 in the SLNB arm. At the time of publication, there was insufficient follow-up time to make to make definitive observations regarding axillary recurrence and its impact on overall survival[16].

Sentinel lymph node biopsy is a new procedure, relatively speaking. Long term follow up for axillary recurrence will be the ultimate measurement of its success. The identification rates and false negative rates demonstrated in the single institution and the multi-center trials led to the use of the SLNB without ALND when pathologic evaluation of the sentinel node did not reveal evidence of metastatic disease. Table 1 below lists the published studies of patients who have had negative SLNB without subsequent ALND. The median follow up period for each of these studies ranges from 14 months to slightly more than 4 years. To date, the rate of axillary recurrence

Table 1. Published studies on axillary recurrence after sentinel lymph node biopsy without follow-up axillary lymph node dissection

First author	Year of publication	Number of patients	Median follow-up (Months)	Number of axillary recurrences
Giuliano[20]	2000	67	39	0
Veronesi[21]	2001	285	14	0
Roumen[22]	2001	100	24	1
Schrenk[23]	2001	83	22	0
Chung[24]	2002	206	26	3
Reitsamer[25]	2002	116	22	0
Blanchard[26]	2003	685	29	1
Naik[27]	2004	2,340	31	10
Jeruss[17]	2005	592	28	1
Subset node positive without ALND		*73*	*27*	*0*
Smidt[28]	2005	439	26	2
Veronesi[29]	2005	953	38	3
			Mean Follow-Up (Months)	
Guenther[18]	2003	46	32	0
Fant[19]	2003	31	30	0

is lower than anticipated given the average false negative rate of 5-6%. Special note should be given to three studies in which the SLNB showed evidence of disease but follow up ALND was not performed at the patient's request. After a mean follow-up time of 27.6 months, Jeruss et al report no axillary recurrences in a subset of 73 patients with mean tumor size of 1.9 cm and median nodal metastasis size of 1 mm[17]. Similarly, at a mean follow up time of 32 months, Guenther et al reported no local axillary recurrences in 46 patients with positive SLNB. Fifty percent of the patients had IHC detected cellular metastases and only 15% of the patients had macrometastatic disease[18]. Finally, Fant et al reported 1 distant failure but no local failures in 31 patients at a mean follow-up period of 30 months[19].

The medical community anxiously awaits the final results of the NSABP B-32 trial and ACOSOG Z0010 trials to determine if sentinel lymph node biopsy does indeed impart long-term equivalent local control when compared to standard axillary lymph dissection. The NSABP B-32 is a phase III clinical trial comparing sentinel node resection to ALND in clinically node negative patients. The primary aim is to determine if SLNB is equivalent to ALND with regard to long-term regional control, overall survival and disease free survival. Additionally, investigators intend to compare morbidity between SLNB alone versus SLNB followed by ALND. In ACOSOG Z0010, the study design is to determine the prevalence and significance of micrometastatic lymph node disease detected by IHC alone in patients presenting with T1-2 tumors and clinically negative axillas. The investigators also intend to determine the hazard rate of regional recurrence in patients with negative SLN by H&E staining alone. These two trials will augment our understanding not only of the role of SLNB plays in staging women presenting with clinically negative axilla but also our understanding of the prognostic significance of IHC only detected micrometastatic lymph node disease in this patient population.

Large Primary Tumors and Sentinel Lymph Node Biopsy

In an era where SLNB is the preferred method of axillary evaluation and staging, it is important to be cognizant of the patient population in which the first sentinel lymph node studies were performed. The original validation studies included small, predominantly T1 lesions. While SLNB is used ubiquitously for women presenting with larger lesions and clinically negative axilla, there are only two reports in the literature that specifically address the validity of SLNB in this patient population. In a dual institution, prospective study of T2 and T3 lesions, Bedrosian et al reported the results of 103 women with 104 tumors. The elected treatment of the breast primary was lumpectomy in 54% of the patients and the majority of the patients (84%) had a completion ALND after SLNB. Pathologic evaluation of the sentinel nodes varied slightly between institutions but in essence, each node was evaluated via hematoxylin and eosin staining (H&E) and immunohistochemistry (IHC) staining either alone or in combination. Non-sentinel nodes were evaluated with H&E staining alone. Axillary lymph nodes contained metastatic disease in 59% of the cases. This was dependent on the size of the primary lesion, 85% of

tumors great than 5 cm had axillary involvement while only 54% of patients with tumors 2-2.9 cm had axillary involvement. Of the 60 patients with positive SLN and completion ALND dissection, 2 metastasis identified in the non-SLN resulted in a false negative rate of 2%. Additionally, the authors reported a 37.5% incidence of disease in the non-sentinel node when the SLN had a micrometastatic focus as compared to a 95.5% incidence when macrometastatic disease was identified in the SLN. They concluded SLNB is technically feasible with a similar accuracy profile as smaller lesions and advocated its use in women presenting with large primary tumors and clinically negative axilla[30].

In another smaller study, Chung et al looked at role of SLNB when the primary breast tumor was greater than 5 cm in size at presentation. In this study of 41 women, 2 of whom had neoadjuvant chemotherapy, 85% of the tumors ranged in size > 5 cm. Each patient received peritumoral injection of isosulfan blue as their only means of SLN identification. Once the SLN was identified, all patients underwent completion level I and II ALND. Initial pathologic evaluation of each SLN was by H&E and, if no tumor was identified, the node was further assessed with IHC. The authors report 100% IR and axillary disease was identified in 31 of 41 patients (76%). Of those patients with micrometastatic disease in the SLN, none had further axillary disease in the non-sentinel lymph nodes. SLN was positive in 30 of 31 patients with axillary lymphatic disease resulting in a false negative rate of 3% an accuracy rate of 98%. Chung et al also conclude SLNB is accurate and feasible in women with large primary breast lesions and clinically negative axilla. Interestingly, 24% of the women in the Chung et al study and 40-50% of the women in the Bedrosian et al study did not have pathologic evidence of axillary disease thereby indicating a negative SLNB could avoid ALND and its associated co-morbidities in a significant number of women[31].

Interestingly, a recent study of concerning neoadjuvant chemotherapy and the timing of SLNB, Cox et al reported the results of a subset of 47 women with locally advanced breast cancer (primary tumor ≥ 4.5 cm) undergoing SLNB prior to initiating chemotherapy. The investigators were able to map the SLN in 46 of 47 patients either by gamma probe identification or visualization of blue lymph node(s) in the axilla resulting in a 98% IR. However, because completion axillary lymph node dissection was not performed until after neoadjuvant chemotherapy, a false negative rate can not be calculated[32].

Despite the data from these studies, The American Society of Clinical Oncology (ASCO) Expert Panel concluded there is insufficient evidence on the accuracy of SLNB in women with T4, non-inflammatory tumors and therefore does not recommend the use of SLNB for axillary staging in women presenting with clinically negative axilla and large (>5 cm) primary breast tumors[33].

Multifocal and Multicentric Breast Cancer and Sentinel Lymph Node Biopsy

Though various definitions exist, traditionally multicentric breast cancer is defined as documented disease present in two different quadrants in the same breast while

multifocality refers to more than one lesion within the same quadrant of the breast. Early validation studies of sentinel lymph node biopsy did not include patients with multicentric or multifocal disease because of a concern that more than one dominant lymphatic channel existed for each lesion which would increase the false negative SLN biopsy results. This theory was supported in the findings of Veronesi et al in a study of 160 patients in whom SLN biopsy accurately predicted the axillary lymph node status in 156 patients (97.5%). In 2 of the 4 cases where the SLNs were disease free but micrometastatic disease was found in non-sentinel lymph nodes, the primary breast disease was multicentric. This led the authors to conclude the risk of false negative SLNB could be further reduced by excluding women with multicentric disease from undergoing SLN biopsy[9].

However, several subsequent publications emerged suggesting a consistent lymphatic drainage of the entire breast irrespective of tumor location. These reports implied the sentinel node represents the first draining lymph node of the entire breast and is not necessarily specific to a primary breast tumor. Klimberg et al published the results of 68 SLNB in which peritumoral injection of blue dye was compared to subareolar injection of radionucleotide. The authors report an identification rate of 89.9% with blue dye alone and 94.2% when additional nodes were identified with the gamma probe. They noted all blue nodes were radioactive and concluded subareolar injection was as accurate as peritumoral injection and had the potential to enable SLN biopsy to be used in multicentric breast cancer[34]. Additional publications such as that by Tuttle et al further supported the findings of Klimberg et al. The authors reported the results of 158 SLN biopsies and found the subareolar injection of radionucleotide drained to the same sentinel nodes as the peritumoral injection of blue dye[35]. These findings spurred interest in the use of SLN biopsy in multifocal and multicentric disease. Schrenk and colleagues first reported the results of 19 women with multicentric disease who underwent SLN biopsy with injection of blue dye and/or radionucleotide material in the subareolar location followed by complete axillary dissection. They identified a mean of 1.7 sentinel nodes and no false negative results[36]. In a study of 122 women of which 21 had multicentric disease, Ozmen and colleagues injected blue dye into the parenchyma surrounding the tumor or into the wall of the evacuated lumpectomy. They reported and overall SLN identification rate of 91% and a false negative rate of 11.3%[37]. In a retrospective study of 59 women with palpable and non-palpable multicentric or multifocal disease who received intradermal injection of radiocolloid over each of the tumors and peritumoral injection blue dye, identification rate was 93.5% and axillary lymph node dissection was performed in 48 of the 59 patients without any false negative SLN results[38]. Goyal et al reported on behalf of the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial the results of the validation phase in which 75 patients with multifocal disease who received peritumoral injections of a radiotracer and blue dye. Successful identification of the sentinel node occurred in 71/75 patients (94.7%), the axilla was accurately staged in 95.8% of the patients and a false negative rate of 8.8%[39].

Table 2. Published studies on sentinel lymph node biopsy in multifocal/multicentric breast cancer

First author	Publication year	Number of patients	False-negative	Accuracy	Identification rate
Schrenk[36]	2001	19	0%	100%	100%
Ozmen[37]	2002	21	11.3%	93.7%	85.7%
Kim[41]	2002	5	0%	100%	100%
Kumar[38]	2003	59	0%	100%	93.5%
Tousimis[42]	2003	70	8%	96%	96%
Kumar[43]	2004	10	0%	100%	100%
Goyal[39]	2004	75	8.8%	95.8%	94.7%
Knauer[40]	2006	142	4%	97.3%	91.5%
Ferrari[44]	2006	31	7.1%	96.8%	100%
Gentilini[45]	2006	42	–	–	100%

Finally, in another multi-institutional validation study 142 patients were identified as having multicentric disease. Blue dye and radionucleotide were injected in combination or alone to identify the SLN and follow up completion level I/II ALND was performed in 125 of 142 patients. The authors reported an identification rate of 91.5%, an overall accuracy of 97.3% and a false negative rate of 4%. Interestingly, the false negative rate was 3.1% for those patients who had subareolar injection of blue dye or radiocolloid tracer[40]. The results of these and other studies are summarized in Table 2.

Multifocality and multicentricity was once thought to be a relative contraindication to SLN biopsy. With further understanding of the lymphatic drainage patterns of the breast and the recognition that the sentinel node represents the first draining node of the breast parenchyma as a whole and not the specific tumor, SLN biopsy in multifocal/multicentric disease appears to be feasible, accurate and with acceptably low false negative rates and can be used in this patient population presenting with clinically negative axilla.

Neoadjuvant Chemotherapy and Sentinel Lymph Node Biopsy

As the use of neoadjuvant chemotherapy becomes more ubiquitous in the treatment of breast cancer, the use and reliability of SLN biopsy in this patient population becomes very important. The predominant use of neoadjuvant was initially for locally advanced breast cancers as a means of cytoreduction allowing for resection of the primary tumor. In this setting, axillary lymph node dissection was performed at the time of operative intervention. More recently, neoadjuvant chemotherapy has been shown to have equal overall survival as well as disease free survival when compared to adjuvant chemotherapy[46]. In addition, neoadjuvant studies have shown an important and significant conversion rate from mastectomy to breast conservation therapy[47]. This increase use in neoadjuvant chemotherapy for T1-2 tumors as well as locally advanced tumors has raised interest and concern regarding the impact neoadjuvant chemotherapy has on axillary staging. Certainly T1-2 tumors have a

lower probability of nodal involvement compared to locally advanced breast cancer and committing such a patient to an axillary lymph node dissection because of concerns about feasibility and accuracy in a neoadjuvant setting is to confer a higher risk of the morbidities associated with axillary lymph node dissection. Additionally, larger randomized trials have demonstrated neoadjuvant chemotherapy can sterilize the axilla in 30-40% of patients with known axillary disease[48].

Among the important issues are: 1)How does chemotherapy affect the lymphatic channels from the breast to the sentinel lymph node?, 2)Does chemotherapy affect the sentinel lymph node as it does the primary lesion in the breast?, 3)Does chemotherapy affect the sentinel lymph node and the non-sentinel lymph nodes equally?, 4)Is sentinel lymph node biopsy feasible, accurate and reliable in the neoadjuvant setting? Three of the earliest single institution studies address these very concerns and demonstrated varied results. A study by Nason et al from the University of Washington identified a subset of 15 of 82 women receiving neoadjuvant chemotherapy who had SLN biopsy followed by ALND. All patients received peritumoral injections of radiocolloid and peritumoral injection of isosulfan blue dye. Lymphatic mapping was successful in 13 of 15 patients (87%). False negative rate in patients treated with neoadjuvant chemotherapy was 33% versus 16% for the remainder of the patient cohort and overall accuracy of SLNB in the neoadjuvant population was 77%. The authors concluded, acknowledging the small sample size, that SLN biopsy had unacceptable high false negative rates and should not be performed outside clinical trials[49]. Around the same time, two studies from MD Anderson provided data supporting the use of SLN biopsy in patients who had received preoperative chemotherapy. Breslin et al reported the results of SLN biopsy in women receiving neoadjuvant chemotherapy in a total of 51 women of whom all but three (patients refused procedure) had completion ALND. The authors divided the patients into three groups relative to surgeon experience with the procedure. They report an overall identification rate of 84% but when analyzed according to time (experience), the earliest (least experience) group IR was 64.7% and the latest group IR was 94.1%. The overall false negative rate was 12% and the accuracy of SLNB representing the axillary status was 93%[50]. The second study, by Cohen et al, was of 38 patients with a median tumor size of 4.5 cm who underwent lymphatic mapping by peritumoral injection of isosulfan blue dye alone or in combination with nucleocolloid followed by ALND. They identified at least one sentinel node in 31/38 (82%) of patients and 3 false negative biopsies (false negative rate of 10%) when both H&E staining and IHC staining were performed on the SLN[51]. Both studies concluded SLN biopsy was feasible and an accurate representation of the axilla in women treated with neoadjuvant chemotherapy and could be considered when planning surgical treatment after neoadjuvant chemotherapy.

Subsequently, numerous additional single institution studies published their results of patients who underwent SLN biopsy after neoadjuvant chemotherapy (Table 3). These studies were limited by small sample size, variability in lymphatic mapping and often were subject to the learning curve associated with starting to

Table 3. Published Studies of Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy

First Author	Year of Pub.	Number	Stage	Mode of Detection	Identification Rate	False Negative Rate
Nason[49]	2000	15	T1-4	Radionucleotide / Blue Dye	86%	33%
Breslin[50]	2000	51	II-III	Radionucleotide / Blue Dye	84%	12%
Cohen[51]	2000	38		Radionucleotide / Blue Dye	82%	27% (decreased to 17% with IHC†)
Haid[53]	2001	33	T1-3	Radionucleotide / Blue Dye	88%	0%
Tafra[54]	2001	29	T1-2	Radionucleotide / Blue Dye	100%	0%
Fernandez[55]	2001	40	I-III	Radionucleotide	94%	22%
Julian[56]	2001	31	I-II	Radionucleotide / Blue Dye	93.5%	0%
Stearns[57]	2002	34	LABC	Blue Dye	85%	14% (decreased to 6% without IBC*)
Brady[58]	2002	14	I-IIIB	Radionucleotide or Blue Dye	93%	0%
Julian[59]	2002	34	I-IIIA	Radionucleotide / Blue Dye	91.2%	0%
Miller[60]	2002	35	T1-4	Radionucleotide / Blue Dye	86%	0%
Balch[61]	2003	32	II-III	Radionucleotide / Blue Dye	97%	5%
Schwartz[62]	2003	21	II-III	Blue Dye	100%	9%
Piato[63]	2003	42	T1-2	Radionucleotide	97.6%	16.7%
Lang[64]	2004	53	II-III	Radionucleotide / Blue Dye	94%	4%
Mamounas[52]	2005	428	T1-3, N1-2	Radionucleotide / Blue Dye	84.8%	10.7%
Lee[65]	2007	238	T1-4, N1	Radionucleotide / Blue Dye	77.6%	5.6%

*IBC = Inflammatory breast cancer; † = Immunohistochemistry

perform the SLNB procedure. In a large, multi-institutional study of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27, a subset of 428 patients underwent SLNB after neoadjuvant therapy. The study compared neoadjuvant doxorubicin/cyclophosphamide (A/C) chemotherapy to neoadjuvant A/C followed by neoadjuvant docetaxel to neoadjuvant A/C followed by adjuvant docetaxel. The authors identified patients with palpable, operable breast cancers who had SLN biopsy before the mandatory level I and II ALND. Because SLN biopsy was not a mandatory part of the study, a set protocol for lymphatic mapping was not established and therefore not outlined in the study. Successful lymphatic mapping and SLN identification was achieved in 363 patients for an IR of 84.8% which the IR was higher when radiocolloid tracer was used either alone or in

combination with blue dye when compared to blue dye alone. There was a trend toward improved identification with increasing calendar year that did not achieve statistical significance. The non-sentinel lymph nodes were positive when the SLN was negative in 15 patients (false negative rate 6.9%) and the SLN biopsy accurately predicted the axillary status 95.6% of the patients. They noted a trend to higher rate of false negative results with increasing clinical tumors size which did not reach statistical significance. The authors concluded that the results of this study of SLN biopsy after neoadjuvant chemotherapy were comparable to other multicenter studies evaluating the efficacy of SLN biopsy prior to adjuvant chemotherapy[52].

There are no randomized controlled trials specifically addressing the feasibility, accuracy or timing of SLNB in neoadjuvant chemotherapy. A recent meta-analysis estimated the reliability of SLNB in this patient population based on the data from clinical studies. The total number of patient in whom a SLNB was attempted was 1273 and successful biopsy was achieved in 1142 yielding an overall IR of 90%. Based on Bayesian models, the sensitivity of the SLNB was estimated to be 88% with a false negative rate of 12%. The authors concluded that SLNB is an accurate and feasible after neoadjuvant chemotherapy[66].

There are centers advocating for the performance of SLN biopsy to stage the axilla at the time of diagnosis, prior to initiation of neoadjuvant chemotherapy. Those endorsing this sequence of intervention believe the varying false negative and identification rates in the literature subject the patient to an increased risk of inadequate staging of the axilla. Sabel et al reported a 100% identification rate in 25 patients with T1c and T2 primary tumors and clinically negative axilla. Fifty percent had axillary disease at the time of SLNB, all of whom underwent ALND upon completion of their chemotherapy. Residual disease was noted in 60% of the patients[67]. In a subsequent publication from the same institution, Khan and colleagues describe a comprehensive approach to axillary evaluation by undergoing axillary sampling either via ultrasound guided FNA or SLNB, the patient then proceeded to chemotherapy. If the axillary lymph node contained metastatic disease, the patient underwent SLNB followed by ALND at the time of the definitive surgery in this subset of patients. SLN was successfully identified in 32 of 33 patients (97%) after neoadjuvant chemotherapy and 1 false negative sentinel node was identified (FN rate 4.5%). Residual axillary disease was seen in 69% of the patients. Interesting, of the 33 patients initially found to be node-positive, 11 (33%) were free of axillary disease at the time of the ALND. To that end, the authors concluded future studies are necessary to support these findings with the intent to spare those women in whom chemotherapy has sterilized the axilla the risk of the morbidities associated with ALND[68].

Reoperative Sentinel Lymph Node Biopsy

The shift in the surgical treatment of early stage breast cancer toward breast conservation has resulted in a 10-20%, 10 year risk of ipsilateral recurrent breast cancer[69,70]. The end result is the emergence of a unique patient population – women

with ipsilateral tumor recurrence with prior axillary surgery. Traditionally, this subset of patients was treated with salvage mastectomy and axillary lymph node dissection. However, emerging data indicates there may be a role for SLNB. In its infancy, prior axillary surgery was considered a contraindication for SLNB due to the belief that the previous surgery irreversibly damaged the lymphatic pathways from the breast making SLNB procedure difficult if not impossible to perform and certainly not accurate. However, as with the other supposed contraindications to SLNB, recent studies have indicated SLNB is indeed feasible and may actually be helpful in identifying aberrant lymphatic drainage patterns in recurrent breast cancer.

In the first study published on reoperative SLNB, Port and colleagues reported successful identification of SLN in 24 of 32 patients who had previously undergone axillary surgery. They noted the success rate varied depending on the number of lymph nodes removed at the initial surgery, 87% IR if < 10 nodes were removed versus 44% IR if ≥ 10 nodes. Of the 8 failures, 6 had prior ALND with ≥ 9 nodes removed. The authors attempted SLNB in 4 patients with previous mastectomy (injections performed in the skin adjacent to the recurrence) with successful localization achieved in 2 patients. Three patients had positive SLN, 2 did not have further non-sentinel node involvement and 1 patient had 12 additional metastatic lymph nodes[71]. The same group published a larger series of 117 SLNB performed in 115 patients in which the overall success rate was lower at 55%. If the patient underwent prior SLNB, the success rate was 74% as compared to 38% if the previous axillary surgery has been ALND. They noted successful localization of repeat the SLN was inversely related to the number of lymph nodes removed at the initial axillary operation (less than 2 nodes – 80%, greater than 9 nodes – 38%). Of the 53 patients with failed SLN localization, 24 patients had additional non-sentinel nodes removed and only one case was a positive node identified. Several other interesting points were noted in this study. One, the use of blue dye alone identified only 6% of the reoperative SLN[72], a point echoed in the work of Dinan et al in which blue dye localized only 2 of the 11(18%) SLNs[73]. The second is that 30% of patients had drainage to nodal basins outside the ipsilateral axilla and 84% of those patients had prior ALND[72].

These findings are supported in the work by Intra et al and Taback et al. Intra and colleagues report the results of reoperative SLN in 18 women with ipsilateral breast cancer recurrence that previously underwent breast conservation therapy and SLNB. They identified all repeat SLN in the ipsilateral axillary lymphatic basin. Because completion ALND was only done in the 2 patients with positive SLN, false-negative rates can not be calculated[74]. Taback and colleagues report successful identification of repeat SLN in 11 of 15 attempts. The authors noted preoperative lymphoscintigrams showed 7 cases of aberrant lymphatic drainage resulting in operative exploration of non-traditional basins. In 9 of the 11 cases, non-sentinel nodes were obtained and, in all instances, the SLN accurately predicted the involved lymphatic basin. They conclude SLNB is feasible and accurate in the setting of

reoperative axillary surgery but caution imaging of the contralateral axilla as well as other lymphatic basins may be needed preoperatively if the ipsilateral axilla is not the primary drainage basin[75]. These findings are echoed in the work of Roumen et al when they reported the results of reoperative SLNB in 12 patients with previous breast and axillary surgery. Ten patients had successful SLN identification, 50% of whom the surgical plan was altered as a result of the lymphoscintigraphy and SLNB. Preoperative lymphoscintigraphy identified contralateral axillary SLN in patients who had undergone previous ALND in 4 patients thereby adding contralateral axillary exploration to the surgical plan. One patient, with a negative repeat SLN, did not undergo completion ALND. They concluded reoperative lymphatic mapping is feasible and provides useful information in the subset of patients with recurrent ipsilateral breast cancer[76].

These studies highlight the ever growing knowledge of sentinel lymph node biopsy and its utility. Prior axillary surgery was once thought to be a contraindication to SLNB but it now appears the procedure may be very helpful in identifying lymphatic basins that would otherwise not be explored when a patient presents

Table 4. Published studies of reoperative sentinel lymph node biopsy

First author	Year of Pub	# of patients	Identification rate	Non-axillary localization
Port[71]	2002	32	75%	Not reported
<10 nodes previously			87%	
≥10 nodes previously			44%	
Agarwal[77]	2005	2	100%	All to contralateral axilla
Dinan[73]	2005	16	69%	25% to ipsilateral axilla; 19% to contralateral axilla; 25% elsewhere
Intra[74]	2005	18	100%	All to ipsilateral axilla (all patients only had prior SLN)
Boughey[78]	2006	21	62%	Alternate lymphatic drainage seen in 20% patients with prior SLN biopsy and 40-50% of patients with prior ALND
Prior SLN only			100%	
Prior ALND			67-70%	
Roumen[76]	2006	12	83%	63% of patients had aberrant drainage patterns
Prior SLN only			100%	
Prior ALND			80%	
Taback[75]	2006	15	73%	Ipsilateral axilla 5 cases; ipsilateral supraclavicular 1 case; internal mammary 2 cases; interpectoral 2 cases, contralateral axilla 3 case
Prior SLN only			83%	
Prior ALND			67%	
Newman[79]	2006	10	90%	8 cases to contralateral axilla; 3 cases to ipsilateral internal mammary; 1 case to ipsilateral axilla (no prior axillary surgery)
Port[72]	2007	117	55%	30% of patients had aberrant drainage patterns
Prior SLN only			74%	
Prior ALND			38%	

with recurrent ipsilateral breast cancer. Traditional therapy dictated salvage mastectomy with ipsilateral ALND. However, as the previously mentioned studies indicate (as well as those seen in Table 4), the ipsilateral axilla is often not the primary lymphatic drainage basin, particularly if the patient had prior ALND with greater than 10 nodes removed. As a result, the SLN biopsy can guide the surgeon to explore extra-axillary lymphatic basins when recurrent disease arises. Admittedly, all the published studies are small, single institution patient cohorts, but the opportunity for large randomized trials will likely not present itself considering the low incidence of ipsilateral recurrent breast cancer. Therefore, the use of SLNB in recurrent breast cancer with prior axillary surgery is encouraging and may guide the surgeon to explore non-traditional lymphatic basins and, ultimately, may change the patient's systemic management.

Ductal Carcinoma in situ and Sentinel Lymph Node Biopsy

Ductal carcinoma in situ (DCIS) is the proliferation of neoplastic epithelial cell derived from terminal ductal lobular units that have not breached the mammary duct basement membrane. Therefore, by definition, this form of breast cancer can not metastasize to the lymphatic system. And yet, historically there is an approximate 1% incidence in axillary disease in patients diagnosed with pure DCIS[80]. This is most often explained by an invasive component not detected on routine pathologic evaluation of the primary breast lesion. There is a subset of DCIS patients with microinvasion (DCISM) as defined by the presence of cancer cells outside the basement membrane but without a focus greater than 1mm in greatest dimension[81]. This pattern of DCIS seen on diagnostic sampling has higher propensity to be upstaged to invasive disease on final pathology and an increased risk of axillary metastasis. Prior to the use of SLNB for axillary staging, the low incidence of axillary metastasis in this patient population and the relatively high incidence of morbidity associated with ALND resulted in a near complete abandonment of axillary staging in patients diagnosed with DCIS. Because SLNB imparts a reduced risk of morbidity and because there is a real, all be it small, risk of lymphatic metastasis in the DCIS patient population, some groups advocate for axillary staging for DCIS.

The pathologic evaluation of the SLN is much more rigorous than traditional non-sentinel node evaluation. Not infrequently, the consequence is the discovery of occult metastasis when formerly node-negative lymph node specimens of patients with invasive cancer were analyzed according to current sentinel node protocols[82,83]. This stage migration also occurred in the non-invasive patient population. In an initial study from the H. Lee Moffit Cancer Center of 87 patients with newly diagnosed pure DCIS, H&E and IHC stains were done on all SLN. The authors report 5 patients had positive SLN (6%) with 3 of the 5 found by IHC only. No additional lymph nodes contained metastatic disease on completion ALND[84]. The same group updated their results of SLNB performed in 675 patients with either DCIS or DCISM. Of the 613 patients initially diagnosed with pure DCIS, 55 (9%) were upgraded to invasive disease and 11 of the 62 (18%) patients with DCISM

were also found to have invasive disease on final pathology. A 5% incidence (27/559) of positive SLN was detected in the group with pure DCIS of which 19 were found by IHC alone. There was a higher incidence of axillary disease in the subgroup of patients with microinvasion, 14% (7/51). In this series, tumor upstaging was more frequent in patients initially diagnosed by core biopsy and tumors with higher grade but was not associated with histiologic subtype. Additionally, the tumor was twice as likely to be upstaged to invasive disease if the lesion was palpable and associated with calcifications on imaging. The authors recommended SLNB for patients undergoing mastectomy, those with DCIS with microinvasion, high grade DCIS and those with mass seen on mammography[85].

Two additional small single institution studies report similar findings with slight variations. Intra et al reported a 3.1% rate of SLN involvement in 223 patients with pure DCIS. Micrometastasis were identified in 5 of 7 patients with a positive SLN and the SLN was the only node involved in the 6 patients who underwent follow-up ALND. Low prevalence of axillary metastasis resulted in the authors recommending SLNB be performed for DCIS only when the patient is undergoing mastectomy and that completion ALND is not warranted when the SLN only contains micrometastatic disease[86]. Finally, the work of Yen et al shows a similar 3% incidence of axillary disease is patients with pure DCIS. Interestingly, in an initial population of 398 patients, 80 were upgraded to invasive disease on final pathology (66 of whom were diagnosed with core needle biopsy). Of the 398 patients, 141 (35%) underwent SLNB and 42 of those patients ultimately were found to have invasive disease. Independent predictors of invasive disease on final pathology were younger age, diagnosis by core needle biopsy, DCIS ≥ 4 cm by mammographic measurements, and high-grade DCIS. Thus, 99 patients with pure DCIS were evaluated with SLNB of which 3 had positive nodes for microinvasive disease. The only independent predictor of positive SLNB was a clinically palpable lesion. The authors conclude SLNB should not be performed on all patients with a diagnosis of DCIS but should be considered in those patients who have a higher likelihood of underlying, undetected invasive disease such as those who are younger, diagnosed by core needle biopsy, large (≥ 4 cm) high grade DCIS and patients undergoing mastectomy[87].

Clinically, what does the increased incidence of axillary metastasis predominantly diagnosed by IHC mean to a patient's overall survival? Mabry and colleagues collected information on 1236 patients with pure DCIS of whom 564 had axillary sampling either by ALND or SLNB. Of those patients evaluated by ALND (and thus standard pathologic evaluation of the lymph node), the incidence of axillary metastasis was 0.5% but those who underwent SLNB (and the more rigorous pathologic analysis including IHC) the incidence of nodal disease was 5.8%. The presence of lymphatic disease did not predict the poor outcome of the 6 women who developed invasive, metastatic disease and ultimately died[88]. Two additional studies support the finding that IHC positive lymph nodes in DCIS do not impact overall survival. The first, a retrospective study of 102 patients diagnosed with

node-negative DCIS, the lymph nodes from the lymphadenectomies were serially sectioned and using IHC staining. Thirteen patients were identified as having occult metastasis. With a mean follow up period of 19 years, twelve patients were noted to have had recurrences, none of those were retrospectively found to have occult metastases. The authors concluded the IHC detected micrometastasis had no clinical bearing on long term survival[89]. Finally, in a similar study El-Tamer et al reported an initial 1.2% incidence of positive axillary lymph node disease in patients with pure DCIS that increased to 6% when IHC was used to further evaluated nodes taken from axillary lymphadenectomies. With a median follow up time of 127 months, the Kaplan-Meier overall and breast cancer-specific survival estimates were similar between those patients with IHC positive lymph nodes and IHC negative lymph nodes leading the authors to query the utility of IHC in evaluating SLN taken in patients with pure DCIS[90].

Currently, the guidelines from the American Society of Clinical Oncologists (ASCO) generally recommends SLNB in those patients undergoing a mastectomy because axillary staging by SLNB is impossible if incidental invasive disease is found at the time of final pathology. Otherwise, the ASCO panel does not recommended SLNB for patients diagnosed with DCIS[33].

Internal Mammary Lymph Nodes and Sentinel Lymph Node Biopsy

It is well known the breast lymphatics drain predominantly to the ipsilateral axilla. There is, however, a percentage of lymph drainage to the ipsilateral internal mammary lymph nodes (IMLN) which has been shown to vary depending on the quadrant of the breast. While Halstead's original mastectomy included the resection of the axillary lymphatic basin, it did not incorporate the resection of the IMLNs. Later groups, recognizing the IMLNs as a possible significant lymphatic drainage basin of the breast, advocated for the extended radical mastectomy in which the internal mammary lymphatic chain and its associated pleura were resected. The intent was to improve local control and overall survival. However, a randomized international cooperative trial initiated in 1962 was unable to demonstrate improved prognosis with the radical dissection of the internal mammary nodes at 10 year follow up[91]. Therefore, the radical excision of the IMLNs was believed to incur greater risk to the patient without clear overall benefit. With the widespread implementation of sentinel lymph node biopsy, there has been a renewed interest in the role of internal mammary node evaluation. At issue is whether IM nodes should be sampled if they are identified as a sentinel node and what, if any, impact this has on a patients treatment and ultimately, on their overall survival.

It is important to look back to the earlier studies initiated as a result of the international cooperative trial from which single institutions have reported their results. Veronesi et al addressed the risk of internal mammary lymph node metastasis in 1085 women undergoing Halsted mastectomy and internal mammary lymph node dissection. They found younger women with larger tumors and axillary lymph node involvement were at higher risk for IMLN disease and that the location of

the primary lesion was not a predictor of involvement on multivariate analysis. They also reported a 10 year overall survival rate of 50-60% when the internal mammary nodes were involved[92]. In a subsequent publication by the same group analyzing 1119 women who had radical mastectomy with IM dissection, they again demonstrated IMLN involvement was dependent on age, size of primary tumor, ALN involvement, and independent of primary tumor location. They found 29% of women with axillary disease had concomitant IM disease. More importantly, 51/563 (9.1%) of the women had isolated metastasis to the internal mammary nodes without ALN involvement[93], implying these women could potentially be erroneously classified as having N0 disease when in fact disease was present outside the in-breast primary with clear implications regarding the decision for systemic therapy. However, it is important to note, tumors in the study were broadly categorized as <2 cm or >2 cm and it is unknown how many of the 51 patients with IMLN only disease had tumors <1 cm. It is this subset of patients (primary tumors <1 cm) that would benefit the most from being identified as having N1 disease because identifying nodal involvement would likely result in the recommendation for adjuvant chemotherapy when it otherwise might not have been because of the size of the primary breast lesion.

More recent studies using the sentinel lymph node technique have validated the findings of Veronesi et al. To assess feasibility as well as impact on nodal staging, van der Ent et al performed SLN biopsy on 256 women. Using lymphoscintigraphy, gamma probe detection and blue dye mapping, they identified and dissected both IMSLN and axillary SLN. They found 95% of the women (243/256) had axillary SLN and an additional 65/256 (25%) had IMSLN identified. Biopsy was successful 63% (41/65) of the patients with IMN and axillary SLN biopsy was successful in 97% of the cases. Of the 41 patients with biopsied IMSLNs, 11 women had IM nodal disease and a total of 3/41 (7.3%) women had isolated IM disease. They concluded the IMSLN biopsy is a safe and effective procedure and can provide additional nodal staging, particularly in the subset of women with isolated IM nodal disease[94]. Similarly, Dupont et al reported in another single institution study the results of 1273 women undergoing lymphatic mapping for breast cancer. IM sentinel node(s) were removed in 30 women of which 5 (16.7%) had metastatic disease to the IM sentinel lymph node (IMSLN). Three of the 5 patients had lymphatic metastasis limited to the IMSLN and no evidence of disease was detected in the axillary SLN indicating 10% of the patients had isolated IMSLN metastasis. In contrast to the studies of Veronesi et al, Dupont et al found 73.3% (22/30) of the primary breast lesions were located in the inner quadrants of the affected breast. The authors conclude IMSLN detection is possible with minimal risk procedure that can guide IMSLN dissection when indicated as a means to augment adjuvant treatment planning[95].

To determine who most will benefit from IMSLN biopsy, it is important to recognize how the results will alter the patient's adjuvant treatment. In the current National Comprehensive Cancer Network (NCCN) Guidelines, patients with

invasive tumors ≥ 1 cm receive the recommendation for systemic chemotherapy and even those with tumors ≥ 0.6 cm may consider adjuvant chemotherapy[96]. Therefore, IMSLN biopsy would play a role in those patients with tumors less than 5mm with a positive IMSLN because the recommendation for systemic chemotherapy would be added to the patient's adjuvant regimen. Additionally, isolated metastasis to the IMLN could potentially broaden the radiation therapy fields to include the internal mammary chain. The current NCCN guidelines recommend radiation therapy to the internal mammary lymphatic chain if there is clinically or pathologically evidence of involvement. Therefore, IMSLN biopsy has the potential to provide further nodal staging and thereby alter adjuvant loco-regional treatment as well as systemic therapy in a small subset of patients.

Pregnancy and Sentinel Lymph Node Biopsy

Breast cancer is the second most commonly associated malignancy of pregnancy with an estimated frequency of 1:3000 deliveries. The physiologic changes of pregnancy affect the breast parenchyma resulting in increased volume that ultimately makes clinical breast examinations as well as imaging modalities difficult. This often results in a delay of diagnosis that could translate to increase risk of lymphatic involvement and thereby alter the patient's prognosis. An estimated 56-83% of women with pregnancy associated breast cancer will have axillary involvement at the time of diagnosis[97]. In a mathematical model, Nettleton and colleagues estimated there is a 0.9% increased risk of axillary metastasis for every 1 month delay in diagnosis of breast cancers in tumors with moderate growth rates and 1.8% in lesions with rapid growth patterns[98]. The traditional approach to axillary staging in women with pregnancy associated breast cancer has been axillary lymph node dissection. This is due to the unknown risk radionucleotide incurs on the fetus via two mechanisms, the potential for fetal exposure to the radionucleotide via the transplacental route and the second is the mother as a source of teratogenic radiation exposure. The greatest risk is that of the mother acting as a radiation source. Additionally, the use of isosulfan blue dye in pregnancy has not been approved by the Federal Drug Administration and therefore is not available in pregnancy associated breast cancer as a means of identifying the sentinel nodes.

Recently, much work has been done to estimate the theoretical exposure of the fetus to Tc-99 m when used for lymphoscintigraphy in sentinel lymph node biopsy. Keleher and colleagues estimated radiation exposure to a fetus in early development, at 3 months, 6 months and 9 months gestation in 2 non-pregnant females. They used large (220 nm) particle Tc-^{99} peritumoral injections at concentrations of either 18.5 mBq (if surgery planned for the same day of injection) or 92.5 mBq (if surgery planned for the subsequent day) and estimated exposure if (1) the nucleotide remained in the breast parenchyma and regional lymphatics (2) if the entire tracer went directly to the bladder or (3) if the sum total of the tracer was injected into the blood stream. They found the maximal dose exposure to the fetus was 4.3 mGy in the event that all the 92.5 mBq radionucleotide went directly to the

bladder. Given the threshold of absorbed dosage causing adverse events to a fetus is 50 mGy, the authors conclude the risk to the embryo/fetus was small enough to endorse the use of sentinel lymph node biopsy in staging the axilla[99]. These findings are supported in a study by Gentilini et al. They measure potential exposure to the fetus in 26 non-pregnant females undergoing lymphoscintigraphy by thermoluminescent dosimeters (TLDs) placed externally in positions on the abdomen that would correspond to a fetus in the three trimesters of gestation. After peritumoral injection of Tc 99-labelled human albumin colloid particles (average activity 12.1 MBq), 23 of the 26 women had activity of the abdominal TLDS below the sensitivity of the device and three women had absorption patterns well below radiation-induced malformation thresholds of 100-200 mGy. They found safe urinary excretion patterns (<2% injected dose) and blood activity (<1% injected dose)[100]. Finally, a more recent study by Pandit-Taskar et al used standard internal absorbed dose assessment methodologies for reference phantoms and phantom models. Each of the 1021 patients had a single intra-dermal injection of Tc-99 m sulfur colloid with either 3.7 MBq activity if done on the day of surgery or 18.5 MBq activity if done the day prior to surgery. The highest absorption doses estimated for the fetus were at 9 months gestation and the two day protocol with an estimated absorption of 0.014 mGy. In fact, the authors report this estimation is less than 3% of the Nuclear Regulatory Commission (NRC) monthly guidelines and less than 0.3% of the NRC occupational exposure limits during the fetus' gestational period. Therefore, they conclude the use of Tc-99 m is safe for the fetus and can be used for staging of the axilla in women with pregnancy associated breast cancer[101].

Until this point, only models estimating the amount of radioactive exposure were published in the literature. In 2007, Mondi and colleagues reported their initial clinical experience using radionucleotide and/or isosulfan blue for sentinel node biopsy in nine gravid women in either their second or third trimester. Within this small cohort of patients, three were breast cancer patients and six were being treated for melanoma. The authors reported a 100% IR, and average of 2.3 SLN per patient and two patients with positive SLN, both of whom were breast cancer patients. All nine children were born at term and, to date they do not appear to have any sequella from the SLNB procedure[102].

Some investigators question the use of SLN biopsy in a patient population where the rate of nodal involvement exceeds 50% and further argue that little is known about the potential alterations in the lymphatic system of the breast in the gravid patient[103]. At the Consensus Conference on the use of sentinel lymph node biopsy in breast cancer in 2001, the recommendation was made not to use SLN biopsy in the pregnant patient[104] and this was echoed by the American Society of Clinical Oncology Guidelines which concluded there was not enough evidence at this time to support the use of sentinel node in pregnancy and therefore do not recommend its usage at this time[33]. A more recent panel of international experts expressed the opinion that SLN biopsy could be offered to the patient as long as an extensive discussion took place regarding the risk exposure to the fetus but also the potential

reduced sensitivity and specificity of the procedure with the use of only one tracer as isosulfan blue has not been approved by the Federal Dug Administration for use in pregnant women[105]. There are still many unanswered questions regarding the use of sentinel lymph node mapping in women diagnosed with pregnancy associated breast cancer and it is currently not considered standard of care to perform in the gravid patient.

Inflammatory Breast Cancer and Sentinel Lymph Node Biopsy

The standard method of axillary staging in women presenting with inflammatory breast cancer is axillary lymph node dissection at the time of their mastectomy. Inflammatory breast cancer has been considered a contraindication to sentinel lymph node biopsy because of the belief that the disease blocks the lymphatic channels and therefore the blue dye or radionucleotide would not be able to migrate to the sentinel node. In the literature, no study specifically addresses the use of sentinel lymph node biopsy in this setting but one study, looking at the accuracy of SLN biopsy after neoadjuvant chemotherapy in locally advanced and inflammatory breast cancer, identifies 8 women with inflammatory breast cancer. Stearns et al report substandard results with a identification rate of 75% (SN not identified in 2 of 8 women) as compared to an identification rate of 89% after neoadjuvant therapy in the women with locally advanced tumors[57]. The conclusions drawn by these investigators, SLNB is not reliable and therefore not indicated in inflammatory breast cancer. This was echoed in a review on the surgical aspects of inflammatory breast cancer by Kell and Morrow[106]. Sentinel lymph node biopsy for axillary staging is contraindicated in women presenting with inflammatory breast cancer.

Complications of Sentinel Lymph Node Biopsy

The long-term morbidities associated with SLNB have yet to be completely defined. In general, the morbidities associated with SLNB are much less than those of the traditional ALND. Unique to SLNB is the well published allergic reaction seen when isosulfan blue dye is use for node localization. This reaction can be mild such as transient hypotension seen in the operating room not requiring intervention to severe complications such as anaphylaxis. In a single institution, retrospective review of 639 SLNBs performed for breast cancer, seven patients (1.1%) had anaphylactic reactions requiring aggressive intraoperative resuscitation and intensive care unit stay. All patients were successfully treated and no deaths were reported[107]. A larger, multi-institutional study, Wilke and colleagues published on behalf of the American College of Surgeons Oncology Group (ACOSOG) Z0010, reporting only 5 of 4975 patients (0.1%) suffered anaphylaxis as a result of isosulfan dye use[108].

Perhaps the most disconcerting complication associated with ALND is chronic lymphedema. While the incidence of lymphedema with SLNB is less than ALND, it is not necessarily zero. In a single institution study, Francis et al. reported a 17%

incidence of acute lymphedema in those undergoing SLNB alone and 47% of women treated with ALND[109]. In a large, multi-institutional study (ACOSOG Z0010), using arm circumference measurements 10 cm above and below the medial epicondyle and a circumference difference of greater than 2 cm from baseline, Wilke et al found at six months a 7% overall incidence of lymphedema in women where staged with SLNB[108]. Other complications associated with axillary surgery such as paresthesias, wound infection, seroma formation and reduction in range of motion at the shoulder all appear to have a lower incidence with SLNB as compared to ALND[109,16].

CONCLUSION

Since its introduction in 1993, sentinel lymph node biopsy has rapidly become an essential component of the surgical management of patients with breast cancer. Once thought to be only applicable in early stage disease, sentinel lymph node biopsy is now used to stage patients presenting with large primary tumors, multicentric/multifocal breast cancer, patients who have received neoadjuvant chemotherapy, and is now emerging as an acceptable procedure in patients with ipsilateral breast cancer recurrence and a history of former axillary surgery. Ultimately, outcome studies of the sentinel lymph node biopsy procedure are necessary to compare traditional axillary lymph node dissection to sentinel lymph node biopsy before definitive conclusions can be made regarding local control achieved by sentinel lymph node biopsy.

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3. ADVANCES IN ADJUVANT CHEMOTHERAPY OF EARLY STAGE BREAST CANCER

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INTRODUCTION

Breast cancer is an increasing global public health burden with more than one million new cases anticipated worldwide[1] and more than 200,000 new cases anticipated in the United States in 2007 (www.cancer.org). Early stage disease accounts for an increasing proportion of these incident breast cancer diagnoses, largely as a result of improvements in public education, screening programs, technology and treatment[2, 3] However, despite the increasing proportion of early stage diagnoses, a significant proportion of women will experience a distant relapse leading to death from recurrence-related complications. These distant treatment failures indicate that some women have clinically undetectable micrometastatic disease at diagnosis which cannot be cured with locoregional therapy alone. Systemic chemotherapy aimed at eradicating these clinically occult micrometases is thus an integral component of the adjuvant treatment strategy for many women with early stage disease. Over the last several decades, investigators have endeavored to optimize disease specific outcomes and thus, improve patient survival through therapeutic innovation, while minimizing treatment-related toxicity. These efforts have manifested as refinements of the adjuvant chemotherapy prescription; innovations in scheduling, drug delivery and dosing; and the incorporation of biologic/targeted therapies. Specific advances in the adjuvant chemotherapy strategy for women with early stage breast cancer will be reviewed here.

RATIONALE FOR ADJUVANT CHEMOTHERAPY

Systemic chemotherapy has been an integral component of the adjuvant treatment strategy for many women with early stage breast cancer since investigators reported improved outcomes with single agent chemotherapy after radical mastectomy in the 1970s. The adjuvant strategy has since undergone numerous refinements as investigators strive to improve patient outcomes while minimizing treatment related toxicity. An early modification to the adjuvant strategy was the administration of polychemotherapy, whereby two or more agents are administered in combination. The first compelling evidence for this strategy was demonstrated in a study of 12 monthly cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy or no further therapy after radical mastectomy among women with node-positive breast cancer.[4,5] Significant relapse free survival (RFS; relative risk 0.65) and overall survival (OS; relative risk 0.76) benefits were reported with CMF polychemotherapy. These benefits were subsequently sustained through almost 20 years of follow-up. The argument for adjuvant polychemotherapy has more recently been corroborated with the 2005 reporting of the fourth collaborative meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), or Oxford overview.[6] In this study, data from more than 145,000 women participating in 194 trials of adjuvant chemotherapy were reported, although modern taxane, trastuzumab and aromatase inhibitor-containing regimens were not evaluated. When adjuvant polychemotherapy was compared with single-agent strategies, significant relapse free survival (RFS) and overall survival (OS) benefits were reported. With adjuvant polychemotherapy administration, the 15-year risk of recurrence and death were decreased by 12.3% and 10.0%, respectively, among women younger than 50 years, and by 4.1% and 3.0%, respectively, among women aged 50-69 years. In subgroup analyses, these benefits proved particularly pronounced among women with ER-poor tumors. Thus, although the magnitude of the therapeutic benefit varied between subsets, the rationale for polychemotherapy was established.

RATIONALE FOR ANTHRACYCLINE-CONTAINING REGIMENS

The CMF chemotherapy regimen has endured as a reasonable treatment strategy for many women with early stage breast cancer. However, the incorporation of anthracyclines into the adjuvant paradigm has permitted further improvements for many subgroups. In the 2005 Oxford overview, several anthracycline-containing regimens including combinations of 5-fluorouracil and cyclophosphamide with either doxorubicin or epirubicin (FAC or FEC, respectively), were evaluated.[6] Overall, six months of treatment with an anthracycline-containing regimen proved more efficacious than six months of treatment with a non-anthracycline regimen such as CMF, particularly among women less than 50 years of age compared with those aged 50 to 69 years. Specifically, anthracycline-containing regimens were associated with a 38% decrease in the annual breast cancer death rate among women less than 50 years of age and a 20% decrease among women 50 to 69 years

of age, largely irrespective of tamoxifen use, ER status and nodal status. The benefits for women aged 70 years or older, however, are largely uncertain as this is a typically under-represented population in clinical trials.

Modern adjuvant anthracycline-containing regimens include doxorubicin and cyclophosphamide (AC); cyclophosphamide; doxorubicin and 5-fluorouracil (CAF or FAC); 5-flourouracil, epirubicin and cyclyophosphamide (CEF or FEC); docetaxel, doxorubicin and cyclophosphamide (TAC); and AC followed by either paclitaxel (AC-T) or docetaxel (AC-D). There is indirect evidence from studies conducted in France and Canada that epirubicin is at least as efficacious as doxorubicin in the adjuvant setting.[7–10] However, because many of these regimens have not been directly compared in randomized control trials, the superiority of any singular regimen has not been clearly established, nor have the benefits of any specific regimens among specific subgroups been clearly delineated.

TOTAL DOSE AND DURATION OF ANTHRACYCLINE-CONTAINING REGIMENS

For many women, the expected benefit from an anthracycline-containing regimen is a factor of the number of cycles administered. In two National Surgical Adjuvant Breast and Bowel (NSABP) studies, 4 cycles of AC proved equally as efficacious as 6 cycles of CMF among node-positive and node-negative women.[11,12] In a National Cancer Institute of Canada (NCIC) trial, 6 cycles of CEF conferred improved RFS and OS compared with 6 cycles of CMF among pre-menopausal women with node positive breast cancer. These benefits proved particularly pronounced among women with 4 or more involved lymph nodes.[9,10] Similar benefits were reported in a Danish trial of CEF versus CMF in premenopausal women with node-positive and node-negative breast cancer.[13] Thus, 6 cycles of an anthracycline-containing regimen appears to confer superior efficacy when compared with 4 cycles.

Dose Escalation

In an effort to improve upon conventional adjuvant strategies, investigators have explored dose escalation strategies, whereby the efficacy of varying doses of specific therapeutic agents is evaluated, with variable success. In NSABP B22 and B25, dose escalation of cyclophosphamide beyond standard doses of 600 mg/m^2/dose did not improve patient outcomes, and in one study demonstrated a significantly increased risk of myeloproliferative disorders.[14,15] Cancer and Leukemia Group B (CALGB) 9,344 and 8,541 demonstrated a threshold dose of 40 mg/m^2/dose for doxorubicin, but no benefit beyond 60 mg/m^2/dose.[16,17] Three studies investigating epirubicin dose-escalation demonstrated improved survival with doses as high as 100 mg/m^2/dose.[7,9,10,18,19] However, a small study of CMF versus EC among high-risk premenopausal patients with epirubicin administered at 120 mg/m^2/dose did not demonstrate any survival benefit.[20] Because the survival benefits reported from a few small, relatively uncontrolled clinical trials with myeloablative doses of chemotherapy followed

by peripheral stem cell transplantation, were not successfully reproduced in several subsequent randomized control trials, this strategy has since been abandoned outside of the clinical trial setting.[21–24]

COMBINING ANTHRACYLINE AND NON-ANTHRACYCLINE REGIMENS

Given the benefits observed with both anthracycline- and nonanthracycline-containing regimens, investigators have endeavored to further optimize the chemotherapy strategy by combining the two approaches. Studies of block-sequential anthracycline-CMF strategies have demonstrated superiority over alternating anthracycline-CMF strategies or CMF alone in some studies[25–27] but not others.[28] However, reinduction with CMF 6 months after adjuvant anthracycline administration does not appear to confer any benefit.[11]

Taxanes

A number of studies have recently demonstrated superior efficacy with adjuvant strategies which incorporate a taxane, either paclitaxel or docetaxel. Modern adjuvant taxane-containing regimens include AC-T; AC-D; TAC and FEC followed by docetaxel (FEC-D). In CALGB 9344, women with node-positive breast cancer were randomized to AC-T comprised of 4 cycles of AC followed by 4 cycles of paclitaxel at 175 mg/m^2/dose with dose escalated doxorubicin or 4 cycles of conventional dose AC.[17] Although no benefit was observed with doxorubicin dose escalation beyond 60 mg/m^2, the paclitaxel-containing regimen was associated with significant 5-year disease free survival (DFS; 70% vs 65%) and OS (80% vs 77%) benefits, particularly among women with estrogen receptor (ER)-negative tumors. Whether the benefits were attributable to the addition of the taxane or the difference in the total number of treatment cycles is unknown. NSABP B28 evaluated a similar strategy among women with node-positive breast cancer, although paclitaxel was administered at a slightly higher dose (225 mg/m^2/dose).[29] The paclitaxel-containing regimen was associated with a significant 5-year DFS benefit (76% vs 72%) but no OS benefit. Although it is difficult to account for the discrepant survival outcomes between these two studies, patients in the NSABP trial were older and had lower risk disease with fewer involved lymph nodes when compared with the CALGB study patients. Furthermore, the administration of tamoxifen concurrently rather than sequentially with chemotherapy in women with hormone receptor-positive disease may have blunted the expected benefits in the NSABP study. However, in a recent pooled analysis of 15,598 patients participating in nine adjuvant taxane trials, the taxane-containing strategies were associated with significant DFS and OS benefits both overall and in the node-positive subset.[30] The absolute DFS and OS benefits in favor of the taxane-containing strategies ranged from 3.3% to 4.6% and from 2.0% to 2.8%, respectively. It is anticipated that the benefits of adjuvant taxane therapy will be further defined in an upcoming meta-analysis by the Oxford overview investigators.

Is There a Superior Taxane or Taxane-Containing Regimen?

Despite a growing body of literature supporting the administration of taxane-containing regimens among specific subsets of breast cancer patients, there has been longstanding controversy regarding the superiority of paclitaxel versus docetaxel. This controversy was fuelled, in part, by evidence from the metastatic breast cancer literature suggesting superiority of docetaxel over paclitaxel.[31] The efficacy of adjuvant docetaxel was first evaluated by Breast Cancer International Research Group (BCIRG) investigators who randomized women with node-positive disease to 6 cycles of TAC or 6 cycles of FAC.[32] TAC was associated with significant 5-year DFS (75% vs 68%) and OS (87% versus 81%) benefits, particularly among the HER2-overexpressing cohort. The docetaxel regimen, however, was associated with significantly increased rates of neutropenia, febrile neutropenia, asthenia, hypersensitivity and stomatitis. In a French study, node-positive women were randomized to 6 cycles of FEC or 3 cycles of FEC followed by 3 cycles of docetaxel (FEC-D).[33] The docetaxel-containing regimen was associated with significant 5-year DFS (78% vs 73%) and OS (91% vs 87%) benefits. In subgroup analyses, however, the benefits were limited to women with only 1 to 3 involved lymph nodes (versus those with 4 or more lymph nodes). In contrast to the Oxford overview, the docetaxel-associated DFS benefits were primarily limited to women aged 50 years or older. Furthermore, women receiving adjuvant tamoxifen derived no benefit with the addition of docetaxel. Although it is difficult to account for these results, it is anticipated that the benefits of docetaxel among specific subsets will be further defined with the reporting of ongoing studies conducted by NSABP and BCIRG investigators.

Despite the benefits demonstrated with adjuvant docetaxel, the toxicity profile has deterred some clinicians from adopting adjuvant docetaxel-containing regimens. The recently reported Eastern Cooperative Oncology Group (ECOG) 1199 study was designed to evaluate the selection of paclitaxel versus docetaxel as well as taxane scheduling.[34] Almost 5000 women were randomized after standard dose AC to either weekly or q3weekly paclitaxel or docetaxel. Although there was a trend in favor of improved DFS with weekly paclitaxel, particularly among patients with ER-negative disease, no significant DFS or OS benefits were observed with either taxane or with either schedule. Treatment may be further improved upon with innovations in drug delivery strategies such as nanoparticle albumin-bound paclitaxel (Abraxane) which has proven safe and efficacious in the metastatic setting. Clinical trials of adjuvant nanoparticle albumin-bound paclitaxel are currently underway.

Dose Density

A recent innovation designed to optimize tumor cell kill is the dose-dense strategy. The dose dense strategy was developed from the Norton-Simon mathematical model of tumor cell growth.[35] This model predicts that the most efficient way to treat a heterogeneous population of cancer cells is to sequentially eradicate the

numerically dominant, more rapidly proliferating cell populations first, then the more indolent, resistant cell populations.[36] The magnitude of the chemotherapy impact depends on several variables including the extent of cell kill with each dose, the duration of therapy and the rate of tumor growth during and between treatments. Regrowth of treatment-resistant tumor cells is believed to be a principal cause of treatment failure. Thus, by decreasing the interval between treatments, the fixed cell kill with each cycle may be optimized, thereby improving the overall impact of therapy. However, dose dense regimens may also affect other rapidly proliferating cells, including bone marrow progenitor cells, thereby increasing the potential risk for infection. This obstacle has been largely overcome with the development of hematopoeitic growth factors such as (granulocyte-colony stimulating factor) G-CSF, which may be administered concurrently with chemotherapy. Consequently, dose dense regimens may now be administered relatively safely without compromising dose size or total dose.

One of the first studies to explore the principles of dose density compared sequential and alternating doxorubicin and CMF regimens among women with node-positive breast cancer.[26] The sequential strategy is considered "dose dense" compared with the alternating strategy because the doxorubicin and CMF regimens were delivered over shorter periods of only 9 and 21 weeks, respectively. Ultimately, the sequential strategy proved clinically superior to the alternating strategy. The first large randomized control trial to specifically evaluate the dose dense approach was CALGB 9741.[37] Dose density has since been evaluated in clinical trials with a number of other chemotherapy regimens.[38-42] Further refinements of the dose dense strategy are ongoing as investigators endeavor to further optimize the adjuvant treatment strategy and thus, patient outcomes.

CALGB 9741: The Pivotal Trial of Dose Dense Chemotherapy

CALGB 9741 was the first large phase III study to specifically apply and evaluate the Norton-Simon model.[37] In this study, 2005 women with node-positive breast cancer were randomized to standard doses of sequential doxorubicin (A), paclitaxel (T) and cyclophosphamide (C) or concurrent doxorubicin/cyclophosphamide followed by paclitaxel (AC-T) in a 2X2 factorial design (Figure 1). Each regimen was administered at either standard intervals every 3 weeks, or at dose dense intervals every 2 weeks with G-CSF support. Of note, this was a pure study of dose density, as the same number of drug cycles and the same cumulative dose of each drug were administered in all patients.

All four treatment schedules in CALGB 9741 proved feasible and safe. In fact, the incidence of grade 4 neutropenia and treatment delays due to hematologic toxicity were reduced with the dose dense strategy. A planned interval analysis after a median 36 month follow-up period demonstrated significant disease free survival (DFS; risk ratio [RR] 0.74) and overall survival (OS; RR 0.69) benefits in favor of the dose dense strategy when compared with the conventional q3weekly strategy. These benefits proved particularly pronounced among the cohort of women with

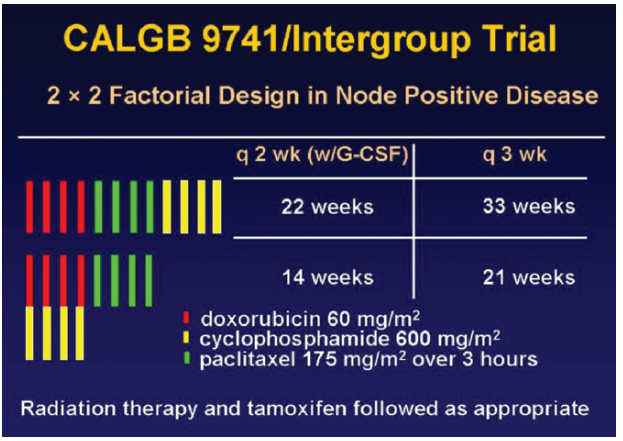

Figure 1. Schema for CALGB 9741.[37]

ER-negative tumors, and have endured after a median 6.5 year follow-up period with DFS and OS hazard ratios in this cohort of 0.75 and 0.77, respectively.[43] Thus, these findings not only supported the Norton-Simon hypothesis but they also provided a foundation for further applications of the dose dense strategy.

Dose Dense Epirubicin

The results of a multi-center German study evaluating dose dense sequential epirubicin, paclitaxel and cyclophosphamide (ETC) versus conventionally scheduled EC followed by T (EC-T) were initially reported in 2004 and updated in 2006.[38,39] In this study, 1284 women younger than age 65 with 4 or more involved axillary lymph nodes were randomized to receive three sequential cycles of each of E (150 mg/m^2), T (225 mg/m^2) and C (2500 mg/m^2) at q2weekly intervals with G-CSF support or four cycles of EC (90/600 mg/m^2) followed by four cycles of T (175 mg/m^2) at q3weekly intervals (Table 1). The dose dense arm was associated with increased rates of hematologic toxicity (7% vs. 2%) despite G-CSF support, dose reductions and treatment discontinuations. However, after a median follow-up period of 62 months, significant improvements in RFS (70% vs 62%, $p = 0.00079$; hazard ratio 0.72) and OS (82% vs 77%, $p = 0.029$; hazard ratio 0.76) were reported. These results represent the most impressive survival benefits reported in a trial of dose density to date. Ideally, however, in a pure study of dose density, the same number of drug cycles and the same cumulative dose of each drug should be administered in all patients. In this study, the results are somewhat confounded by the introduction of both dose density and dose intensity. However, given the evidence from other studies suggesting a limited dose-response relationship for all

Table 1. Dose and scheduling of epirubicin (E), paclitaxel (T) and cyclophosphamide (C) in the AGO study[38,39]

			Epirubicin (E)		Paclitaxel (T)		Cyclophosphamide (C)	
Regimen	Schedule	Total cycles/drug	Per cycle	Total	Per cycle	Total	Per cycle	Total
ETC	q2weekly	3	150 mg/m^2	450 mg/m^2	225 mg/m^2	675 mg/m^2	2500 mg/m^2	7500 mg/m^2
EC-T	q3weekly	4	90 mg/m^2	360 mg/m^2	175 mg/m^2	700 mg/m^2	600 mg/m^2	2400 mg/m^2

ETC, sequential epirubicin, paclitaxel and cyclophosphamide; **EC-T**, epirubicin/cyclophophamide followed by paclitaxel.

three drugs in the evaluated dose ranges, one may envision the study as delivering the same *functional* doses of each drug. Consequently, it may be argued that the dose dense scheduling more than compensated for the decreased number of drug administrations (from 4 to 3 per drug).

The GONO-MIG (Gruppo Oncologico Nord Ovest-Mammella InterGuppo) Study

Given the neurotoxicity associated with taxane-containing regimens and some evidence to suggest that not all women benefit from taxanes, there has been considerable interest in evaluating dose density in nontaxane-containing regimens. In one such Italian study, 1,214 women with node-positive or "high risk" node-negative early stage breast cancer were randomized to six cycles of adjuvant 5-fluorouracil/epirubicin/cyclophosphamide (FEC) chemotherapy administered in a q2weekly dose dense schedule with G-CSF support or a conventional q3weekly schedule.[40,41] "High risk" in the node-negative cohort was defined as age 35 years or younger, hormone receptor-negative disease, tumor size ≥2 cm, poor histologic grade and/or high proliferative rate. Unfortunately, however, the event rate in this study was lower than expected and the study lost statistical power. Although a trend was observed favoring the dose dense strategy for hazard of recurrence and death after a median 10.4 year follow-up period, these were not statistically significant findings. The dose dense strategy did prove safe, however, with fewer dose reductions, treatment delays and discontinuations than the conventionally scheduled regimen. As in CALGB 9741, no cases of AML or MDS were reported; however, dose dense FEC was associated with more asthenia, bone pain, anemia and thrombocytopenia.

Tailoring the Adjuvant Chemotherapy Strategy

Can adjuvant chemotherapy be eliminated altogether for specific subsets of women with early stage breast cancer?

Decisions regarding adjuvant systemic therapy are often challenging for patients with small, node-negative, ER-positive early stage breast cancer who are at a relatively low risk of recurrence. Hormonal maneuvers remain the therapeutic cornerstone for this cohort and the additional benefit of cytotoxic chemotherapy is often

difficult to quantify. Recently, several multigene assays including Onco*type* DX™, the Amsterdam signature and the Rotterdam signature have been developed which quantify an individual's risk of recurrence, thereby improving the risk-benefit calculus for systemic chemotherapy decisions.[44–47] Although these tools are discussed in detail in a separate chapter, it is important to note that these innovations represent an important advance in clinical decision-making regarding adjuvant chemotherapy, whereby adjuvant prescriptions are increasingly tailored to the biology of an individual's tumor.

Can anthracyclines be eliminated from the treatment paradigm for specific subsets when adjuvant chemotherapy is considered?

Given the potential risk of anthracycline-mediated cardiotoxicity and the limited benefit for women at low risk of recurrence, it would be ideal to eliminate anthracyclines from the adjuvant chemotherapy prescription for this subset. To date, however, subsets who may forgo adjuvant anthracyclines have not been clearly defined. Consequently, significant variability in regional clinical practice patterns is observed. Anthracycline-containing regimens are often reserved for younger women at higher risk of recurrence while patients with lower risk, node-negative disease; advanced age; or a contraindication to anthracycline-containing regimens are often treated with CMF or docetaxel/cyclophosphamide (TC). As previously outlined, CMF is an efficacious regimen which has been extensively evaluated over the past 3 decades. The efficacy of TC was recently reported in a study of 4 cycles of AC versus TC administered every 3 weeks among women with node-positive and node-negative breast cancer.[48] TC was associated with modest DFS improvements compared with AC but no significant OS benefit. However, TC was also associated with increased incidence rates of myalgias, arthralgias, edema and febrile neutropenia.

The adjuvant chemotherapy paradigm is also evolving as a result of recent innovations in targeted/biologic therapies. Although targeted therapy is reviewed elsewhere, the efficacy of these generally well-tolerated agents may enable clinicians to forgo the administration of potentially toxic systemic therapies such as anthracyclines and taxanes. Furthermore, our growing knowledge about the pathophysiology of breast cancer is enabling clinicians to better define the subsets of patients who may benefit from specific strategies. For example, in a recent pooled analysis of 7 randomized control trials, a 29% reduction in risk of relapse and a 27% reduction in risk of death were reported among adjuvant trastuzumab-naïve, anthracycline-treated women with HER2-overexpressing breast cancer when compared with the non-overexpressing cohort.[49] Conversely, no benefit was observed with anthracycline-containing regimens in the HER2-negative cohort. The authors concluded that the superiority of anthracycline-containing adjuvant chemotherapy appears to be limited to the HER2-overexpressing cohort. This finding is compatible with a study among premenopausal women, where HER2 overexpression was associated with increased clinical responsiveness to an adjuvant anthracycline-containing

regimen compared with a non-anthracycline regimen.[50] The enhanced sensitivity of HER2-overexpressing breast cancers to anthracyclines is postulated to reflect, in part, co-amplification of the HER2 receptor and topoisomerase IIα, the DNA replication and recombination enzyme targeted by anthracyclines. However, the evidence for this hypothesis has been conflicting. Furthermore, there is also evidence to suggest that topoisomerase deletions are also predictive of clinical responses to anthracyclines.[51-54] Regardless of the specific mechanism(s) for the enhanced anthracycline sensitivity observed among women with HER2+ breast cancer, the findings of the pooled analysis support the evolving practice of adjuvant therapy recommendations which are tailored to the biology of individual tumors.

Can taxanes be eliminated from the treatment paradigm for specific subsets when adjuvant chemotherapy is considered?

In Canada, oral cyclophosphamide/epirubicin/5-fluorouracil (CEF) is frequently used to treat women with high risk breast cancer while in the United States some combination of A, C and T is frequently used. Given that a prior co-operative trial in women with locally advanced breast cancer demonstrated equivalent efficacy with dose dense epirubicin/cyclophosphamide (EC) for 3 months when compared with six months of CEF,[55] these investigators postulated that dose dense EC followed by a taxane would demonstrate superior efficacy when compared with CEF and AC-T. Consequently, in NCIC MA.21, women with node-positive or high risk node-negative breast cancer were stratified by nodal status, ER status and primary surgery and randomized to either 6 cycles of CEF, four cycles of AC followed by 4 cycles of paclitaxel (AC-T) or 6 cycles of q2weekly EC followed by 4 cycles of q3weekly paclitaxel (EC-T) (Table 2).[42] Of note, both G-CSF and erythropoietin

Table 2. Dose and scheduling of the regimens evaluated in NCIC MA.21[42]

			Anthracycline				
Regimen	Schedule	Total cycles	Per cycle	Total	Taxane	Cyclophosphamide	5FU
CEF (with abx)	q3w	6	60 mg/m2 IV D1 & D8	720 mg/m^2	N/A	75 mg/m2 po D1-14	500 mg/m2 IV D1 & D8
AC-T	q3w	8	60 mg/m2 IV D1	240 mg/m^2	175 mg/m2 IV D1	600 mg/m2 IV D1	N/A
EC-T (with GCSF & EPO with EC & T)	ECq2w→ Tq3w	10	120 mg/m2 IV D1	720 mg/m^2	175 mg/m2 IV D1	830 mg/m2 IV D1	N/A

CEF, cyclophosphamide/epirubicin/5-fluorouracil; **AC-T**, adriamycin/cyclophosphamide-paclitaxel; **EC-T,** epirubicin/cyclophosphamide-paclitaxel; **D1,** day 1; **D8,** day 8; **N/A,** not applicable.

Table 3. Results of NCIC MA.21[42]

Treatments evaluated	Hazard ratios for recurrence (95% CI)	P-value
EC-T vs. CEF	0.89 (0.64, 1.22)	0.46
AC-T vs. CEF	1.49 (1.12, 1.99)	0.005
AC-T vs. EC-T	1.68 (1.25, 2.27)	0.0006

CI, confidence interval; **EC-T,** epirubicin/cyclophosphamide-paclitaxel; **CEF,** cyclophosphamide/epirubicin/5-fluorouracil; **AC-T**, adriamycin/cyclophosphamide-paclitaxel.

support were administered throughout the duration of the EC-T regimen and prophylactic antibiotics were administered with the CEF regimen.

The hazard ratios for recurrence in NCIC MA.21 are outlined in Table 3. The stratification-adjusted 3-year RFS for the CEF, EC-T and AC-T regimens were 90.1%, 89.5% and 85.0%, respectively. In an exploratory analysis there was a trend toward superiority with EC-T compared with CEF in the ER-negative subgroup, however, these findings were not statistically significant (HR 0.78, $p = 0.23$). However, in the same subgroup analysis, q3weekly AC-T proved inferior to both CEF and EC-T with HR's of 1.67 ($p = 0.007$) and 2.15 ($p = 0.0002$), respectively. However, CEF and EC-T were associated with increased rates of febrile neutropenia, thromboembolic events and delayed cardiotoxicity compared with AC-T. Thus, this trial demonstrated that conventionally scheduled AC-T is inferior to both CEF and dose dense EC-T. The authors further concluded that given the equivalent efficacy of CEF with dose dense EC-T, taxane-containing regimens may not be necessary in selected patients. However, given that the subset of women who can forgo taxane-containing regimens has not been clearly identified, this warrants further investigation.

BIG 2-98 was designed to evaluate not only the role of adjuvant taxanes, but also the role of sequential versus concurrent anthracycline-taxane strategies.[56,57] In this study, women with node-positive breast cancer were randomized to one of four arms: Ax4 → CMF x3; Ax3 → Tx3 → CMFx3; or ATx4 → CMFx3 (where T=docetaxel). Not only was there was no OS benefit for any of the evaluated regimens, but also in a CNS substudy of incident brain metastases detected post-mortem, there was no difference in CNS relapse rates at death for taxane versus non-taxane treated patients.

Timing of Dose-Dense Docetaxel Relative to Anthracycline

By convention, when a sequential adjuvant anthracycline-taxane strategy is employed, the anthracycline-containing component is typically administered prior to the taxane. This convention was challenged in a randomized phase II study investigating 4 cycles of docetaxel (75 mg/m^2/dose) before or after 4 cycles of conventional dose AC (60/600 mg/m^2/dose).[58] All cycles were administered in a dose-dense schedule every 2 weeks with G-CSF support. As outlined in Table 4, the investigators demonstrated that the relative dose intensity (RDI) was greater with

Table 4. Mean relative dose intensity (RDI) as a function of dose-dense anthracycline (AC)-docetaxel (D) sequencing[58]

	D → AC	AC → D	P-value
D mean RDI	96%	82%	<.001
AC mean RDI	95%	98%	.28
D dose reductions	5/28 (18%)	14/28 (50%)	.02
D dose delays	8/28 (29%)	7/28 (25%)	1.0

D, docetaxel; **AC**, adriamycin/cyclophosphamide; **RDI**, relative dose intensity.

upfront taxane administration, primarily as a result of fewer dose reductions in this arm (18% vs 50%, $p = 0.02$). This data suggests that further refinements to specific dose dense regimens may confer additional clinical benefits. Clinicians should note, however, that the dose of docetaxel here is decreased compared to the "standard" 100 mg/m^2 when this agent has followed conventional AC in most prior studies. The trade-off in efficacy and toxicity for these two approaches is not defined.

Concurrent versus Sequential Anthracycline-Taxane Therapy

The results of an exploratory analysis from a phase III study of concurrent versus sequential anthracycline-taxane therapy in which 617 patients with node-positive operable breast cancer were randomized to receive adjuvant epirubicin either sequentially (EC-T) or concurrently (ET) with either paclitaxel or docetaxel were recently reported.[59] There was no significant DFS difference between the study arms, regardless of the specific taxane administered. There was a non-significant trend toward an increased incidence of serious adverse events in the concurrent versus the sequential cohort (23.7% vs 12.5%, respectively). These findings are consistent with the ECOG 1199 results reported at SABCS 2005 wherein the superiority of a specific taxane (or taxane schedule) was not demonstrated.

Metronomic Chemotherapy

Metronomic chemotherapy is a variation of the dose dense strategy whereby chemotherapy is administered at relatively low, minimally toxic doses at frequent, regular intervals. This approach was evaluated in a neoadjuvant study of 5 cycles of q3weekly AC (60/600 mg/m^2) followed by 12 weekly cycles of paclitaxel (80 mg/m2) versus 15 cycles of weekly doxorubicin (24 mg/m^2/week) with cyclophosphamide (60 mg/m^2/d) with weekly G-CSF support followed by 12 weekly cycles of paclitaxel (80 mg/m^2) among women with locally advanced or inflammatory breast cancer. [60]The metronomic regimen was associated with significant improvements in pathologic complete response (31% vs 19%, $p = 0.03$), less nausea/vomiting and febrile neutropenia, but more hand-foot syndrome (13% vs 0%) and stomatitis (11% vs 2%). Whether the observed improvements in pathologic complete response will translate into survival benefits has not yet been

determined. However, trials comparing metronomic and conventional dose dense strategies are currently underway in the adjuvant setting.

Future Dose Dense Strategies

As the adjuvant strategy becomes increasingly tailored to specific subsets of women and the biology of their individual tumors, the incorporation of targeted therapy onto the dose dense foundation represents an ongoing area of investigation. For example, the addition of trastuzumab to dose dense AC-T in women with HER2-overexpressing early stage breast cancer has proven safe and well-tolerated.[61] Studies of adjuvant dose dense AC with the anti-VEGF antibody bevacizumab and nanoparticle albumin-bound paclitaxel are also currently underway. Thus, ongoing refinements to the dose dense strategy are anticipated, with the incorporation of biologic therapy in appropriate subsets.

OTHER ADJUVANT STRATEGIES

Gemcitabine

The tolerability of adjuvant gemcitabine (G) was recently reported in a preliminary report of the tANgo study of EC-T vs EC-GT with 1250 mg/m^2 of G administered days 1 and 8 of each 21-day cycle.[62] The addition of gemcitabine was associated with significantly increased rates of neutropenia, infection, fatigue and nausea/vomiting. In a quality-of-life substudy, the addition of gemcitabine was also associated with worse global health and cognitive function scores during chemotherapy, although these differences did not persist long-term. Efficacy data have not yet been reported.

Capecitabine

Safety analyses from two studies of adjuvant capecitabine were recently reported. In an interim analysis from the first 100 patients participating in the ICE study of ibandronate with or without capecitabine (at 1000 mg/m^2 po bid on days 1 to 14 q21 days) in the elderly, 80% received all planned capecitabine therapy and dose reduction were required in only 6.3% of cycles.[63] There were no grade 3/4 hematologic and no grade 4 non-hematologic adverse events. Thus, the authors concluded that this dose and schedule of adjuvant capecitabine is safe and well-tolerated among patients 65 years or older. In a safety analysis of ET-capecitabine with or without vinorelbine, the addition of vinorelbine was associated with increased rates of marrow suppression, febrile neutropenia and infection.[64] Efficacy analyses for both adjuvant capecitabine studies are still pending.

CONCLUSION

Systemic chemotherapy is an integral component of the adjuvant treatment strategy for many women with early stage breast cancer and accounts for significant improvements in breast cancer specific mortality.[2,3] However, the optimal adjuvant

chemotherapy paradigm has not yet been established. Furthermore, decisions regarding adjuvant chemotherapy are becoming increasingly complex with the advent of new therapeutic strategies, a growing body of literature on the molecular biology and natural history of breast cancer and advances in therapeutic techniques and early detection. Investigators endeavor to further optimize the adjuvant treatment strategy by refining formulations, doses and schedules while minimizing treatment-related toxicity. The dose dense strategy represents an important innovation in the management of women with early stage breast cancer and trials endeavoring to further refine current strategies are ongoing. Although the ideal treatment strategies for specific subgroups have not yet been determined, recent advances in prognostic profiling have facilitated the individualization of treatment to the biology of an individual cancer and the needs of the affected individual. Ongoing advances in our understanding of the pathophysiology of breast cancer should permit further refinements of the adjuvant systemic therapy paradigm resulting in therapy recommendations which are truly tailored to the affected individual and the biology of their cancer.

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4. OVERVIEW OF RANDOMIZED TRIALS OF SYSTEMIC ADJUVANT THERAPY

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INTRODUCTION

Since the first edition of this text adjuvant therapy for early stage breast cancer has changed in several important ways.

- Several trials have further elucidated the impact of adjuvant chemotherapy for breast cancer.
- Several trials have confirmed the promise of aromatase inhibitors for adjuvant endocrine therapy.
- A new targeted therapy, trastuzumab, has been shown to be highly effective as part of adjuvant therapy for HER2-positive breast cancer.
- An updated meta-analysis of the benefits of adjuvant therapy of breast cancer has appeared.

Because of these advances adjuvant therapy options available to women today are quite different than those of just 5 years ago.

The purpose of this chapter is to review where our current therapy options have succeeded and where adjuvant therapy options have limited effectiveness or other associated problems. As a starting point we will review the results of the most recently published EBCCTG meta-analysis.

CHEMOTHERAPY

As with prior meta-analyses, the most recent meta-analysis published in 2005[1] shows polychemotherapy programs are more effective that monochemotherapy programs, and that age of the patient appears to impact the efficacy of poly-

chemotherapy with younger patients benefiting more than older patients (see Fig. 1). As before, for patients 70 years and older it is unclear whether there is a survival advantage because of the low numbers of patients in this age range recruited to clinical trials and corresponding large confidence intervals for these patients. For patients in monochemotherapy trials only 8% (309 of 3994) were >70 years old and for patients in the polychemotherapy trials only 4% (1,224/28,764) were >70 years old. Thus for this meta-analysis the patients were stratified into women <50, 50–69, and the women 70 and older were excluded from most of the other analyses.

Figure 2 shows the outcome (in terms of recurrence and breast cancer mortality) for patients who participated in adjuvant trials of chemotherapy versus no chemotherapy. Most of these women had received CMF-based therapies, but about one third had received anthracycline-based therapy. There was no apparent advantage of anthracycline based therapy over CMF-based therapy in these trials comparing chemotherapy versus no chemotherapy. These curves in this figure show that:

- For both women <50 and from 50–69 years of age adjuvant chemotherapy results in long-term benefit.
- Adjuvant chemotherapy seemed somewhat more effective in younger women.
- Breast cancer-related relapses and breast cancer mortality occur over periods considerably longer that 5 years.

What a close examination of this figure (Fig. 2) suggests but is difficult to see in this format, is the time course for the effects of adjuvant chemotherapy. Using data from the EBCCTG meta-analysis the effect of adjuvant chemotherapy over time can be plotted and this is shown in Figure 3.

Note that for women <50 years of age that there is a major proportional risk reduction (PRR, the proportion of negative events, in this case recurrences, that are prevented by the therapy) in the first 2 years. This reduction is sustained throughout the first 10 years and perhaps longer. This results in the proportional risk reduction seen in the first 2 years (48% in this case) being similar to the cumulative reduction over 15 years (37%).

This is in marked contrast to the time course of the PRR in women 50-69 years of age, where there is only significant PRR in the first 2 years, and little of no effect thereafter. As a result the PRR in the first 2 years (36%) is much higher than the cumulative PRR (19%).

These observations have both practical and theoretical implications. The practical implication is that adjuvant chemotherapy trials that report their results at only 2–3 years of follow-up may report estimates of the PRR (which is the mathematical inverse of the better known hazard ratio [HR]) that will make the therapy look more favorable than that seen when the trial is more mature.

The probable explanation of why this effect is so much more prominent in older women than in younger women is that chemotherapy causes both endocrine (early menopause) and cytotoxic effects, while in older women it will only cause

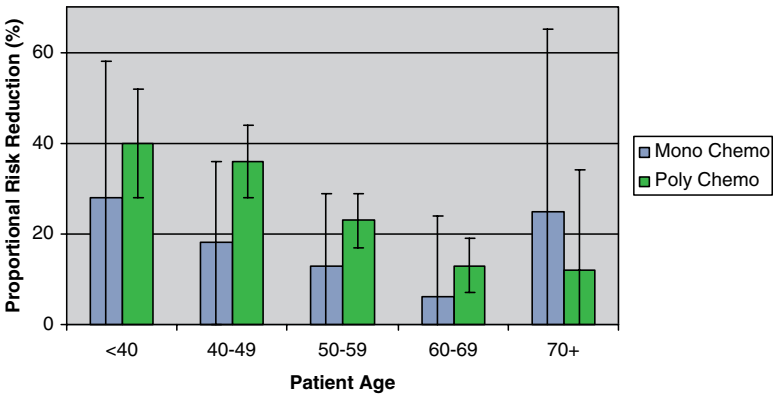

Figure 1. The effect of age and chemotherapy class (monotherapy vs poly chemotherapy on the effectiveness of adjuvant chemotherapy.

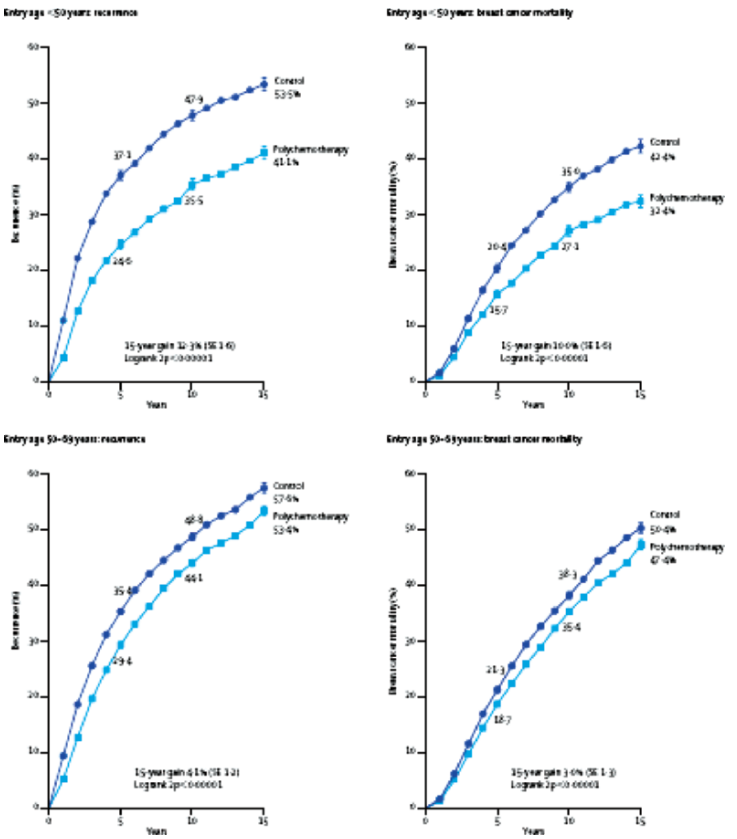

Figure 2. The time course of relapse and breast cancer related mortality for women <50 and 50–69 years of age (with permission from Lancet …….)

cytotoxic effects. Because the endocrine effects in younger women are usually long term the effects of chemotherapy will appear to be sustained.

In a clinical sense these observations are also important because they suggest that there is set of events (beyond 2 years of follow-up) that the cytotoxic aspects of chemotherapy do not affect. These later events are one of the problem areas for adjuvant therapy where other modalities (endocrine therapy) and new strategies (targeted therapies) may provide significant contributions.

Subset Analyses

Subset analysis were done by classical nodal staging and within node negative patients by tumor size. Staging did not appear to affect the relative efficacy of polychemotherapy either in younger of older patients as measured in terms of proportional risk reductions or hazard ratios. This is an important observation because it suggests that the overall estimates of efficacy can be applied to patients with Stage 1 disease and although they are often based on trials done in patients with more advanced disease.

Effectiveness by ER status in chemotherapy vs nil trials

	Recurrence		Breast cancer mortality	
ER Status	PRR	2se	PRR	2se
<50 Years Old				
ER poor	39 %	14 %	32 %	16 %
ER positive	44 %	14 %	31 %	20 %
50–69 Years Old				
ER poor	33%	14 %	26 %	16 %
ER positive	16 %	14 %	5 %	26 %

Another important subset analysis similar in younger and older patients is that chemotherapy appeared as effective in both patients who did, and who did not receive tamoxifen. The implication of this finding is that the effects of chemotherapy seem independent of endocrine therapy use and therefore can basically be added to estimates of the effectiveness of tamoxifen.

Some other subset analyses are of interest. One is that for patients aged 50 years and older there was a suggestion that adjuvant chemotherapy might be more effective in ER negative patients (although this effect did not reach formal statistical significance).

Improving Chemotherapy With Anthracyclines As Viewed in the Meta-Analysis

Part of the meta-analysis was an analysis of randomized trials that compared anthracycline- based regimens to CMF-like regimens. This analysis found anthracycline based regimens in direct comparison with CMF were on average were modestly better with a PRR of 11% (2se 6%) for recurrence and a PRR of 16% (2se 6%) for breast cancer related mortality.

It is important to note that there was obvious heterogeneity between trial types with the more complex three-agent, anthracycline-based regimens (i.e., FAC, FAC)

being superior to CMF while the two-agent, anthracycline- based regimens seemed less effective. Ideally the meta-analysis would have concentrated its subset analysis on the more complex regimens but the subset analysis included both the more and less effective anthracycline-based regimens.

	Recurrence		Breast cancer mortality	
Regimen	PRR	2se	PRR	2se
FAC vs CMF	17 %	14 %	25 %	16 %
FEC vs CMF	19 %	12 %	26 %	12 %
A + Other	6 %	10 %	9 %	10 %
E +/− Other	3 %	16 %	7 %	20 %

	Recurrence		Breast cancer mortality	
Age	PRR	2se	PRR	2se
< 50	10 %	8 %	16 %	8 %
50–69	13 %	10 %	16 %	12 %
70 +	–	–	–	–

*Too few cases for a meaningful analysis

One of the more interesting aspects of the subset analysis is that it appears that there was not a difference by age in the additional relative efficacy of anthracyclines. This result of a lack of additional efficacy in younger patients at first seems surprising, but a possible explanation is that the additional efficacy of chemotherapy in the younger patients receiving chemotherapy versus no chemotherapy trials was due to the additional endocrine effects only occurring in the chemotherapy treated patients. Because in the anthracycline- based chemotherapy versus CMF-based trials both groups had about the same degree of induced menopause, the additional benefit of anthracyclines would have to depend on direct cytotoxic not endocrine effects and would not appear to be dependent on age. This hypothesis seems born out in that even through two-thirds of the patients in these trials were <50 years of age, the benefit of chemotherapy was only evident in the first 2 years after diagnosis and there was no statistically significant benefit thereafter (see Fig. 4).

Chemotherapy Issues Not Addressed by Meta-Analysis

Because the most recently published meta-analysis only includes trials that had opened prior to 1995, there was little data available of adjuvant taxanes and questions addressing taxane use were not included in the analyses. Although interesting recent work has suggested that Her2 expression or amplification, and perhaps measures of topoisomerase are predictive of anthracycline responsiveness in adjuvant therapy, this information was analyzed as part of the meta-analysis.

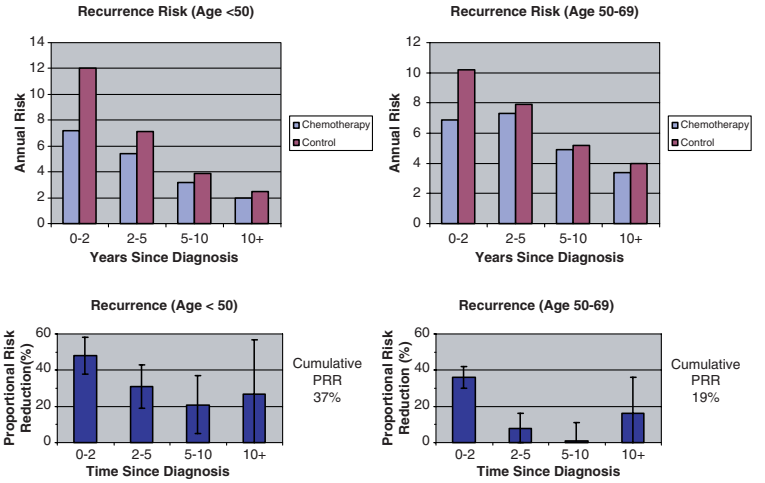

Figure 3. For women participating in chemotherapy clinical trials. Top; annual recurrence risk by time period. Bottom; proportional risk reduction by time period.

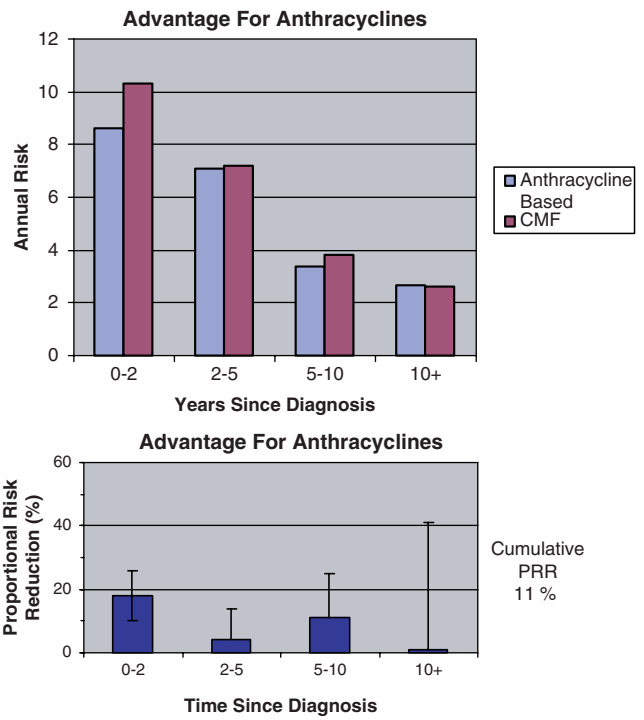

Figure 4. For women participating in trials comparing anthracycline based regimens to CMF. Top; annual recurrence risk by time period. Bottom; proportional risk reduction by time period.

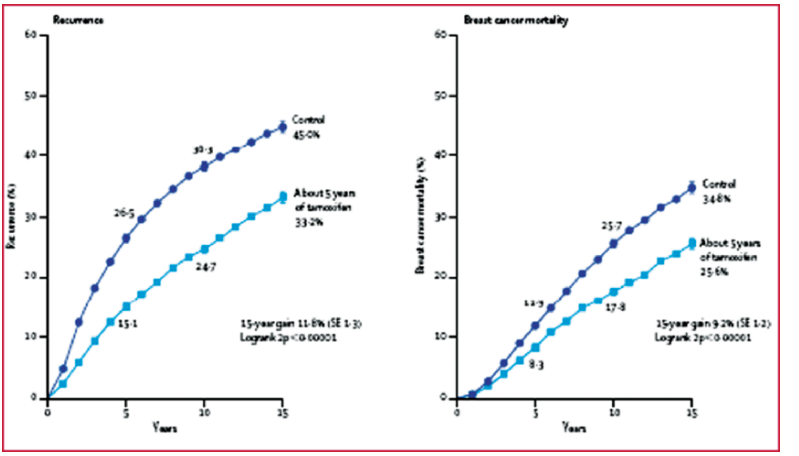

Figure 5. The time course of relapse and breast cancer related mortality in trials of ~5 years of tamoxifen for women with ER-positive (or ER-unknown) disease. (with permission from Lancet …….)

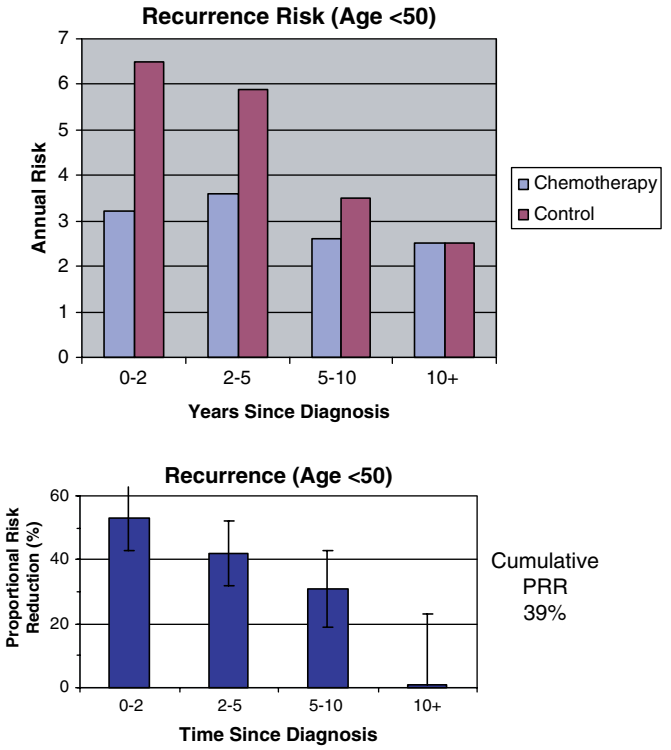

Figure 6. For women with ER positive or unknown disease participating in tamoxifen clinical trials. Top; annual recurrence risk by time period. Bottom; proportional risk reduction by time period. (with permission from Lancet …….)

Tamoxifen and the Overview

The EBCCTG meta-analyses has previously shown the superiority of 5 years of tamoxifen to shorter durations, and this result is again demonstrated. Again the meta-analysis showed that the benefit of 5 years of adjuvant tamoxifen was only evident in patients with ER positive or ER unknown tumors. An analysis showed no statistically significant difference in the effectiveness of adjuvant tamoxifen by age so unlike the analysis for chemotherapy versus nil, there is no stratification by age. Figure 5 shows the results of 5 years versus no tamoxifen. Again it shows the protracted period of recurrence and breast cancer related death.

An analysis by time period of follow-up is shown in Figure 6. An interesting feature of this figure is that it shows the effectiveness through the first 5 years of follow-up, but also a "carry-over" effect into years 5–10, and a suggestion of no additional effectiveness beyond year 10.

Subset analyses were done to determine if patient subsets could be identified that particularly benefited from tamoxifen. Nodal status was not a predictor of benefit, nor was tumor size in node -negative patients. The additional benefit of adjuvant tamoxifen was seen irrespective of another modality of therapy (chemotherapy). Thus the effectiveness of adjuvant tamoxifen was essentially additive with the effectiveness of adjuvant chemotherapy.

The level of ER positivity appeared to confer a difference in benefit. In patients with strongly ER-positive tumors(++), the PRR was 49% (2se 8%) while for patients who were positive, but not strongly positive (+) the PRR was 36% (2se 12%). For ER positive patients, the expression of the progesterone receptor did not make a difference in terms of PRR for tamoxifen.

Trastuzumab and the Overview

The most recently published EBCCTG only includes information from trials initiated by 1995 so there is no information about the impact of trastuzumab in the adjuvant setting. Because the trastuzumab adjuvant trials only started in ~2000 and have very short follow-up, the next EBCCTG meta-analysis (publication 2008?) will probably not include any information about trastuzumab. Never the less the current meta-analysis has important implications for the interpretation of trastuzumab trials, because it shows the potential impact of adjuvant therapy on both early and late events. This can have a major effect on the apparent value of an adjuvant therapy.

At this time the major trastuzumab trials have been reported with very short median follow-ups (< 3 years) and as a result, the magnitude of the long term benefit of these therapies, while it is almost certainly to be positive, is still very uncertain.

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5. ADJUVANT HORMONAL THERAPY FOR EARLY-STAGE BREAST CANCER

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INTRODUCTION

Adjuvant hormonal therapy is standard treatment for all patients with hormone receptor-positive early stage breast cancer following primary surgery. Hormonal therapy benefits patients whose breast cancer expresses estrogen or progesterone receptors, but not those with hormone receptor-negative disease.[1] The goal of adjuvant hormonal therapy is to prevent breast cancer cells from receiving endogenous estrogen stimulation. There are multiple options for adjuvant hormonal therapy in early-stage breast cancer patients.

Beatson first observed the role of estrogen deprivation in treatment of breast cancer over 100 years ago after observing the regression of advanced breast cancer following oophorectomy.[2] After Beatson's historic observation, ovarian ablation by either oophorectomy or irradiation became standard for patients with advanced breast cancer. Ovarian ablation has gradually been replaced by pharmacologic hormone therapy. Selective estrogen receptor modulators such as tamoxifen block the action of estrogen at the estrogen receptor. Luteinizing hormone-releasing hormone agonists act centrally to suppress estrogen synthesis, and aromatase inhibitors prevent the peripheral conversion of androgens to estrogen leading to estrogen deprivation. Recommendations for adjuvant hormonal therapy for pre- and postmenopausal early-stage breast cancer patients will be discussed in this chapter.

POSTMENOPAUSAL WOMEN

Selective Estrogen Receptor Modulators

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) that is currently FDA-approved for the treatment of all stages of hormone-responsive breast cancer and for the prevention of breast cancer in high-risk women. Tamoxifen has been demonstrated to inhibit breast cancer cell growth by competitive antagonism of estrogen at the estrogen receptor (ER). The Early Breast Cancer Trialists Collaborative Group (EBCTCG) is an international group that meets every five years to assess the results of systemic adjuvant therapies on breast cancer recurrence and survival.[1] The most recently published EBCTCG overview in 2000 analyzed the 10-year and 15-year effects of 5 years of adjuvant tamoxifen.[3] Long-term follow-up is particularly important for ER-positive breast cancer since disease recurrence may occur many years after initial diagnosis.

Among all women with ER-positive breast cancer, 5 years of adjuvant tamoxifen resulted in a 41% relative risk reduction of recurrence and 34% relative risk reduction of death. This corresponded to an absolute risk reduction of recurrence at 15 years of 12% (33% vs. 45%) and 9% absolute risk reduction of mortality (26% vs. 35%). The effect on recurrence was primarily seen during the first five years of follow-up, while patients were usually taking tamoxifen. However, the effect on breast cancer mortality was primarily seen after the completion of 5 years of adjuvant tamoxifen, and continued to increase over the 15 years of follow-up[3] (Table 1).

The benefit of tamoxifen in women was independent of the use of chemotherapy. In women of all ages, the absolute risk reduction of recurrence for the addition of tamoxifen to chemotherapy was 10.6% (17.5% vs. 28.1%). The absolute risk reduction of recurrence for the addition of tamoxifen to chemotherapy was slightly greater in women over 50 years of age at 12.3% (14.7% vs. 27%) compared to chemotherapy alone. The risk reductions seen in trials of tamoxifen at 20 mg/day appeared similar to the risk reduction seen in trials of higher doses, and consequently, the 20 mg/day dose has become standard in the United States. Adjuvant tamoxifen reduced the annual relative risk of developing contralateral breast cancer by 39% in the 2000 EBCTCG overview[3] (Table 1).

Table 1. Improvement in disease free and overall survival with 5 years of adjuvant tamoxifen: summary results from Early Breast Cancer Trialists Collaborative Group 2000 overview**

	Disease free survival*		15-Year overall survival	
	Tamoxifen	Placebo	Tamoxifen	Placebo
Overall population	66.8%	55.0%	74.4%	65.2%
Women over age 50	85.3%	73.0%	–	–
Women under age 50	84.3%	74.5%	–	–

*15-year disease free survival (DFS) reported for overall population; 5-year DFS reported for women over age 50 and women under age 50.
**Dashes indicate not applicable.

There have been multiple trials investigating the optimal treatment duration of adjuvant tamoxifen. Based upon lower risk of recurrence and improved overall survival demonstrated in trials comparing 2 vs. 5 years of tamoxifen, 5 years has become standard of care.[4–7] Three trials have compared five years of adjuvant tamoxifen to extended treatment duration. In both the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial and the Scottish Adjuvant Tamoxifen trial, there was no additional benefit in continuing tamoxifen beyond five years. In the NSABP study, there was actually a slight advantage in progression-free survival to patients who discontinued the tamoxifen. In both studies the incidence of endometrial cancer increased with extended tamoxifen therapy.[8,9] In contrast to the NSABP and Scottish trials, the Eastern Cooperative Oncology Group (ECOG) trial studying indefinite tamoxifen therapy was limited to lymph node-positive patients. Although this trial did not show a statistically significant improvement in outcome, there was a trend towards improvement in disease-free survival (85% vs. 73%) with extended treatment with tamoxifen.[10] The adjuvant Tamoxifen Treatment – offer more? (ATTOM) and Adjuvant Tamoxifen – Longer against Shorter (ATLAS) trials are also examining the use of longer durations of tamoxifen. Until there is longer follow-up and until the results from other trials are available, 5 years of tamoxifen will remain the standard.

Adjuvant tamoxifen therapy is typically begun after the completion of systemic chemotherapy and radiation treatment. Preclinical evidence has suggested that radiosensitivity may be reduced by concurrent administration of tamoxifen.[11] Tamoxifen has also been associated with increased risk of radiotherapy-related pulmonary fibrosis.[12,13] Several retrospective studies have been published to compare outcomes when radiation treatment is given concurrently or sequentially with tamoxifen. No significant differences were seen in recurrence or survival in these studies.[14–16] In the absence of a randomized trial comparing sequential and concurrent tamoxifen, sequencing of tamoxifen and radiation treatment remains standard of care, although it is reasonable to give concurrent radiation and tamoxifen in patients with very high risk disease.

Tamoxifen has anti-estrogenic effects on some tissues including the breast and has partial estrogenic effects elsewhere in the body. This complex mechanism of action results in side effects of treatment which are both beneficial and detrimental. In postmenopausal women treated with tamoxifen, clinical studies have shown an increase in trabecular bone density and a trend towards decreased loss of cortical bone density.[17,18] The NSABP P-1 chemoprevention trial demonstrated fewer osteoporotic fracture events in women who received 5 years of tamoxifen compared to placebo, however the results did not reach statistical significance. This reduction is mainly limited to postmenopausal women.[19]

Tamoxifen has been shown to have beneficial effects on the lipid profile. In adjuvant breast cancer trials, tamoxifen significantly lowers total cholesterol, mainly due to its effect on low-density lipoprotein (LDL) cholesterol.[20] Tamoxifen also lowers fibrinogen, lipoprotein(a), and homocysteine, all factors that contribute to

cardiovascular risk.[21–23] However, until recently, no trial had demonstrated a reduction in cardiac events in patients taking tamoxifen. Extended follow-up of the Swedish tamoxifen adjuvant trial demonstrated reduced mortality from coronary heart disease in patients receiving 5 years of adjuvant tamoxifen, compared to those receiving 2 years of treatment.[24]

Tamoxifen has been associated with an increased incidence of endometrial carcinoma in both treatment and prevention of breast cancer.[1,19] The relative risk of endometrial cancer in the tamoxifen-treated women from the NSABP P-1 prevention trial was 2.5. The increased risk was predominantly seen in women over the age of 50 in whom the relative risk was 4. All the endometrial cancers seen in the tamoxifen-treated women were International Federation of Gynecology and Obstetrics (FIGO) stage I. The tumors were of good prognosis, and none of the women treated with tamoxifen died from endometrial cancer. There was also an increased incidence of deep venous thrombosis in the tamoxifen-treated women in the NSABP P-1 trial. The relative risk of pulmonary embolism in the tamoxifen group was 3.0.[19]

Aromatase Inhibitors

Background

In postmenopausal women, peripheral aromatization of androgens to estrogens is the major source of plasma estrogen. Aromatase inhibitors (AIs) inhibit this reaction and consequently suppress the production of circulating estrogen in postmenopausal women. Therefore, AIs present an alternative to tamoxifen for antagonizing estrogenic effects on the breast. In contrast to tamoxifen, AIs do not have partial agonist activity, leading to a different side-effect profile. Third-generation AIs, including anastrozole (Arimidex; AstraZeneca, Wilmington, DE), letrozole (Femara; Novartis, East Hanover, NJ), and exemestane (Aromasin; Pfizer, New York, NY), were initially used in postmenopausal patients with ER-positive metastatic breast cancer, and multiple randomized trials have been performed to assess the role of AIs in the adjuvant setting. Based upon the results of these trials, AIs have been increasingly used as adjuvant therapy, either as initial therapy or after tamoxifen, in postmenopausal patients with early stage breast cancer.[25]

Initial Therapy

There have been two randomized trials comparing initial adjuvant therapy with tamoxifen to an aromatase inhibitor. The ATAC (Arimidex, Tamoxifen Alone or in Combination) trial randomized 9,366 postmenopausal early-stage breast cancer patients to 5 years or tamoxifen, 5 years of anastrozole, or 5 years of the combination of tamoxifen and anastrozole. The combination of tamoxifen and anastrozole did not improve outcome compared to tamoxifen at a follow-up of 3 years, and we await further results from the combination arm.[26] After a median follow-up of 68 months, anastrozole significantly improved disease-free survival (DFS), time to

recurrence (TTR), and incidence of contralateral breast cancer compared to the tamoxifen. There were significantly fewer disease recurrences in the anastrozole arm compared to tamoxifen (575 vs. 651 events, hazard ratio (HR) 0.87, 95% CI 0.78 to 0.97, $p = 0.01$). There is to date no difference in overall survival (OS) between anastrozole and tamoxifen (HR 0.97, $p = 0.7$)[27,28] (Table 2).

The Breast International Group (BIG) 1–98 study randomized 8,010 postmenopausal early-stage breast cancer patients to 5 years of letrozole or tamoxifen, 2 years of letrozole followed by tamoxifen or 2 years of tamoxifen followed by letrozole. An early analysis was performed after a median follow-up of 26 months looking at the outcome for patients in the primary core. The primary core includes patients randomized to five years of tamoxifen combined with patients randomized to receive tamoxifen for 2 years followed by letrozole, compared to patients randomized to five years of letrozole combined with patients randomized to receive letrozole for 2 years followed by tamoxifen. The primary core analysis, therefore, includes all 8,000 patients randomized on the trial. Event-free survival (EFS) was significantly improved in the letrozole group compared to tamoxifen (351 vs. 428 events, HR 0.81, 95% CI 0.70 to 0.93, $p = 0.001$). The 5-years DFS estimates were 84.0 percent vs. 81.4% respectively.[29] Longer follow-up is needed before results of the sequential arms are available (Table 2).

Sequential Therapy with Aromatase Inhibitors after Tamoxifen

There have been several randomized trials comparing tamoxifen alone to tamoxifen followed by an aromatase inhibitor. The MA-17 trial randomized 5,187 postmenopausal women following the completion of 5 years of adjuvant tamoxifen to either 5 years of letrozole or placebo. The study was terminated early after a preplanned interim analysis was performed at a median follow-up of 2.4 years. Four-year DFS was significantly improved by letrozole after completion of adjuvant tamoxifen (94 vs. 90%, HR 0.58, 95% CI 0.43 to 0.84, $p = 0.002$). There was no difference in overall survival between the two arms (95% in each arm). A planned subgroup analysis of lymph node-positive patients (1175 women) did demonstrate an improvement in overall survival for the letrozole arm (HR 0.61,

Table 2. Trials of aromatase inhibitors vs. tamoxifen as initial adjuvant therapy for postmenopausal early-stage breast cancer patients

Trial	Drugs	No. of subjects	Disease free survival[†]	Hazard ratio (95% CI)[‡]
ATAC[*]	Anastrozole	3125	81.6%	0.87 (0.78, 0.97)
	Tamoxifen	3166	79.4%	$p = 0.01$
BIG 1–98[**]	Letrozole	4003	84.0%	0.81 (0.70, 0.93)
	Tamoxifen	4007	81.4%	$p = 0.001$

[*]ATAC = Arimidex, Tamoxifen Alone or in Combination
[**]BIG 1–98 = Breast International Group (BIG) 1–98
[†]Median follow-up of 68 months in ATAC trial; estimated 5-year DFS reported after median follow-up of 25 months in BIG 1–98 trial.
[‡]95% CI = 95% confidence interval

95% CI 0.38 to 0.98, $p = 0.04$).[30,31] Because the MA-17 trial was stopped early, the optimal duration of letrozole therapy after 5 years of adjuvant tamoxifen is unknown. An exploratory analysis examining hazard ratios associated with different durations of letrozole suggests that longer durations of letrozole are associated with improved outcomes, at least up to 4 years of treatment.[32] An extension of the MA-17 trial is being performed in which women who received 5 years of letrozole are randomized to five additional years vs. placebo (Table 3).

Several trials have studied switching to an aromatase inhibitor after two to three years of tamoxifen. The Intergroup Exemestane Study (IES) randomized 4,742 postmenopausal women to 2 to 3 years of tamoxifen followed by exemestane or continued tamoxifen to complete five years.[33] An updated analysis was reported at the 2006 American Society of Clinical Oncology (ASCO) with a median follow-up of 58 months. There was a 24 percent improvement in DFS by switching to exemestane (354 vs. 454 events, HR 0.76, 95% CI 0.66 to 0.88, $p = 0.0001$). There was a trend towards improvement in overall survival in women who switched to exemestane (HR 0.85, $p = 0.08$), which was significant in patients with ER-positive or ER-unknown cancers ($p = 0.05$).[34]

Three trials have studied switching to anastrozole versus continuing tamoxifen, demonstrating similar improvements in outcome. A combined analysis was performed of two studies, the German Adjuvant Breast Cancer Group (ARNO 95) trial and the Austrian Breast and Colorectal Study Group (ABCSG trial 8). A total of 3,224 postmenopausal women with early-stage breast cancer were randomized after 2 years of tamoxifen to either anastrozole or continuation of tamoxifen for a total of 5 years of therapy. Women in the combined analysis were not randomized until completion of 2 years of tamoxifen, compared to the IES study in which women were randomized between switching to an AI versus continuation of tamoxifen at the beginning of tamoxifen therapy. At a median follow-up of 28 months, there was a significantly decreased risk of recurrence in the anastrozole arm (67 vs. 110 events,

Table 3. Trials of sequencing aromatase inhibitors after tamoxifen as adjuvant therapy for postmenopausal early-stage breast cancer patients

Trial	Drugs	No. of subjects	Disease free survival†	Hazard ratio (95% CI)‡
MA-17	Tam × 5 years →			
	Letrozole	2593	94.4%	0.58 (0.45, 0.76)
	Placebo	2594	89.8%	p < 0.001
IES*	Tam × 2–3 years →			
	Exemestane	2362	85.0%	0.76 (0.66, 0.88)
	Tamoxifen	2380	80.9%	p = 0.0001
ARNO95/	Tam × 2 years →			
	Anastrozole	1618	95.9%	0.60 (0.44, 0.81)
ABCSG**	Tamoxifen	1606	93.2%	p = 0.0009

*IES = Intergroup Exemestane Study
**ARNO95 = German Adjuvant Breast Cancer Group trial; ABCSG = Austrian Breast and Colorectal Study Group trial 8.
† 4-year disease-free survival (DFS) in MA-17 with median follow-up of 30 months; DFS in IES study reported after median follow-up of 58 months; DFS in ARNO95/ABCSG trial reported after median follow-up of 28 months.
‡ 95% CI = 95% confidence interval

HR 0.60, 95% CI 0.44 to 0.81, $p = 0.0009$).[35,36] The primary endpoints of breast cancer events were defined differently in the combined analysis and IES. In addition to locoregional and distant relapse which were included as events in the combined analysis, IES also included contralateral breast cancer or intercurrent death as breast cancer events.[34] Differences in the time of randomization and the definition of breast cancer events may account for the differences in risk reduction seen between IES and the combined analysis (HR 0.76 vs. 0.60, respectively).

Prior to the study of aromatase inhibitors in the adjuvant treatment of postmenopausal women with early-stage breast cancer, 5 years of tamoxifen was the standard of care. Based upon the results of multiple clinical trials demonstrating improved DFS, aromatase inhibitors are recommended in the ASCO guidelines as part of the adjuvant treatment of postmenopausal early-stage breast cancer. The optimal duration of therapy with AIs remains unanswered. It is also unclear whether AIs should be used initially or in sequence with tamoxifen. Two groups have used decision model analysis to assess the optimal adjuvant hormonal therapy; however results from these two studies were conflicting.[37,38] Until results from ongoing clinical trials are available, the optimal timing and duration of AIs will remain unresolved.

Side effect profile

Aromatase inhibitors have been well-tolerated in clinical trials and have a different side effect profile than tamoxifen due to their lack of partial estrogenic activity. The most common side effects seen are hot flashes, musculoskeletal pain, vaginal dryness, and headache. In contrast to tamoxifen, AIs have not been associated with an increased risk of endometrial cancer or thromboembolic disease. However, the profound suppression of estrogen levels by AIs has lead to increased incidence of bone fractures and osteoporosis. In the ATAC and BIG 1–98 trials, changes in bone mineral density (BMD) and incidence of bone fractures were reported. In the ATAC trial, the overall incidence of fractures was greater with anastrozole compared to tamoxifen (11% vs. 7.7%; $p < 0.001$).[27] A bone substudy of the ATAC trial was performed to assess changes in BMD. Anastrozole resulted in a decrease in lumber spine (LS) BMD at 1 and 2 years (-2.6%, -4.0%) and a decrease in hip BMD after 1 and 2 years (-1.7%, -3.2%) compared to the control arm (LS -0.2%, 0.3%; hip 0%, 0.01%). As expected, tamoxifen treatment was associated with an increase in BMD after 1 and 2 years.[39] Longer follow-up in the ATAC bone substudy will help determine if the decrease in BMD stabilizes over time or if it continues throughout the course of treatment. The BIG 1–98 trial demonstrated an increase risk of fractures in the letrozole arm compared to tamoxifen (5.7% vs. 4.0%) after a median follow-up of 25.8 months.[29] Changes in BMD will be assessed over time in this trial. Of note, neither the ATAC nor BIG 1–98 trial controlled for calcium, vitamin D, or bisphosphonate use.

In the IES study, participants who switched to exemestane after 2 to 3 years of tamoxifen had a significantly greater decrease in BMD (-3.2% in LS, -2.1% hip)

compared to those who continued on tamoxifen (-0.2% LS, -0.6% hip; *p*-value for both <0.001).[40] Bone toxicities have also been evaluated in the trials of AIs after 2 to 3 years of tamoxifen. In the combined analysis of the ABCSG/ARNO 95 study performed after a median follow-up of 28 months, there were significantly more fractures in the group that switched to anastrozole compared to those who only received tamoxifen (2% vs. 1%, $p = 0.015$).[36] In the initial analysis of the MA-17 trial, participants who received letrozole following the completion of 5 years of adjuvant tamoxifen did not have a statistically significant increase in risk of fracture (3.6% vs. 2.9%, $p = 0.24$) or osteoporosis (5.8% vs. 4.5%; $p = 0.07$) compared to patients in the placebo arm.[31]

Taken together, there is clear evidence that adjuvant treatment with AIs results in a decline in bone health due to an increased risk of fracture and osteoporosis. All women who are initiated on an AI should be advised about daily calcium and vitamin D supplementation, smoking cessation, and the importance of exercise in maintaining good bone health.[41] A baseline BMD should be obtained and monitored annually or bi-annually for declines while taking an AI. Women should be initiated on bisphosphonate therapy based upon National Osteoporosis Foundation Guidelines. If their T-score is -2 or below and they have no risk factors for osteoporosis, they should begin bisphosphonates. If their T-score is 1.5 or below and they have any risk factors such as advanced age, smoking, chronic corticosteroid use, or personal history of fracture they should begin treatment with bisphosphonates.[42] The Zometa/Femara Adjuvant Synergy Trials randomized participants to treatment with zoledronic acid (4 mg IV infusion every 6 months) at the initiation of letrozole treatment versus delaying treatment until there was a decrease in T- score. These trials demonstrated that immediate treatment with zoledronic acid resulted in a mean increase in LS BMD by 2.02% compared to a mean decrease of 2.61% in the delayed group ($p < 0.001$) but to date there is no demonstrable decrease in fractures.[43] This study suggests that treatment with a bisphosphonate at the initiation of an AI may prevent a decline in bone health.

Role of progesterone receptor and HER2/neu

There is emerging evidence to suggest that ER-positive cancers that do not express PR and/or express HER2/neu are somewhat intrinsically resistant to tamoxifen. Arpino et al have demonstrated an increased relapse rate in patients with ER-positive, PR-negative cancers, compared to ER-positive, PR-positive cancers, treated with tamoxifen.[44] Patients treated with tamoxifen with ER-positive, HER2-positive metastatic breast cancers have a shorter time to treatment failure compared to ER-positive, HER2-negative cancers.[45] In fact, Arpino et al have demonstrated an increase in both HER1 and HER2 in ER-positive, PR-negative cancers, compared to ER-positive, PR-positive cancers, suggesting an interplay between the ER and epidermal growth factor pathways.[44]

Two very small trials demonstrated a significantly increased clinical response rate in patients with ER-positive, HER2-positive cancers, treated with pre-operative

aromatase inhibitors, compared to pre-operative tamoxifen.[46,47] This led to a widely accepted hypothesis that aromatase inhibitors were a better choice than tamoxifen in patients with ER-positive, HER2-positive cancers. However, an analysis of the BIG-1–98 trial demonstrates that letrozole improves outcome compared to tamoxifen in ER-positive, HER2-positive cancers (HR 0.68) and in ER-positive, HER2-negative cancers (HR 0.72). A recent sub-analysis of the ATAC trial demonstrated a significantly improved outcome in ER-positive, HER2-negative cancers (HR 0.66) but not in ER-positive, HER2-positive cancers (HR 0.92), but this may have been because of the small number of patients in the HER2-positive group.[48]

Are HER2-positive cancers somewhat resistant to not just tamoxifen, but also to aromatase inhibitors? A recent trial randomized patients with HR-positive, HER2-positive metastatic breast cancers to anastrozole alone or to anastrozole plus trastuzumab. Although there was no significant difference in overall survival, possibly because patients randomized to anastrozole alone could receive trastuzumab at disease progression, time to progression was doubled from 2.4 months in the anastrozole alone arm to 4.8 in the combined arm ($p = 0.0016$).[49] The clinical benefit rate in the combination arm was 42%, significantly higher than in the anastrozole alone arm. A trial that evaluated single agent trastuzumab as first-line therapy for patients with HER2-positive cancers demonstrated a clinical benefit rate of 48%.[50] This suggest the intriguing possibility that HR-positive, HER2-positive cancers are driven by the HER2 pathway, which renders the cancers partly resistant to hormonal therapies,

An initial evaluation of the ATAC trial using case report forms revealed that TTR was longer for anastrozole in both ER+/PR+ and ER+/PR– subgroups, but the benefit was more pronounced in the ER+/PR– subgroup (HR 0.84, 95% CI 0.69 to 1.02, vs. 0.43, 95% CI 0.31 to 0.61).[51] Importantly, the ER and PR analyses were not performed centrally. More recently, a central analysis of about 2000 patients on the ATAC trial demonstrated similar improvements with the use of anastrozole compared to tamoxifen regardless of PR-status (HR anastrozole versus tamoxifen 0.72 for ER-positive, PR-positive and 0.66 for ER-positive, PR-negative).[48] In the BIG-1–98 trial, similar benefits for letrozole compared to tamoxifen were seen in the ER+/PR+ and ER+/PR- subgroups.

Based on this data, decisions regarding whether to start a patient on tamoxifen or an aromatase inhibitor should not be made based on PR or HER2 status. Further molecular profiling, such as the Oncotype DX assay, may help in the future in making decisions regarding optimal hormonal therapies.

PREMENOPAUSAL WOMEN

The goals of adjuvant hormonal therapy are the same for both pre- and post-menopausal patients with early stage breast cancer: to prevent breast cancer cells from being stimulated by endogenous estrogen. Hormonal therapy has been shown to reduce the risk of recurrence and improve overall survival for

early-stage breast cancer patients.[3] The optimal type of hormonal therapy for premenopausal women has not been clearly established. Currently, tamoxifen is the standard hormonal therapy for premenopausal patients with HR-positive early stage breast cancer. Aromatase inhibitors should not used in premenopausal women since their use results in an increase in gonadotropin secretion due to reduced feedback of estrogen on the hypothalamus and pituitary. The increase in gonadotropin leads to increased stimulation of the ovaries, and does not significantly reduce estrogen levels.[25] AIs are often administered sequentially after tamoxifen to women who became menopausal following adjuvant chemotherapy and tamoxifen. AIs should be used with caution in this population since there is accumulating evidence that they may promote recovery of ovarian function. If AIs are given sequentially to this population, careful monitoring of ovarian function, including estradiol and gonadotropin levels, should be performed.[52]

Tamoxifen

The most recent 2000 EBCTCG overview analysis, 5 years of adjuvant tamoxifen compared to no adjuvant therapy resulted in a decreased 15-year risk of recurrence (33.2% vs. 45.0%; $p < 0.00001$) and decreased breast cancer mortality (25.6% vs. 34.8%; $p < 0.00001$). Additional analysis was performed by age group, demonstrating that the absolute risk reduction in recurrence and mortality was similar for all age groups. In women less than 50 years old, 5 years of adjuvant tamoxifen decreased risk of recurrence from 25.5 to 15.7% compared to control.[3] The benefit of adjuvant tamoxifen was also demonstrated in the International Breast Cancer Study Group Trial 13–93, in which 1,246 premenopausal, axillary node-positive women were randomized to receive anthracycline-based chemotherapy followed by either tamoxifen or observation. Tamoxifen significantly improved DFS in the ER-positive group at a median follow-up of 7 years (HR 0.59, 95% CI 0.46 to 0.75; $p < 0.0001$).[53] The trials investigating the optimal duration of adjuvant tamoxifen therapy were primarily composed of postmenopausal women. Based upon the results of these trials, 5 years of adjuvant tamoxifen is the current standard of care. The side effect profile for tamoxifen is similar in pre- and postmenopausal women. The relative risk of endometrial cancer does not appear to be significantly increased in premenopausal women taking tamoxifen. In the NSABP P-1 prevention trial, the relative risk of endometrial cancer in women under 50 was not significantly increased compared to control (1.42, 95% CI 0.55 to 3.81).[19,54]

Ovarian Function Suppression

There are multiple methods of suppressing ovarian function in premenopausal women including surgical oophorectomy, radiation-induced ovarian ablation, and luteinizing hormone releasing hormone (LHRH) agonists. The benefit of ovarian

function suppression (OFS) by surgery or radiation as adjuvant therapy for both node-positive and node-negative, premenopausal women was demonstrated by the 1995 EBCTCG overview. The 15-year overall survival was improved significantly by the addition of adjuvant OFS (52.4 vs. 46.1%, logrank 2 $p = 0.001$).[55] The 2000 EBCTCG overview investigated the effect of using LHRH agonists as OFS for women under 50 years of age. At 15 years, OFS reduced the likelihood of breast cancer recurrence by 13% (59% vs. 46%) and the likelihood of breast cancer mortality by 10% (59% vs. 49%). However, there was no additional benefit when OFS plus chemotherapy was compared to the same chemotherapy alone.[3] This could be attributed to premature ovarian failure induced by adjuvant chemotherapy, thereby limiting any additional benefit from OFS.

Several studies have specifically examined the impact of LHRH agonists in adjuvant treatment of premenopausal women. The Zoladex in Premenopausal Patients (ZIPP) trial randomized women with early stage breast cancer to tamoxifen, goserelin, the combination, or observation. Women were allowed to receive adjuvant chemotherapy. In an analysis after a median follow-up of 5.5 years of 2,710 women, those who received goserelin had a significant benefit in EFS (HR 0.80; 95% CI 0.69 to 0.92, $p = 0.002$) and overall survival (HR 0.81; 95% CI 0.67 to 0.99; $p = 0.038$). However, the absolute benefit in OS was small (87.6% vs. 84.9%), and the overall benefit was greatest in the group that had not received adjuvant chemotherapy.

Multiple trials have compared OFS alone to cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy. The Zoladex Early Breast Cancer Research Association (ZEBRA) trial randomized 1640 lymph node-positive, premenopausal women to receive either goserelin or CMF chemotherapy as adjuvant treatment. After a median follow-up of 6 years, there was no difference in DFS for ER-positive women (74% of study participants) between goserelin and CMF (HR 1.01; 95% CI 0.84 to 1.20).[56] After 7.3 years of follow-up, there was no significant difference in either DFS or OS.[57] Quality of life analysis was also performed, indicating that goserelin offered improved quality of life during the first 6 months compared to CMF. There were no significant differences in quality of life at one, two, or three years.[58] Similar results were obtained in the IBCSG trial VIII, in which 1,063 pre- or perimenopausal women with node-negative breast cancer were randomized to 2 years of goserelin, 6 cycles of CMF, or CMF followed by 18 months of goserelin. After a median follow-up of 7 years, there were no significant differences in 5-year DFS for women with ER-positive breast cancer.[59]

Further trials with larger numbers of patients are required to assess the benefit of OFS, particularly when added to adjuvant systemic chemotherapy. OFS appears to be as effective as adjuvant CMF in premenopausal ER-positive patients. However, these trials were not adequately powered to demonstrate equivalency and did not include newer chemotherapy regimens incorporating taxanes and trastuzumab. It is also unclear if there is any additional benefit with OFS in women who become postmenopausal during adjuvant chemotherapy. Current treatment guidelines rec-

ommend that premenopausal women with ER-positive, early-stage breast cancer receive 5 years of adjuvant tamoxifen. If tamoxifen is contraindicated, then OFS is an acceptable alternative. Recommendations of the International Consensus Panel on the Treatment of Primary Breast Cancer differ slightly from the National Comprehensive Cancer Network (NCCN) for women less than 35 years of age with intermediate or high-risk breast cancer where they recommend the combination of tamoxifen and OFS.[60,61]

There are several ongoing trials investigating the role of OFS in adjuvant treatment of premenopausal, early-stage breast cancer patients. The Suppression of Ovarian Function Trial (SOFT) is randomizing women who are premenopausal after the completion of chemotherapy to tamoxifen alone for 5 years, OFS plus tamoxifen for 5 years, or OFS plus exemestane for 5 years. Women in the Tamoxifen and Exemestane Trial (TEXT) will receive the LHRH agonist triptorelin at the beginning of adjuvant treatment, including with adjuvant chemotherapy. They will be randomized to receive either tamoxifen or exemestane in combination with triptorelin for 5 years. The Premenopausal Endocrine Responsive Chemotherapy trial (PERCHE, IBCSG 26-02, BIG 4-02) is assessing the benefit of adding chemotherapy to optimal hormonal therapy. All study participants will receive OFS with either tamoxifen or exemestane, and will be randomized to either chemotherapy or no additional treatment. In addition to better defining the benefit of OFS in the setting of adjuvant chemotherapy, these studies will also define the role of aromatase inhibitors in the treatment of premenopausal women with early-stage breast cancer.

MALE BREAST CANCER

In male breast cancer patients, approximately 90% express ER and over 80% express PR.[62,63] Clinical trials to assess treatments of early-stage, male breast cancer patients, have been difficult to perform due to its low incidence. Therefore, treatment recommendations typically are the same for male and female breast cancer patients. Five years of adjuvant tamoxifen is recommended for ER-positive male breast cancer patients following mastectomy. A retrospective analysis of 39 men who were treated with 1 to 2 years of adjuvant tamoxifen, demonstrated significantly improved actuarial DFS (56% vs. 28%, $p = 0.005$) and OS (61% vs. 44%, p=0.006) compared to historical controls.[64] Tamoxifen might not be tolerated as well by men compared to women. In one analysis of side-effects among 24 male breast cancer patients, tamoxifen was associated with decreased libido (29.2%), weight gain (25%), hot flashes (20.8%), and depression (16.6%). Nearly 21% of male breast cancer patients had discontinued tamoxifen in less than 1 year due to side effects, significantly higher than for women (65). There is currently insufficient data to support the role of aromatase inhibitors in the treatment of male breast cancer patients. There is data to suggest that AIs may not suppress estrogen levels in males as low as in women, and therefore, 5 years of adjuvant tamoxifen remains standard of care for early-stage male breast cancer patients.[66]

CONCLUSIONS

Adjuvant hormonal therapy has improved disease-free survival and overall survival of patients with hormone receptor-positive early stage breast cancer. For many years, tamoxifen was the standard of care for all patients, and has remained standard treatment for premenopausal women and men with early stage breast cancer. Recent studies of aromatase inhibitors in the adjuvant treatment of postmenopausal women, have demonstrated improved disease-free survival compared to tamoxifen alone or in sequence with tamoxifen. Longer follow-up is needed from ongoing clinical trials to determine the optimal timing and duration of therapy with aromatase inhibitors. Aromatase inhibitors are currently not recommended for treatment of premenopausal women, however, there are several ongoing trials investigating a possible role of aromatase inhibitors in combination with ovarian function suppression. Adjuvant hormonal therapy will continue to evolve with the goal of improving outcomes for early-stage breast cancer patients.

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6. SURGICAL ISSUES AND PREOPERATIVE SYSTEMIC THERAPY

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INTRODUCTION

Neoadjuvant (preoperative) chemotherapy was initially developed as a treatment strategy for patients presenting with locally advanced breast cancer, as a means of improving resectability and locoregional control. This treatment sequence has now become standard, conventional practice for patients with bulky cancers of the breast and axillae. Two important advantages identified from this experience have resulted in extension of the neoadjuvant therapy approach to include early-stage breast cancer patients as potential candidates:

(i) primary disease downstaging, thereby increasing lumpectomy eligibility
(ii) earlier assessment of chemosensitivity versus identification of patients with resistant disease, thereby providing opportunities to individualize therapy

Furthermore, several studies have documented the finding that response in the breast correlates with survival, thereby demonstrating that primary tumor downstaging is an excellent surrogate marker for systemic therapy effectiveness. Many breast cancer patients will benefit from systemic therapy to control occult micrometastases in distant organs. As insights broaden regarding the heterogeneity of tumor biology, and as we learn more about treatment toxicity, it has become abundantly clear that expansion of the systemic therapy armamentarium is warranted. Assessment of novel therapies in the prospective adjuvant randomized clinical trial setting typically requires several thousand patient-years of follow-up, and these studies are extremely costly. Ability to evaluate new regimens in the neoadjuvant setting offers the promise of determining chemoeffectiveness within a few

months, by using pathologic extent of tumor response from surgery as a surrogate for results achieved in distant organs.

Neoadjuvant chemotherapy has therefore become an advantageous treatment sequence for many reasons, and may be considered for application in any breast cancer case where the multidisciplinary oncology team is confident that chemotherapy is a necessary component of the patient's comprehensive therapy. The decision to proceed with neoadjuvant chemotherapy is accompanied by several special considerations that must be handled by the surgeon, and these considerations involve the pre-treatment/diagnostic phase as well as local and regional management.

PRETREATMENT/DIAGNOSTIC AND IMAGING CONSIDERATIONS

Type of Biopsy

Percutaneous needle biopsy is the preferred diagnostic maneuver in the effort to optimize the pool of patients that may benefit from neoadjuvant therapy. The surgical scarring and postoperative changes associated with open, excisional biopsies will distort, and frequently eliminate the patient's "measureable disease," thereby negating the ability to monitor chemosensitivity.

Percutaneous core needle biopsy is therefore the preferred diagnostic procedure in breast cancer patients that are candidates for neoadjuvant systemic therapy. This biopsy may be performed freehand or with image guidance. The freehand core needle biopsy is a quick and efficient strategy for evaluation of large, easily palpable tumors. A negative/benign pathology report in the setting of a clinically-suspicious lesion (especially if accompanied by malignant breast imaging correlates) should be considered discordant, and followed-up by an image-guided or open surgical incisional biopsy for more definitive histopathology. Image guidance (via stereotactic mammography or ultrasound-guided) will maximize diagnostic accuracy, and this approach is mandatory for poorly-defined and/or non-palpable primary breast lesions. Regardless of whether the core needle biopsy is performed as a freehand or image-guided procedure, it is essential that multiple cores are taken, to insure that the clinically-detected lesion is primarily invasive. Patients with palpable ductal carcinoma in situ (DCIS), or extensive DCIS associated with microinvasion, will not require any chemotherapy in their management. Inadvertant overestimation of the disease stage for such cases and delivering neoadjuvant chemotherapy would constitute gross overtreatment.

Fine needle aspiration (FNA) biopsy will sometimes confirm the presence of cancer within a breast mass, but is associated with a significant sampling error[1] false negative rate greater than 10%). Also, FNA biopsy will not definitively demonstrate the invasive versus the in situ nature of disease, since parenchymal architecture will not be apparent on cytology smears. Lastly, even a diagnostic cytology specimen will be limited in available cancer cells for evaluation, and having adequate tissue for immunohistochemical determination of critical molecular markers such as estrogen receptor (ER), progesterone receptor (PR), and HER2/neu. Furthermore, several prominent neoadjuvant therapy investigators have begun exploring the

use of genetic profiling and microarrays to predict responsiveness to neoadjuvant therapy,[2–4] and application of this technology requires a more substantial supply of the invasive tumor.

FNA biopsy of a palpable axillary lymph node, or ultrasound-guided biopsy of a morphologically-abnormal lymph detected sonographically, can provide definitive proof of the invasive nature of the associated breast lesion. Axillary ultrasound is increasing in popularity,[5–7] however the surgeon must bear in mind that ultrasound sensitivity for detection of micrometastases smaller than 5–10 mm is quite limited. Obtaining a positive axillary FNA will clearly add to the baseline staging information, however it is nonetheless critical to obtain additional biopsy material from the primary breast lesion for documentation of marker studies, as discussed in the preceding paragraph.

A final biopsy option is the performance of a punch biopsy. Breast tumors that have obvious local extension into the skin (T4a/locally advanced tumors) are ideal candidates for this approach. Punch biopsies can also be helpful in diagnosing inflammatory breast cancer, as the finding of cancer cells in the dermal lymphatics will be supportive of T4d disease (but not essential, as this diagnosis can also be based upon purely clinical grounds). Documentation of inflammatory breast cancer can be quite important, as this high-risk disease should routinely be treated with neoadjuvant chemotherapy, modified radical mastectomy, and locoregional post-mastectomy radiation.[8] The diagnosis of inflammatory breast cancer will therefore impact on local, regional and systemic therapy decisions.

Diagnostic Imaging

Baseline bilateral mammography is essential. Particular attention should be addressed to extent of associated microcalcifications; evidence of multifocal/multicentric tumors; and presence of contralateral breast abnormalities. Ultrasound frequently adds to the strength of the baseline staging, and as noted above, axillary ultrasound can facilitate assessment of nodal status.

Diffuse, suspicious-appearing microcalcifications on mammography and multicentric tumors should be documented prior to delivery of chemotherapy, because these findings constitute contraindications to breast conservation surgery regardless of extent of clinical response to treatment.[9] Any indeterminate contralateral breast findings should be referred for prompt biopsy as opposed to short-term imaging follow-up, as changes related to chemotherapy will obscure the ability to detect possible bilateral breast cancer.

Large unicentric tumors that completely lack microcalcifications can be transformed into excellent candidates for lumpectomy after neoadjuvant chemotherapy, but they require some type of radio-opaque marker or clip to identify the tumor bed at time of surgery. Ideally, this marker should be inserted prior to initiating neoadjuvant chemotherapy, or within the first couple of cycles delivered. These clips serve as the target for a wire localization lumpectomy in cases of complete clinical response. If there is no marker in place to guide a lumpectomy, then a

mastectomy must be strongly considered in cases where the tumor completely resolves on breast imaging.

Image-guided clip insertion should also be considered for selected cases of satellite lesions that lack microcalcifications. If disease response occurs in a concentric fashion, leaving the patient with tumor markers that are within a short distance from each other, then bracketed (dual) wire localization to resect both lesions within a single lumpectomy specimen may be attempted.

LOCAL THERAPY CONSIDERATIONS

General Issues

Retrospective studies have documented the feasibility and acceptable morbidity risk of surgery in patients that have received neoadjuvant chemotherapy. Broadwater et al.[10] reported the surgical complication rates in 197 patients undergoing mastectomy and stratified the results according to whether or not chemotherapy had been delivered prior to surgery (106 cases) or after surgery (91 cases). The preoperative chemotherapy patients had surgery timed so that evidence of having transitioned through the chemotherapy nadir was apparent; WBC at least 2,500, and platelet count at least 50,000. No significant differences were observed in risk for postoperative infection, flap necrosis, or bleeding. The neoadjuvantly treated patients experienced lower rates of postoperative seroma formation, possibly as consequence of chemotherapy-related fibrosis in the chest wall soft tissues. Similarly, Danforth et al.[11] reported comparable complication rates in breast cancer patients regardless of whether they received neoadjuvant or postoperative chemotherapy.

Singletary et al.[12] conducted a landmark feasibility study of breast-conserving surgery among 143 LABC patients treated with neoadjuvant chemotherapy followed by mastectomy. Meticulous pathology review of the mastectomy specimens revealed that 23% of women became lumpectomy candidates based on resolution of skin changes, shrinkage of the primary tumor to less than 5 cm, and the presence of only unifocal residual disease.

The prospective, randomized clinical trials were therefore well-positioned to study rates of breast conservation as well as outcomes in neoadjuvant chemotherapy patients. As shown in Table 1, several clinical trials conducted internationally have demonstrated the oncologic safety of neoadjuvant chemotherapy by documenting equivalent overall survival among stage-matched breast cancer patients randomized to receive preoperative versus postoperative delivery of the same chemotherapy regimen. Furthermore, these studies have documented significantly higher breast conservation rates among women randomized to the neoadjuvant chemotherapy arms.

The most commonly cited study in the clinical trials of neoadjuvant chemotherapy is the National Surgical Adjuvant Breast Project (NSABP) B-18 trial. This was a randomized trial in 1,523 patients with operable breast cancer that compared preoperative versus postoperative administration of doxorubicin/cyclophosphamide for four cycles. The primary aim of the study was to determine whether preoperative chemotherapy will more effectively prolong disease-free survival and overall

Table 1. Prospective randomized clinical trials of neoadjuvant versus adjuvant chemotherapy

					Rate of BCS (%)		Local recurrence after BCS (%)		Overall survival at median follow up (%)	
Study	N	Stage	Regimen	Median follow up	PreOp CTX	Postop CTX	PreOp CTX	Postop CTX	PreOp CTX	Postop CTX
Institut Curie[64–66]	414	IIa-IIIa	F A C	66 m	82.0	77.0	24	18	86.0	78.0
Royal Marsden[67–69]	309	I-IIIb	Mx Mt Mth Tam	48 m	89.0	78.0	3	4	80.0	80.0
N.N. Petrov Research Institute of Oncology[70]	271	IIb-IIIa	Th M F	53 m	–	–	–	–	86.0	78.3
NSABP B-18[14–16]	1523	I-IIIa	A C	108 m	68.0	60.0	10.7	7.6	69.0	70.0
EORTC[71]	698	I-IIIa	F E C	56 m	37.0	21.0	18.1	11.9	82.0	84.0
Gazet et al.[72]	210	T1-T4 No-N2	Mth Mx Mt +gosrelin, formestane	60 m	65.0	87.3	–	–	79.0	87.0
Danforth et al.[73]	53	II	F L A C, G-CSF	108 m	42.3	40.7	–	–	88.5	77.8

survival than the same chemotherapy given postoperatively. Secondary aims of the study included the evaluation of clinical and pathologic response of primary breast cancer to preoperative chemotherapy, the determination of the down-staging effect of preoperative chemotherapy in the axillary nodes and the determination of whether preoperative chemotherapy increases the rate of breast conserving surgery. In addition, the study attempted to determine whether primary breast cancer response to preoperative chemotherapy correlates with disease-free survival and overall survival.

Results on the effect of preoperative chemotherapy on tumor response[13,14] indicate that following administration of preoperative chemotherapy, 36% of patients obtained a clinical complete response and 43% of patients obtained a clinical partial response for an overall response rate of 79%. More importantly, 13% of the patients achieved a pathologic complete response (absence of invasive tumor in the breast specimen following neoadjuvant chemotherapy). Administration of preoperative chemotherapy resulted in significant pathologic axillary lymph node down-staging in 37% of the patients presumed to be node-positive at the time of administration of preoperative chemotherapy. Patients receiving preoperative chemotherapy were significantly more likely to receive a lumpectomy than were patients receiving postoperative chemotherapy (67% vs. 60%, $p = 0.002$). When the two treatment groups were compared in terms of outcome,[15] there was no difference in the disease-free survival, distant disease-free survival or overall survival between the two groups. There was evidence of significant correlation between pathologic response of primary breast tumors to preoperative chemotherapy and disease-free and overall survival. Patients achieving a pathologic complete response (pCR) had a statistical significant improvement in disease-free survival and overall survival compared to those who had a clinical complete response but residual invasive carcinoma in the breast specimen (pINV) or those who had a clinical partial response (cPR) or a clinical non-response (cNR). When the prognostic effect of pCR was examined after adjusting for other known clinical prognostic factors such as clinical nodal status, clinical tumor size and age, pCR remained a significant independent predictor for disease-free survival and a borderline significant predictor for overall survival. Recently updated outcome results from the B-18 study continue to demonstrate that the equivalence between preoperative and postoperative chemotherapy and the significant correlation between pCR and outcome has persisted through nine years of follow up.[16]

The B-18 protocol also provided an opportunity to study patterns of local failure as a function of preoperative versus postoperative systemic therapy. At 9 years the rate of IBTR was slightly higher in the preoperative group (10.7% vs 7.6%) although this difference was not statistically significant.[16] Risk of local recurrence was somewhat higher in the subset of lumpectomy patients that were down-staged to become BCT-eligible in comparison to the BCT patients who were BCT candidates at presentation.[15] However this subset of down-staged BCT cases was predominantly comprised of T_3 tumors, and since local recurrence is largely

a reflection of underlying tumor biology, it would be expected that the more advanced stage lesions might have increased local recurrence rates regardless of surgery type and treatment sequence. Also, radiation boost doses were not consistently used in the lumpectomy patients, and tamoxifen therapy was only used in patients over 50 years of age. Both of these interventions, if implemented uniformly, might have influenced local recurrence rates in down-staged tumors.

Monitoring Chemoresponsiveness by Clinical and Imaging Examinations

Baseline mammography (usually accompanied by tumor-targeted and axillary ultrasound when available) are essential baseline studies at presentation and diagnosis. It is important to repeat these studies just prior to surgery, so that the final decisions can be made regarding lumpectomy versus mastectomy (discussed in next section). However, it is potentially useful to assess chemosensitivity during treatment as well. A theoretical advantage of neoadjuvant chemotherapy is that patients experiencing a suboptimal response can then have treatment toxicity limited by either crossing over to an alternative systemic therapy regime, or by proceeding to surgery. Clinical studies have therefore been designed to test the following questions: (i) is our current armamentarium of systemic therapy regimens adequate in terms of available non-cross-resistant agents that can salvage the early non-responders? (ii) is clinical examination adequate to accurately assess response, or should we rely primarily upon imaging modalities?

The Aberdeen trial investigated whether crossover therapies might be effective in neoadjuvant chemotherapy protocols. They compared the crossover strategy to an extended number of chemotherapy cycles in a cohort of responders,[17,18] and evaluated secondary response rates after crossover in a cohort of non-responders. One hundred sixty-two patients with primary tumors of at least 3 cm were given four cycles of doxorubicin-based chemotherapy. Responders were then randomized to either four more cycles of doxorubicin, or crossed over to four cycles of docetaxel, so that all patients received eight preoperative cycles of chemotherapy. Among the responders, the pCR rate for the doxorubicin-only group was 16%, compared with 34% for the responders randomized to the crossover docetaxel regimen ($p < 0.04$), demonstrating that the nature of the agent is more important than the quantity. They also showed that poor responders may benefit from crossover to an alternative regimen. Survival analyses at 3 years also suggest improved outcomes for patients on docetaxel plus doxorubicin. These findings support the potential value of the crossover strategy in initial non-responders.

Clinical examination, mammography, and ultrasound are all somewhat limited in accuracy for predicting a complete pathologic response. In combination however, these approaches can be helpful in at least providing clues regarding extent of chemosensitivity.[9,19] Magnetic resonance imaging (MRI) is increasingly popular as a breast imaging modality.[20,21] On the other hand, several studies have documented significant limitations in MRI-accuracy related to chemosensitivity assessments.[22,23]

The uncertainties and limited data with regard to addressing these two important questions leave the surgeon with basic clinical examination and conventional imaging for following the neoadjuvant chemotherapy patient. Since more than three-quarters of patients will respond to the first-line regimen, it is reasonable to resist crossover unless the evidence of progression or no response is very strong.

Choice of Lumpectomy versus Mastectomy after Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy patients must ultimately undergo either mastectomy or breast-conserving surgery. Patients presenting with inflammatory breast cancer and diffuse microcalcifications must be advised before initiating treatment that they will need to undergo mastectomy regardless of the extent of their response to the systemic therapy. In general, the selection criteria that are applied in breast-conserving surgery decisions are consistent for patients undergoing primary surgery or surgery after neoadjuvant chemotherapy. The patient must have personal desire for breast preservation; she must be willing and able to receive adjuvant breast irradiation; she must have imaging consistent with unifocal disease, or multiple tumors that are amenable to resection within a single margin-negative lumpectomy; absence of skin involvement consistent with inflammatory breast cancer; and there cannot be any prior history of therapeutic radiation to the ipsilateral chest wall.[34,25] The neoadjuvant treatment may have an inconsistent effect on different patterns of breast disease however, and these variations can effect subsequent eligibility for lumpectomy.

Variation in mammographic patterns of disease can become apparent following delivery of neoadjuvant chemotherapy. It is therefore essential for patients to undergo follow-up mammography prior to planning the definitive local surgery. Some patients will have resolution of breast densities, resulting in unmasking of diffuse microcalcifications that then leave her ineligible for lumpectomy. Alternatively, diffuse microcalcifications can be deposited within breast parenchyma over the course of treatment.

Lobular histology has also been implicated in determining eligibility for breast-conserving surgery after neoadjuvant chemotherapy. Invasive lobular histology has a notorious reputation for being poorly defined and associated withsubtle lesions. These features increase the difficulty of successful margin-negative lumpectomy among women undergoing primary surgery, and they are more challenging in cases of neoadjuvant chemotherapy. Lobular histology tumors tend to respond more slowly to neoadjuvant chemotherapy, and they are significantly less likely undergo successful downstaging for lumpectomy eligibility.[9] Cristofanilli et al.[26] reported outcomes in 122 invasive lobular and 912 invasive ductal carcinomas, all managed by neoadjuvant chemotherapy. The invasive lobular tumors tended to be more advanced at time of diagnosis, and they were less likely to have a complete pathologic response (3% versus 15%; $p < 0.001$). However, the lobular lesions paradoxically found to have longer overall and recurrence-free survival rates. Mathieu et al.[27] also documented the more sluggish breast tumor response during neoadjuvant treatment for invasive lobular carcinomas.

Estrogen receptor positivity is another pathologic feature that tends to predict responsiveness (or lack therof) to neoadjuvant chemotherapy.[28] Secondarily, this effect can result in higher lumpectomy failure rates.

Chen and colleagues[29] identified risk factors for loco-regional recurrence and developed selection criteria for women who will be best suited for BCS following neoadjuvant chemotherapy. In this study (a collective review of the M.D. Anderson Cancer Center experience with breast-conserving surgery after neoadjuvant chemotherapy), approximately 9% of women developed locoregional recurrence. Characteristics associated with increased likelihood of loco-regional recurrence included larger tumor sizes, advanced nodal disease, a multifocal pattern of residual disease following neoadjuvant chemotherapy, and the presence of lymphovascular invasion. The study authors propose the following contraindications for BCS following neoadjuvant chemotherapy: residual tumor size greater than 5 cm, residual skin edema or direct skin involvement, chest wall fixation, diffuse calcifications on post-chemotherapy mammography, multicentric disease, and contraindications to radiation therapy. Notably, T3 or T4 tumors did not have an increased risk of locoregional recurrence if another contraindication was not present. Unfortunately, most of the features in this model that predict for lumpectomy failure will only be identified within the lumpectomy specimen. Patients with a margin-negative lumpectomy are likely to have reservations about undergoing completion mastectomy on the basis of these alternative primary tumor features.

The M.D. Anderson group has also published the outcome results from 109 patients undergoing breast-conserving surgery after achieving a complete pathologic response to neoadjuvant chemotherapy. At 6.6 years median follow-up, locoregional recurrence was detected in only 3 patients (2.7%), with 2 of these developing as in-breast recurrences. These data clearly support the safety of breast-conserving surgery in women that experience a strong response to neoadjuvant chemotherapy, even if they presented with locally advanced disease.

Mastectomy and Immediate Breast Reconstruction after Neoadjuvant Chemotherapy

Concerns about the safety of immediate breast reconstruction in mastectomy patients that have received neoadjuvant chemotherapy are related to uncertainty regarding the need for post-mastectomy radiation therapy (PMRT) in these cases; the known damaging effects of radiation on the reconstructed breast; and fears that reconstruction might delay the delivery of any necessary postoperative therapy.

Radiation effects on breast reconstructions have mostly been reported in the context of patients with LABC. LABC (treated by PMRT as standard care) has traditionally been perceived as a contraindication to immediate breast reconstruction. Newman and colleagues[30] studied 50 patients with stage IIB to IIIA breast cancer who underwent mastectomy with IBR and found no adverse effect on surgical complication rates compared with 72 mastectomy patients who had LABC without IBR. There was a slightly prolonged interval for adjuvant chemotherapy among

reconstructed patients; this did not affect recurrence rates. IBR with implants, however, was associated with an excess of radiation-related complications; nearly half of the irradiated patients developed contractures or recurrent infections, necessitating implant removal. Other investigators report favorable outcomes for LABC patients undergoing mastectomy and transverse rectus abdominus myocutaneous (TRAM) flap IBR, although at least one recent study suggests that radiated TRAM flaps exhibit late-onset fibrosis and contracture.[32] Delayed reconstruction is therefore, usually preferred in LABC patients undergoing mastectomy, because of the substantial likelihood that PMRT will be necessary, and the potential damaging effects of radiating the reconstructed breast.

The American Society of Clinical Oncology (ASCO) recommends PMRT for all patients who have four or more metastatic axillary lymph nodes based upon axillary surgical findings at presentation (without neoadjuvant chemotherapy), and that PMRT should be considered for any case of operable LABC.[33] In the setting of neoadjuvant therapy, the precise initial pathologic staging is unknown. Because PMRT appears to provide an outcome advantage as adjuvant treatment for surgically resected high-risk disease, a valid question arises regarding the possibility that neoadjuvant chemotherapy might impair the ability to identify these patients. Patients who have at least four metastatic lymph nodes or 5 cm of residual disease in the breast after chemotherapy have a significant volume of residual/resistant disease, and they clearly benefit from locoregional irradiation; all lumpectomy patients require breast irradiation after neoadjuvant chemotherapy. A conservative (and aggressive) approach would be to recommend radiation to all patients that present with LABC, regardless of chemotherapy response. However, patients with little or no residual breast/axillary disease after chemotherapy may not derive a significant benefit from regional nodal irradiation. Existing data are limited regarding whether or not comprehensive irradiation is absolutely necessary to achieve optimal locoregional control of disease in patients presenting with LABC, but in whom a substantial degree of downstaging occurred with neoadjuvant chemotherapy. Mamounas and colleagues[34] reported patterns of locoregional failure among NSABP B-18 participants, where stage I to III breast cancer patients were randomized to either preoperative or postoperative chemotherapy. Study design prohibited postmastectomy irradiation, and lumpectomy patients received breast irradiation only (ie, without any regional irradiation). Predictors of locoregional failure were the same in both arms of the study, with four or more metastatic axillary nodes identifying patients who clearly benefit from chest wall irradiation regardless of whether or not the patient received chemotherapy prior to surgery. Thus, the NSABP B-18 data suggest that surgical pathology indications for locoregional irradiation are the same for patients that receive neoadjuvant chemotherapy and those that receive postoperative chemotherapy.

In contrast, data from the M.D. Anderson Cancer Center suggest that even among patients with a complete response to neoadjuvant chemotherapy, the presenting stage of disease is predictive for risk of locoregional failure, and that this feature should also be taken into account when deciding on radiation needs.[35]

In summary, the extent to which stage at presentation should contribute to decisions regarding PMRT in neoadjuvant chemotherapy cases is unclear. Pathology findings in the mastectomy specimen are clearly important in these decisions, but we are unable to accurately predict those findings in advance of the surgery. In clinical practice therefore, the oncology team should review each patient in a multidisciplinary fashion, and discussions regarding the complete multimodality management (including final radiation planning) should begin at presentation.

An interesting approach, called,"delayed-immediate" reconstruction, has been promoted by Kronowitz et al from the M. D. Anderson Cancer Center.[36] This strategy may considered for any patient undergoing mastectomy for whom PMRT indications are uncertain, but who is nonetheless motivated to have immediate reconstruction. Many neoadjuvant chemotherapy patients belong in this category. Delayed-immediate reconstruction involves a skin-sparing mastectomy with insertion of a partially or fully inflated tissue expander. When the pathology report becomes available a few days later, a decision is made expeditiously regarding whether or not the patient is to receive PMRT; if she is not to receive PMRT, then she is promptly returned to the operating room, where the tissue expander is removed and a TRAM flap reconstruction is then performed. The tissue expander therefore serves as a "placeholder" for the desired autogenous tissue reconstruction. Patients that are deemed appropriate for PMRT proceed to radiation therapy without tissue-based reconstruction.

REGIONAL THERAPY

Patients with invasive breast cancer routinely underwent axillary lymph node dissection (ALND), regardless of whether they were receiving preoperative or postoperative chemotherapy until approximately ten years ago, when many surgeons adopted the practice of lymphatic mapping and sentinel lymph node biopsy. This strategy is well-documented as an accurate and safe procedure for staging the axilla in patients undergoing primary surgery for early-stage breast cancer.[37] The optimal approach for incorporating this technology into neoadjuvant chemotherapy protocols has not yet been defined. Ideally, we want our patients to benefit from the downstaging advantages of neoadjuvant chemotherapy, and we would also like for them to reap the benefits of minimally-invasive axillary staging via sentinel lymph node biopsy. Unfortunately however, questions persist regarding accuracy of sentinel lymph node biopsy in lymphatic tissue that has been exposed to neoadjuvant chemotherapy.

Many neoadjuvant chemotherapy patients have locally advanced disease or large primary tumors, with a high likelihood of axillary metastases at diagnosis. Both SLN biopsy and ultrasound-guided FNA have been studied to document axillary metastases before the initiation of preoperative chemotherapy. Ultrasound-guided FNA has been shown to be accurate and effective for detection of axillary nodal disease, and aspiration of nonpalpable suspicious axillary lymph nodes is a reliable option for pre-chemotherapy staging of axillary disease.[38] Unfortunately, axillary

ultrasound has a false-negative rate of 15–20%, because of limited sensitivity in detecting metastatic foci smaller than 5–10 mm.

Many centers have opted to routinely perform a pre-neoadjuvant chemotherapy SLN biopsy. While this approach is a logical means of documenting the disease nodal stage at presentation, there are valid reasons why it requires careful scrutiny of results. The relatively larger tumors that are referred for neoadjuvant chemotherapy may have tumor emboli that could obstruct intramammary lymphatic channels, leading to increased non-identification rates. Also, large primary tumors may drain to multiple lymph node basins, raising the question of lymphatic mapping accuracy.

Table 2 summarizes the results from several institutions that have reported on lymphatic mapping performed as a staging procedure prior to delivery of neo adjuvant chemotherapy. Not surprisingly, (given pre-existing experience with lymphatic mapping performed alongside primary breast surgery in early-stage breast cancer management) SLN biopsy before chemotherapy has been shown to be both feasible and accurate in the identification of axillary metastases at time of disease presentation.[39–42] Identification of the SLN was performed without difficulty, and follow-up of those patients who were node-negative before chemotherapy has not revealed evidence of recurrent disease. Furthermore, both Ollila et al and Schrenk et al.[40,41] included routine completion ALND (after neoadjuvant chemotherapy) into the surgical management plan of all cases undergoing SLN biopsy prior to neoadjuvant therapy, regardless of whether or not this initial staging SLN was negative or positive. This study confirmed that patients staged as node-negative by pre-neoadjuvant chemotherapy SLN biopsy will remain node-negative, as the completion ALND revealed no metastatic disease in this subset of cases. Results from these pre-neoadjuvant chemotherapy lymphatic mapping studies suggest that patients who are node-negative by SLN biopsy do not require further axillary surgery upon completion of the systemic therapy, and surgery at that time can be limited to the breast.

An alternative approach involves performing the SLN biopsy after neoadjuvant chemotherapy, so that patients can avoid the additional operative procedure, and so that focus can be placed upon the final, post-neoadjuvant chemotherapy downstaged disease status. SLN biopsy following neoadjuvant chemotherapy has been met with controversy. Some postulate that SLN biopsy will only be accurate if the metastatic deposits within each axillary lymph node respond in the same way to preoperative chemotherapy Others have proposed that neoadjuvant chemotherapy could potentially complicate subsequent ALND(*43*). Neuman and colleagues[44] have reported that fewer lymph nodes are retrieved during ALND performed in patients who have received neoadjuvant chemotherapy, making it difficult to assess whether a complete and therapeutic procedure has been performed. Despite these concerns, SLN biopsy has been shown to be reasonably accurate and feasible in women who receive neoadjuvant chemotherapy. These studies are detailed in Table 3.[45–61]

Early studies evaluating the use of SLN biopsy among women receiving neoadjuvant chemotherapy were limited by small sample size and single-center setting.

Table 2. Studies of sentinel lymph node biopsy performed prior to delivery of neoadjuvant chemotherapy

		Pre-Chemotherapy SLN Biopsy Results		Post-Chemotherapy Status	
Study	Sample size	SLN ID Rate	SLN-pos (%)	Management Strategy	Post-Chemotherapy ALND's negative for residual metastases (%)
Zirngibl, et al 2002	15	14/15 (93%)	6/14 (43%)	Completion ALND in SLN-pos patients only	6/6 (100%)
Sabel, et al 2003	24	24/24 (100%)	10/24 (42%)	Completion ALND in SLN-pos patients only	3/10 (30%)
Olilla, et al 2003	22	22/22 (100%)	10/22 (45%)	Completion ALND in all patients	12 SLN-neg pts: 12/12 (100%) 10 SLN-pos pts: 6/10 (60%)
Schrenk et al 2005	21	21/21 (100%)	9/21 (43%)	Completion ALND in all patients	12 SLN-neg pts: 12/12 (100%) 9 SLN-pos pts: 6/9 (66%)

Table 3. Studies of sentinel lymph node biopsy performed after delivery of neoadjuvant chemotherapy

Study	N	Method of lymphatic mapping	SLN identified (%)	Metastases in SLN only (%)	False negative rate (%)
Breslin et al, 2000[45]	51	Dye alone, Dye + tracer	84.3	45.5	12.0
Nason et al, 2000[46]	15	Dye + tracer	86.7	33.0	20.0
Schwartz et al, 2003[74]	21	Dye alone	100.0	63.6	9.0
Fernandez et al, 2001[48]	40	Tracer	85.0	25.0	22.0
Mamounas et al, 2005[61]	428	Dye alone, Tracer, Dye+ tracer	84.8	56.0	10.7
Julian et al, 2002[49]	34	Dye alone, Tracer, Dye+ tracer	91.2	38.7	0
Haid et al, 2001[50]	33	Dye+ tracer	87.9	37.9	0
Reitsamer et al, 2003[51]	30	Dye+ tracer	86.7	57.1	6.7
Aihara et al, 2004[52]	36	Dye alone	100	0.0	8.0
Kinoshita et al, 2006[53]	77	Dye+ tracer	93.5	45.8	11.1
Khan et al, 2005[7]	38	Dye+ tracer	97.0	33.0	4.5
Miller et al, 2002[54]	35	Dye alone, Tracer, Dye+ tracer	86.0	22.2	0
Tafra et al, 2001[75]	29	Dye+ tracer	93.0	–	0
Balch et al, 2003[56]	32	Dye+ tracer	97.0	55	5
Brady et al, 2002[76]	14	Dye alone, tracer alone (1)	93.0	60.0	0
Stearns et al, 2002[63]	34	Dye alone	85.3	14.7	14.0
Piato et al, 2003[77]	42	Tracer	97.6	–	11.5
Shimazu et al, 2004[59]	42	Dye alone, Tracer, Dye+ tracer	94.0	31.0	12.1
Jones et al, 2005[60]	36	–	80.6	16.7	11.0

Although estimates from these early studies vary widely, the collective data indicate that SLN biopsy among women receiving neoadjuvant chemotherapy has similar success in identifying the sentinel node, and similar false-negative rates as compared with SLN biopsy in women who receive adjuvant chemotherapy. SLN identification rates range from 80% to 100%, and false-negative rates range from 0% to 33%. The NSABP protocol B-27 is a clinical trial of neoadjuvant chemotherapy, however, it includes a large cohort of women that underwent SLN biopsy with completion ALND following delivery of the neoadjuvant therapy. In this study, false-negative rates were comparable to those reported in multicenter studies of women who have early-stagebreast cancer treated with adjuvant chemotherapy. The NSABP authors report a SLN identification rate of 84.8%, and a false-negative rate of 10.7%.[61]

Figure 1 summarizes the advantages and disadvantages of performing a SLN biopsy before versus after delivery of neoadjuvant chemotherapy. Primary disadvantages of the pre-neoadjuvant chemotherapy strategy are related to the need for an additional operative procedure, and the concern that many women whose initial SLN reveals metastatic disease will then be subjected to an "unnecessary" ALND upon completion of the neoadjuvant chemotherapy. The unnecessary ALNDs (completion ALNDs that are negative for residual axillary disease) might occur because the initial metastatic disease was limited to the resected SLN, or because

Sequence	Advantages	Disadvantages
Sentinel lymph node biopsy performed after delivery of neoadjuvant chemotherapy	– Among neoadjuvant chemotherapy patients, there is more widespread experience with lymphatic mapping performed after chemotherapy, because breast and axillary surgery typically have been performed concomitantly upon completion of preoperative chemotherapy. – Surgical sequence consistent with conventional neoadjuvant chemotherapy regimens	– False-negative rates not yet optimizeddrange, 0% to 40% – Significant learning curve SLN biopsy performed before delivery of neoadjuvant chemotherapy
Sentinel lymph node biopsy performed prior to delivery of neoadjuvant chemotherapy	– Significance of nodal status is understood better when axillary staging is performed at presentation. – Preferred by many medical and radiation oncologists, who may modify their treatment recommendations on the basis of pretreatment nodal status – Most surgeons already experienced with lymphatic mapping technology in the pre-chemotherapy setting	– Commits some patients to unnecessary ALND (metastatic disease limited to the excised SLN in 30% to 50%; chemotherapy downstages 25% to 30% of patients to node negativity) – Requires an additional surgical procedure

Figure 1. Advantages and disadvantages of sentinel lymph node biopsy before versus after delivery of neoadjuvant chemotherapy.

the neoadjuvant chemotherapy sterilized all residual axillary metastases. Among women who have known axillary metastases (diagnosed by FNA biopsy), neoadjuvant chemotherapy has been shown to offer complete pathologic response in the axilla in 23–33% of these patients.

Primary concerns regarding the post-neoadjuvant chemotherapy approach are related to skepticism regarding accuracy of lymphatic mapping in this setting. Also, many oncologists believe that definitive axillary staging information at presentation is just as important as knowing the definitive post-treatment stage.

At the University of Michigan, we approach the axilla of neoadjuvant chemotherapy patients in a comprehensive fashion, allowing us to stratify patients into three different categories: node-negative cases at presentation; node-positive cases at presentation that are downstaged to node-negative; and node-positive cases with resistant disease that remains node-positive. We accomplish this stratification by performing pre-chemotherapy axillary ultrasound and ultrasound-guided FNA biopsy of any suspicious nodes. If the ultrasound is negative, then we proceed with definitive axillary staging by SLN biopsy (to rule out a falsely-negative axillary ultrasound). Definitively-node-negative cases do not undergo any additional axillary surgery after the neoadjuvant chemotherapy has been delivered. Node-positive cases undergo

completion ALND after the neoadjuvant chemotherapy has been delivered, but we have been coupling this final ALND with a SLN biopsy, so that the accuracy of lymphatic mapping for identifying downstaged patients can be defined. Our results[7,62] thus far have been promising: our low false negative rate of 8% suggests that the SLN biopsy may be a reasonable strategy for assessing the final axillary stage and determining which of the initially node-positive cases have had their axillae sterilized and can therefore avoid the completion ALND.

SLN biopsy may not be appropriate for all patients receiving neoadjuvant chemotherapy. Stearns and colleagues[63] studied the use of SLN biopsy in women who received neoadjuvant chemotherapy in the setting of inflammatory breast cancer. These authors reported that the SLN was identified successfully in only 75% of women, compared with 89% of women with locally advanced, but not inflammatory, disease. These results, coupled with the generally high locoregional failure rates that are observed for inflammatory breast cancer, indicate that SLN biopsy is inappropriate for inflammatory breast cancer, and these cases should continue to be managed by ALND.

SUMMARY

Neoadjuvant chemotherapy is the standard treatment approach for patients with locally advanced breast cancer, where primary disease downstaging clears improves operability. Previously unresectable disease may then be controlled by mastectomy, and some patients may even become eligible for lumpectomy. The disease downstaging benefits as well as the ability to determine chemosensitivity, have motivated expanded applications for neoadjuvant chemotherapy to include selected cases of early-stage breast cancer. In this setting, many women will become improved candidates for breast conservation surgery performed via smaller-volume lumpectomies. Optimal utilization of the neoadjuvant chemotherapy approach requires special attention by the surgeon regarding diagnostic biopsies (percutaneous needle biopsies are preferred); preoperative planning (insertion of radio-opaque clips to mark tumor bed prior to completion of chemotherapy response; careful imaging to determine extent of disease); and final surgical decision-making (including comprehensive preoperative imaging to decide between lumpectomy and mastectomy).

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7. NEW TOOLS FOR ASSESSING BREAST CANCER RECURRENCE

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INTRODUCTION

Breast cancer is the most common cancer in women in the Western world, and is essentially incurable when distant metastases are detected. Despite an increasing incidence, breast cancer mortality has fallen,[1] largely due to the advent of widespread screening programs, but also partly due to the increasing use of adjuvant systemic treatment and advances in loco-regional control.

In the most recently published update of the Early Breast Cancer Trialists (Oxford) Overview,[2] which included 150,000 patients in 194 randomized adjuvant trials that began by 1995, the benefit of adjuvant therapy was not only significant but also long-lasting. Allocation to about 6 months of anthracycline-based polychemotherapy reduced the breast cancer death rate by about 38% for women younger than 50 years, and about 20% for those of age 50–69 years. In ER-positive patients, 5 years of adjuvant tamoxifen reduced the annual breast cancer death rate by 31%, with similar results during years 0–4 and 5–14. Therefore, the cumulative reduction in mortality is more than double at 15 years as at 5 years after diagnosis.

The results of the EBCTCG overview[2] and other randomized trials provide compelling evidence for adjuvant therapy. However systemic therapy, particularly chemotherapy, can have significant side effects, both as acute and long-term toxicities, which can dramatically affect the quality of life of patients.[3] This is becoming increasingly important in view of the longer survival that is fortunately seen in early breast cancer patients. Adjuvant therapy, therefore, should be prescribed only after careful consideration of the individual risk-benefit ratio.

Outcome prediction models are important tools in establishing risk-benefit ratios and deciding on appropriate treatment pathways. Factors such as histological type, grade, tumor size, lymph node involvement, as well as estrogen receptor (ER) and HER-2 receptor status all influence prognosis and some of these factors, namely histological grade, ER and HER-2, also influence treatment response, thus, with varying emphases, are incorporated into all of the existing treatment guidelines. The most commonly used guidelines are that of the National Comprehensive Cancer Network (NCCN) in the US[3] and in Europe, the International St Gallen Expert Consensus.[4]

These guidelines, based on clinical and pathological factors, however, do not fully capture the clinical heterogeneity of breast cancer. Indeed, amongst patients with similar stages and grades, there can be substantial variability in both the natural history and response to treatment. This heterogeneity amongst histologically similar tumors is a result of molecular differences, and thus, new prognostic and predictive tools need to reflect the underlying breast cancer biology beyond histopathology.

With the sequencing of the human genome, and the advent of microarray technology, molecular profiling of breast tumors has become possible.

This chapter will review the advances in gene expression profiling, made possible with microarray technology, as new tools for assessing breast cancer recurrence. It will discuss the molecular classification of breast cancer subtypes, as well as the various molecular signatures with their prognostic and predictive implications. Two prospective randomized trials, MINDACT and TAILORx, designed to validate this new technology, will be briefly discussed.

MOLECULAR CLASSIFICATION OF BREAST CANCER SUBTYPES

Historically, the classification of breast cancer has always been based on pathological and clinical findings, represented by the TNM staging and that of the American Joint Committee for Cancer Staging. More recently, there have been several studies examining various single genes as potential independent markers in breast cancer patients, but all with limited clinical utility.

Microarray technology (Figure 1), by allowing for a simultaneous study of the expression of multiple genes (10,000–40,000), has been able to identify different breast cancer subtypes, forming a new molecular classification. These molecular "portraits" have been shown to have distinct clinical outcomes and responses to specific therapy, and therefore, provide more prognostic information than single-genes alone.

With the seminal study by Perou *et al*, at least 4 subtypes were identified, based on the expression patterns of 500 'intrinsic genes'.[5] Two subtypes, the basal-like and the HER2+ were characterized by low or absent expression of ER and ER-related genes.

In the basal-like subtype, there was a high expression of basal cytokeratins 5/6 and 17 and proliferation-related genes, as well as laminin and fatty-acid binding protein 7 and in the HER2+ subtype, there was a high expression of genes in the erbb2 amplicon such as GRB7.

MICROARRAY TECHNOLOGY – THE BASICS

MICROARRAY TECHNOLOGY:

Relies on the accurate binding, or hybridization of DNA strands with their precise complementary copies where one sequence is bound onto a solid-state substrate. These are hybridized to probes of fluorescent cDNAs or genomic sequences from normal or tumor tissue. By analyzing the intensity of the fluorescence on the microarray chip, direct comparison of the expression of all genes in normal and tumor cells can be made [47]. At present, there are multiple microarray platforms that either use ***cDNA-based*** or ***oligonucleotide-based*** microarrays. Analysis and interpretation of microarray data can be with the ***supervised*** or ***unsupervised*** approach.

cDNA-based microarrays have double stranded PCR products amplified from expressed sequence tag (EST) clones and then spotted onto glass slides. These are common but have inherent problems with frequent hybridization amongst homologous genes, alternative splice variants and anti-sense RNA [47].
Oligonucleotide-based microarrays are shorter probes with uniform length. Shorter oligonucleotides (25bases) may be synthesized directly onto a solid matrix using photolithographic technology (Affymetrix) and for longer oligonucleotides (55-70 bases), they may be either deposited by an ink-jet process or spotted by a robotic printing process onto glass slides [47].

Supervised approach allows gathering of information about all genes in a tissue, looking for a common quality criterion, without knowledge of clinical endpoints. However, this approach is subjective and results can vary with different mathematical models, and is generally poorly suited fore identifying prognostic variables [47]
Unsupervised approach identifies gene-expression patterns that discriminate tumors on the basis of predefined clinical information, and are better suited for predicting outcomes [47]

Figure 1. Microarray Technology.

Amongst the ER-positive tumors, 2 subtypes were identified; the first group, luminal A, was characterised by a higher expression of ER, GATA3 and X-box binding protein trefoil factor 3, hepatocyte nuclear factor 3 alpha and LIV-1; and the second, group, luminal B was characterised by lower expression of luminal-specific genes.

Not only do they differ in their gene expressions, these molecular subtypes have distinct clinical outcomes and responses to therapy that seem reproducible from one study to the next. The basal-like and HER2+ subtypes were likely to be more aggressive including a higher proportion of TP53 mutations,[6,7] and a markedly higher likelihood of being grade III ($p < 0.0001$, and $p = 0.0002$) than luminal A tumors. Despite a poorer prognosis, they tended to respond better to chemotherapy with a higher pathologic complete response (46% versus 7%, $p < 0.001$) after anthracycline-based and taxane-based neo-adjuvant chemotherapy.[8]

On the other hand, fewer than 20% of luminal subtypes had mutations in TP53, and these tumors were often grade I.[9] They tended to be more sensitive to endocrine therapy, responded more poorly to conventional chemotherapy, but with better clinical outcome.

Despite different microarray platforms and different population groups, subsequent studies also produced similar results. Sotiriou et al,[9] in analyzing a cohort of 99 node-negative and node-positive breast cancer patients and using 7650-probe element

cDNA microarrays, confirmed that the ER status remained the most important discriminator of gene expression pattern and that tumor grade was a distant second. They identified two major groups segregated on ER status and further subdivided them into smaller groups characterized by distinct gene expression signatures involving potentially different oncogene-specific pathways; basal-1, basal-2 and HER2 which were mostly ER negative; and luminal–1, luminal-2 and luminal-3 which were mostly ER positive. The basal-1 and basal-2 subgroups were characterized by higher expression of the oncogenes c-kit, c-myc, and SFRP1, and the HER2 subtype was characterized by higher expression of genes involved in the ras pathway as well as those involved with HER2/neu. In correlating with clinical outcomes, there were differences between subgroups, with relapse-free and survival benefit favoring the luminal subtypes.

Interestingly, other clinically relevant variables such as menopausal status, tumor size and nodal status were not associated with distinct gene expression patterns, suggesting that these prognostic variables may, in fact reflect disease stage rather than the intrinsic biological properties of the tumor.[9]

This identification of distinct expression patterns amongst breast cancer subtypes has provided intriguing insights into tumor biology. It has allowed us to conceptually regard breast cancer not as one disease, but a collection of several biologically different diseases. However, this molecular classification is not without its inherent limitations which render it not yet ready for clinical practice – exactly how many true molecular classes of breast cancer are there? Furthermore, the subjective use of hierarchical cluster analysis, the small number of tumor specimens and the lack of standardized prediction algorithms, which underlie many of its criticisms,[10] still need addressing.

GENE EXPRESSION SIGNATURES AS PREDICTORS OF BREAST CANCER RECURRENCE

Historically, decisions of adjuvant systemic therapy in early breast cancer have relied on risk assessment incorporating both patient-related and tumor-related prognostic factors. These prognostic factors serve to characterize the background level of risk of recurrence against which the benefits and burdens of adjuvant therapies are weighed.[11] Patient-related factors include age, menopausal status and comorbidities. Tumor-related factors include lymph node involvement, tumor size, tumor grade and ER status. More recently, HER2 status has been added to this group of prognostic factors.

These established prognostic markers, when combined to form various prediction models, can provide valuable information regarding risk of relapse, however lack the ability to provide individualized information regarding outcome for a given patient.

Through microarray technology, studies in gene expression profiling have focused on improving upon these traditional prognostic tools in risk prediction for the individual patient. In particular, various gene expression signatures appear to not only have prognostic potential, where the risk of recurrence is predicted, but also, predictive potential, where the likelihood of response to specific therapy can help select treatment regimens.

In general, these studies adopt one of two approaches:

1) The "Top-Down" approach – where the gene expression signature is derived by seeking profiles that are correlated with clinical outcome, without a prior biological assumption.
2) The "Bottom-Up" approach – where a set of genes is generated from specific biological assumptions of cellular mechanisms, before being correlated to clinical outcome to assess relevance.

THE TOP-DOWN APPROACH FOR PREDICTING BREAST CANCER RECURRENCE (UNSUPERVISED APPROACH)

The 70-Gene Prognostic Signature (Figure 2)

Using the "Top-Down" approach looking at a group of patients who relapsed within 5 years and a group who did not, the Netherlands Cancer Institute (NKI) identified a 70-gene prognostic signature in 78 fresh frozen breast cancer samples,[12] using the Agilent platform. These were from patients younger than 55 years of age, with systemically untreated node-negative disease. Of these, 34 had developed distant metastases in 5 years and 44 remained disease-free.

This signature was subsequently validated on a larger set of 295 patients from the same institution,[13] including both node-negative (n = 151) and node-positive disease (n = 144), with 44% receiving adjuvant treatment (chemotherapy 31%, hormonal therapy 7%, and both in 7%).

Despite differences in the 2 cohort of patients, the 70-gene prognostic signature predicted well for 5-year and 10-year distant metastases-free survival (DMFS). At 5 years, the probability of remaining free of distant metastases was 96% in the good-signature group and 83% in the poor-signature group. At 10 years, the probability was 66% and 55% respectively.

Importantly, the 70-gene signature seemed to outperform the St Gallen[4] and NIH[14] criteria in being the strongest predictor for distant-metastasis free survival, independently of adjuvant treatment, tumor size, histological grade and age, both in the node-negative and node-positive cohorts. Particularly, it assigned more patients with node-negative disease to the low-risk category (40%) as compared to the traditional guidelines (St Gallen 15% and NIH 7%), with those identified by gene expression profiling having a higher likelihood of metastases-free survival. Certainly with its ability to better define the low risk category, more of these patients could be potentially spared from unnecessary chemotherapy.

The 76-Gene Prognostic Signature (Figure 2)

Using the Affymetrix platform, the Rotterdam group[15] in collaboration with Veridex LLC (San Diego, USA), identified a 76-gene prognostic signature in 115 node-negative breast cancer patients who received no adjuvant therapy. In this initial training set, 80 patients were ER positive and the classification

	70-gene signature Van de Vijver et al [12,13]	**76-gene signature** Wang et al [14,15]	**21-gene signature** OncotypeDM™ Paik et al [19,22]	**Wound response signature** Chang et al [25]	**Gene Expression Grade Index (GGI)** Sotiriou et al [27]
Tissue	Fresh frozen	Fresh frozen	Paraffin-embedded	Fibroblast cultures	Fresh Frozen
Platform	RNA expression Agilent	RNA expression Affymetrix	RNA expression Genomic Health RT-PCR	RNA expression	RNA expression Affymetrix
No. genes	70	76	16 (+5 ref genes)	512	97
No. tumor samples					
Training	78	115	449	50 fibroblast cultures	64
Validation	295	171	668	295	125
ER expression					
Training	Majority	70%	all	n/a	all
Validation	77%	75%		mixed	majority
Ax LN involved					
Training	None	None	None	n/a	None
Validation	Mixed	None	None	Mixed	None
Adjuvant Rx *H= hormones C=chemotherapy*					
Training	None	None	None	n/a	H only
Validation	H 7%; C 31%; Both 7%	None	None	H 7%; C 31% Both 7%	None

	Good signature 39%	Good signature 34%	Low risk 51% Int risk 22%	Activated (A) 43% Quiescent (Q) 57%	Histo G2	GGI low / high
Risk Categories	Poor Signature 61%	Poor signature 64%	High risk 27%		n=216 *(all data sets)*	124 / 92
	HR distant mets (95%CI) Poor vs good 5.1 (2.9-9.0) (p<0.0001)	*HR for 5y *DMFS (95%CI)* Good vs poor 5.67 (2.59-12.4) (p<0.0001)		*HR for *DMFS (95%CI)* 7.25 (1.75-30.0) (p=0.006)	*HR for recurrence in histo grade 2 tumors (95%CI)* High vs Low GGI 3.61 (2.25-5.78) (p<0.001)	
	*10y *DMFS* Good 85.2% (+/− 4.3%) Poor 50.6% (+/− 4.5%)	*HR for 5y **OS (95%CI)* Good vs poor 8.62 (2.57-27.9) (p<0.0001)	*10y ***DR (95%CI) 10y* Low 6.8% (4.0-9.6) Int 14.3% (8.3-20.3) High 30.5% (23.6-37.4) (p<0.0001)	10y *DMFS Activated 51% Quiescent 75%		

*DMFS – distant metastaes free survival
**OS – overall survival
***DR – distant recurrence

Figure 2. Gene Expression Signatures.

algorithm considered these ER positive patients separately from the ER negative patients.

Subsequent validation in 171 patients confirmed the prognostic ability of the 76-gene signature. Patients with a good signature had a 5-year DMFS rate of 93% compared to 53% in those with a poor signature, and at 80 months, the DMFS rates were 88% and 49% respectively. More recently, a multi-centre validation in 180 patients[16] has been undertaken, with similar results.

A Common Feature of the 70-Gene and 76-Gene Prognostic Signatures

Despite having only 3 genes in overlap, both signatures were able to outperform the traditional treatment guidelines of NIH[14] and St Gallen,[4] especially in correctly identifying the "low-risk" patients, but were limited in identifying the "high-risk" patients as half of those identified in this category did not, in fact, relapse.

These signatures, therefore, may have the highest clinical utility in potentially reducing over-treatment of low-risk patients.

Independent Validation of the 70-Gene and 76-Gene Prognostic Signatures

Independent validation of both the 70-gene and 76-gene prognostic signatures has been conducted by TRANSBIG, a Translational Research Network associated with the Breast International Group.

In 302 node-negative untreated patients[17] from 5 institutions, after a median follow-up of 13.6 years, the 70-gene signature was shown to outperform the clinico-pathologic risk assessment (AdjuvantOnline prediction, Nottingham prognostic index and the St Gallen Consensus) in predicting endpoints of 5-year time to distant metastases (unadjusted HR 2.32, 95% CI 1.35–4.00) and overall survival (unadjusted HR 2.79, 95% CI 1.60–4.87). Even after adjustment for clinical risk, the 70-gene signature remained statistically significant as a prognostic factor.

In this 70-gene validation study, the 10 year overall survival rate for the good-signature gene group was 88% (95% CI 81–95%) compared to 71% (95% CI 63–78%) for the poor-signature group. The somewhat lower performance of this 70-gene signature in this validation series as compared to the initial study is most probably due to the important difference in median follow-up in the 2 series (5 years versus 13.6 years) and to the time-dependency phenomenon (see below).

More recently, TRANSBIG has also undertaken an independent validation of the 76-gene prognostic signature on a smaller group of 198 patients.[18] Of the original 302 patients, 104 samples were excluded due to failed quality control or insufficient material. The same endpoints of 5-year time to distant metastases and overall survival were used and the 76-gene signature also proved to be a powerful prognostic tool. The actual 5-year and 10-year time to distant metastases were 98% (88–100%) and 94% (83–98%) respectively for the good profile group and 76% (68–82%) and 73% (65–79%) for the poor profile group. The actual 5-year and 10-year overall survival were 98% (88–100%) and 87% (73–94%) respectively for the good profile group and 84% (77–89%) and 72% (63–78%) for the poor profile

group. The hazard ratio was 5.78 (95% CI 1.78–18.80) for time to distant metastasis, and 2.87 (95% CI 1.21–6.82) for overall survival.

Interestingly, with the long median follow-up, a strong time-dependency phenomenon was observed in this cohort of patients. Both signatures appeared to be strong predictors of early distant metastases occurring over 5 years, but with increasing follow-up, demonstrated decreasing prognostic ability.[18] Not seen with the clinical risk classification, this may well reflect the different mechanisms proposed to be associated with that of early and late distant metastases.[19]

Oncotype DX™ (Figure 2)

Also using the "Top-Down" approach, Paik et al,[20] in collaboration with Genomic Health Inc. developed a recurrence score based on 21 genes that appeared to predict accurately the likelihood of distant recurrence in tamoxifen-treated patients with node-negative, ER positive breast cancer. Borne from the National Surgical Adjuvant Breast and Bowel Project (NSABP) group, this predictor was initially designed to be a general prognostic tool, and was developed in a mixed population of patients receiving chemotherapy and tamoxifen. Following a literature search of the most important microarray experiments relating to breast cancer prognosis, 250 candidate genes were selected. Of these, 21 genes were chosen and the recurrence score developed by analyzing the results of these genes in three independent preliminary studies involving 447 patients.[21–23] A final panel of 16 cancer-related genes and 5 reference genes thus formed the basis for the Oncotype DX™ Breast Cancer Assay.

The Genomic Health Recurrence Score (RS) classify patients into three risk groups, based on cutoff points from the results of the NSABP trial B-20; high risk of recurrence was assigned if RS >31, intermediate risk if RS 18-30, and low risk if RS <18.

Retrospective validation of this predictor in 675 archival samples from patients with ER positive, node negative breast cancer treated with tamoxifen in the NSABP trial B-14 was published by the same group.[23] Fifty-one percent of patients were classified as having a low risk RS, with only 6.8% distant recurrence rate at 10 years (95%CI 4.0–9.6), 22% as having an intermediate risk RS with 14.3% 10-year recurrence rate (95%CI 8.3–20.3) and 27% of patients as having a high risk RS with a 30.5% 10-year distant recurrence rate. The RS was also significantly correlated with the relapse-free interval and overall survival ($p < 0.001$ for both). Notably, this predictive power was independent of age and tumor size ($p < 0.0001$).

However, the NSABP recurrence score did not consider locoregional relapses as censoring events, and therefore, the RS is only predictive for distant relapses. Also this RS does not have pure prognostic value but rather predictive value regarding response to tamoxifen unlike the Amsterdam 70-gene and the Rotterdam 76-gene signatures.[24]

The reliability of the OncotypeDX™ has also been validated in a population-based case-control study of 227 patients with node-negative breast cancer seen

at 19 Kaiser Permanent hospitals between 1985 and 1995,[25] and untreated with adjuvant chemotherapy. In this study, RS was found to be the strongest predictor of breast cancer death, with a similar 10-year breast cancer death rate to that seen in the NSABP trial B-14.

THE BOTTOM-UP APPROACH FOR PREDICTING BREAST CANCER RECURRENCE (SUPERVISED APPROACH)

Wound-Response Signature

Unlike the "Top-Bottom" approach, the "Bottom-Up" approach starts with a specific biological hypothesis to generate a set of function-specific genes, before being correlated to clinical outcome. By firstly examining the processes involved in wound healing and then drawing similarities with the oncogenic process, Chang et al[26] were able to derive a wound-response signature with prognostic potential. They studied the gene-expression profiles of fibroblasts in response to serum, and found that a common expression of almost 700 genes existed, despite differences in anatomical sites from which these fibroblast cultures were derived. In excluding the genes involved in cell-cycle and proliferation, 512 genes remained and formed the fibroblast Core Serum Response (CSR), reflecting other important processes of matrix remodeling, cell motility and angiogenesis. Using the same patient data sets of van de Vijver et al[8] that were used in developing the 70-gene signature, they showed that an activated wound-response signature was related to worse distant metastasis-free probability and overall survival compared to those with a quiescent wound-response signature. Similar to the 70-gene and 76-gene signatures, the wound-response predictor also out-performed the stratification guidelines of St Gallen[4] and NIH.[14]

When comparing the expression patterns of distinct gene sets provided by the CSR cassette, the 70-gene signature, as well as the intrinsic genes of the molecular breast cancer subtypes, very little overlap was observed[27]—22 common genes between two signatures with 18 of these common genes between the wound-response signature and the intrinsic gene set, but no gene was present in all 3 signatures. Despite this, the signatures gave overlapping and generally consistent predictions of outcomes. Particularly, many patients who subsequently developed metastases expressed both the 70-gene signature and the wound-response signature, as well as the majority of those within the basal-like subtype. By showing the disparity between the gene lists but the consistent prognostic information offered independently, the argument that these signatures could be used together at different levels of the decision-making algorithm becomes attractive.

Gene Expression Grade Index (GGI)

Histological grade is a well-defined pathological parameter, with its various subclasses correlating with varying clinical outcomes. The intermediate-grade tumors (typically grade 2) represent between 30–60% of all patients, displaying the

most heterogeneity both in phenotype and in outcome.[20] In order to see whether gene expression patterns associated with histological grade can improve the prognostic capabilities amongst the intermediate grade, Sotiriou et al[28] analyzed a training set of 33 grade 1 and 31 grade 3 ER positive tumors and developed a Gene Expression Grade Index (GGI) based on 97 genes. Of note, ER negative tumors were deliberately excluded from the training set, since they are almost always high grade. These genes, mainly involved in cell-cycle regulation and proliferation, had differential expression in high and low grade breast carcinomas—the higher the index, the higher the grade, and vice versa. However, amongst the intermediate grade breast carcinomas, there was not a unique gene expression.

Sotiriou et al[28] demonstrated that the GGI was able to re-classify patients with intermediate grade into 2 subgroups with expression patterns matching that of either low or high grade groups. This ability to subdivide amongst intermediate grade tumors will ultimately facilitate better treatment decisions for this otherwise highly heterogeneous cohort of patients.

In examining the genomic grade with ER status, they also found that ER-negative tumors with poor clinical outcome were mainly associated with high GGI, but ER-positive tumors were more heterogeneous with a mixture of GGI levels.[28] Thus, these 2 variables are not entirely independent from each other; with tumor genomic grading capable of providing an extra level of information when stratifying the ER-positive group.

Not surprisingly then, this association was also demonstrated between genomic grade and the various molecular breast cancer subtypes. The basal-like and erbB2-like subtypes, with low or absent expression of ER and ER-related genes, had higher GGI levels and worse clinical outcome, whereas the luminal A subtype, with higher ER expression, had lower GGI levels and the best outcome.[29]

Mutant/wild p53 Signature

A 32-gene expression signature was developed by Miller et al[30] after examining differences between p53 mutant and wild type tumors. Although none of the 32 genes actually represented known transcriptional targets of p53, the signature was better in predicting clinical outcome than p53 mutation status determined by sequencing. Indeed, many of these genes, not entirely surprising, were associated with proliferation and ER-status.

Invasiveness Gene Signature (IGS)

Several studies are now providing evidence that only a minority population of cancer cells within a tumor are actually tumorigenic, typically characterized by CD44 expression but low or undetectable levels of CD24. This CD44+CD24-/low population shares the same capacity for self-renewal as stem cells, whereas the rest of the cancer cells within the tumor are non-tumorigenic.[31,32]

In using gene expression profiling of tumorigenic breast cancer cells and comparing against that of normal breast epithelium, Liu at al[33] generated a 186-gene

"invasiveness" gene signature (IGS) which had a significant association with overall and metastases-free survival ($p < 0.0001$), independent of established clinical and pathological variables, which was also evident in other cancer types including lung cancer, prostate cancer and medulloblastoma. Amongst the high-risk early breast cancer patients determined by NIH guidelines,[14] 2 prognostic categories were identified (good and poor) using IGS with substantially different 10-year metastasis-free survival rate (81% vs 57% respectively, $p < 0.001$).

CLINICAL USEFULNESS OF GENE EXPRESSION PREDICTORS OF OUTCOME

In order to be clinically useful in predicting outcome, the predictor should have a high discriminating power; in other words, be associated with a wide separation of the event-free survival of "good prognosis" patients and those of the "poor prognosis" patients, with the former group showing an event-free survival of 90% or better at 10 years.

Any worse outcome of the so-called "good prognosis" population will lead to adjuvant chemotherapy prescription in any case, thus diluting the potential clinical usefulness of the prognostic tool. With this in mind, the most attractive predictors of outcome are the 70-gene, the 76-gene, OncotypeDx™ and the GGI signatures.

Of note, collaborative work could allow for further improvement in the "clinical performance" of these predictors by using 2 predictors sequentially instead of 1, for example, the wound-response signature followed by the Amsterdam signature.

GENE EXPRESSION SIGNATURES AS PREDICTORS OF THE SITE OF BREAST CANCER RECURRENCE

An interesting theory of breast cancer metastases is that tumors are genetically determined to recur in specific organ sites, and gene expression signatures may be able to serve as site-specific predictors. Massague and colleagues,[34–36] by developing progeny cell lines of MDA-MB-231 with enhanced ability to metastasize to either bone or lung in immuno-compromised mice, identified 2 different gene sets, the bone gene set and the lung gene set. When applying the bone gene set to a cohort of human breast tumors that eventually developed metastases, they could distinguish tumors that preferentially metastasized to bone from those that preferentially metastasized elsewhere. Similarly, by applying the lung gene set to the same dataset used by van't Veer and colleagues,[12] they were able to identify a subgroup of patients with worse lung-metastasis-free survival. The site-specific predictive potential of the gene sets was independent from the ER status and the 70-gene signature.

GENE EXPRESSION SIGNATURES AS A GUIDE TO THERAPEUTICS

The refinement of prognostic tools will be important to help better identify those patients needing or not needing treatment, but knowing which therapy will benefit the individual patient is equally important. Markers that could predict treatment response will ultimately lead to individualization of adjuvant therapy. Currently,

only ER and HER2 status are used in clinical practice for this, but several investigators have applied microarray technology to identify gene expression signatures that could predict for drug sensitivity in breast cancer.

In fact, the best studies looking at chemotherapy sensitivity are those that have been conducted in the neoadjuvant setting, examining pathologic complete response [pCR].

By looking at responders versus non-responders in 89 patients treated with neoadjuvant paclitaxel and doxorubicin for locally advanced breast cancer, Gianni et al[37] found 86 genes that correlated to pCR, which was more likely to occur with a higher expression of proliferation-related genes (including CDC20, E2F1, MYBL2, TOPO2A) and immune-related genes (including MCP1, CD68, CTSB, CD18, ILT-2, CD3z, FasL, HLA.DPB1) and with lower expression of estrogen (ER)-related genes (including ER, PR, SCUBE2, GATA3).

Similarly, the MD Anderson group[38] also developed a 30-probe set of pharmacogenomic predictor for pCR in 82 patients treated with neoadjuvant weekly paclitaxel followed by fluorouracil / doxorubicin / cyclophosphamide (T/FAC). In cross-validation of 51 independent cases, the 30-probe set had high sensitivity in being able to identify 12/13 (92%) patients with pCR, and high negative predictive value in being able to identify 27/28 (96%) patients with residual disease. Compared with the clinical variable-based predictor (ER, grade, and age), this 30-probe set outperformed in sensitivity (92% versus 61%) and negative predictive value (96% versus 86%). Notably, they showed that their classifier had predictive accuracy similar to that of ER and HER2 amplification.

Potti et al,[39] in combining in vitro drug response data, together with Affymetrix microarray data, developed gene expression signatures that could predict for sensitivity to individual chemotherapeutic drugs. By firstly developing the docetaxel response predictor, they then developed a panel of signatures against other drugs that could predict clinical and pathological response. Interestingly, by combining signatures predicting response to individual agents, they could also predict response to multidrug regimens.

Using microarray technology, several studies have also been performed looking at the prediction for endocrine therapy resistance using microarray technology. Using a training set of 50 tumors and a validation set of 15 tumors from ER positive women with advanced disease, researchers from Rotterdam identified 44 genes that predicted for response to tamoxifen in 80% of cases. Ma et al[41] also developed a signature predictive of disease free survival in tamoxifen-treated patients, using the expression ratio of two genes—homeobox B13 (HOXB13) versus IL17BR. From an initial training set of 60 patients treated with only tamoxifen[40] and a subsequent independent validation set of 20 patients, the ratio was shown to have an overall accuracy of 80% (16 out of 20, 95%CI 56–94%)) in predicting for disease-free survival.

Using a different technology of multi-gene real time quantitative PCR (RT-PCR), 2 particular studies have also investigated gene expression and the prediction of tamoxifen response. Sotiriou et al,[42] in examining a series of 326 breast cancer cases, were able to show that the expression levels of both cyclin E1 and E2 were associated

with a poor prognosis, and that cyclin E1 was also a predictor of tamoxifen resistance. Also, the OncotypeDX™ Breast Cancer Assay, previously discussed[20,23] based on 16 cancer-related genes and 5-reference genes, was in fact validated in a group of 675 patients that was treated with tamoxifen in the NSABP B-14 trial. Even though the training set was derived from a population heterogeneously treated with chemotherapy and tamoxifen, the MD Anderson group could not validate the Recurrence Score in a similar untreated group. Thus the Recurrence Score serves more as a predictor of tamoxifen response than it does as a predictor of recurrence in the whole breast cancer population.

LARGE, RANDOMISED PROSPECTIVE TRIALS ASSESSING CLINICAL UTILITY OF GENE EXPRESSION SIGNATURES

The various gene expression signatures so far discussed, bear great potential for facilitating the ongoing revolution in patient care from empirical towards molecular oncology. However, adequate validation in large, randomised prospective trials is critical for assessing the true clinical utility of these gene expression signatures as prognostic and predictive tools before they can be implemented into daily clinical practice. Common criticisms of gene profiling studies, to date, include sample size, the selection bias, the non-standardized mathematical models and the subjective hierarchical cluster analysis.[10] Future clinical trials must be prospective in nature, multi-centered if not international, and hold true to the randomization ideal. In fact, these trials must aim to demonstrate that clinical decision making is clearly improved with these new tools, over and above the traditional clinico-pathologic criteria. Two large trials, MINDACT and TAILORx, incorporating these characteristics are briefly discussed (Figure 3)

MINDACT (MICROARRAY IN NODE-NEGATIVE DISEASE MAY AVOID CHEMOTHERAPY) TRIAL (FIGURE 4)

The MINDACT trial is an international prospective, randomised study assessing the potential added value of the 70-gene signature classifier[7] to the commonly used clinico-pathologic criteria for selecting node-negative breast cancer patients for adjuvant chemotherapy. By hypothesizing that the 70-gene signature will be able to better select appropriate patients for adjuvant treatment, the benefit would be best seen in patients with good prognostic signatures spared from unnecessary chemotherapy.

In this trial,[43] 6,000 node-negative patients will have their risk assessment made by using common clinico-pathological factors (through a modified version of Adjuvant OnLine) and by the 70-gene signature. Those patients who are classified as high risk by both methods will be offered chemotherapy; those classified as low risk by both methods will not be offered chemotherapy; the discordant group, an estimated 33% (1,900 patients) will be randomized between the 2 methods and will receive or not receive chemotherapy according to the result of the assigned method.

FEATURES OF MINDACT AND TAILORx TRIALS		
	MINDACT	**TAILORx**
Groups / Networks	EORTC, BIG, TRANSBIG	US Intergroup
Population		
Axillary nodes	Negative	Negative
ER status	ER +/−	ER+
Assay	70 gene Mammaprint^{R}	21 gene OncotypeDX^{TM}
Tissue	Fresh Frozen	Formalin Fixed Paraffin Embedded
Number	6,000	10,500
Number randomized	1,920	4,390
Randomized group	Discordant risk (32%)	RS 11-25 (40%)
Randomization	Treatment decision based on clinical vs genomic risk	Treat with hormones +/− chemotherapy
Non- randomized group	Both Low risk (13%): HT or nil Both high risk (55%): CT +/- HT	RS < 11: HT RS >25 : CT + HT

Figure 3. Features of MINDACT and TAILORx trials.

It will also have two further randomizations 1) those who will be receiving chemotherapy will be randomized to receive either an anthracycline-based regimen or a docetaxel—capecitabine regimen 2) those eligible for endocrine therapy can be randomized to either 7 years of letrozole, or 2 years of letrozole followed by 5 years of letrozole.

This trial, opened for accrual in March 2007, is in the TRANSBIG and BIG networks and is conducted under the sponsorship of the EORTC.

TAILORx (Trial Assigning Individualized Options for Treatment) Trial (Figure 5)

TAILORx is a large randomized prospective study aimed at validating the 21-gene Recurrence Score (RS),[15] marketed under the name OncotypeDX^{TM}. It is designed to evaluate whether women with node negative, ER positive breast cancer need chemotherapy based on the RS. Patients with a RS less than 11 (low risk) will be given only hormonal therapy. A RS more than 25 (high risk) will mean that patients receive chemotherapy in addition to hormone therapy. Patients with RS 11–25 (intermediate risk) will be randomly assigned to receive hormone therapy or chemotherapy followed by hormone therapy.

Under the auspices of the US Intergroup, the TAILORx trial is expected to accrue over 10,000 patients. It is postulated that 29% of the population will be low risk, 27% will be high risk, and 44% will be intermediate risk, with the latter group consisting of approximately 4,000 patients.

This trial was launched in May 2006, and has already recruited close to 1,000 patients.

Both these trials will also allow for the creation of important biological material banks. In TAILORx, only paraffin embedded tumor samples will be collected. In MINDACT, both fresh frozen and paraffin embedded tumor samples and blood

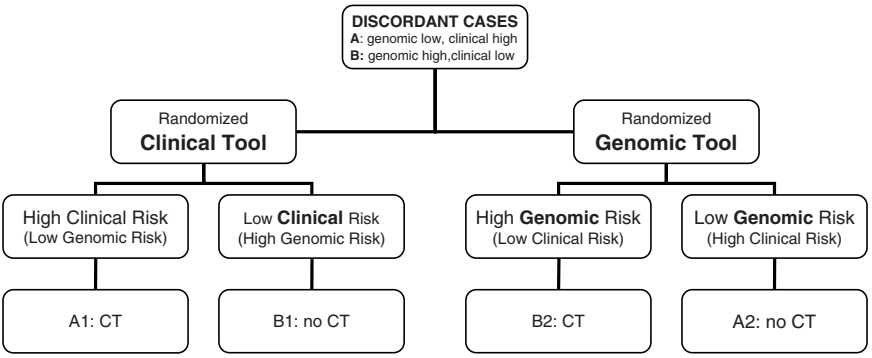

Figure 4. Schema of MINDACT.

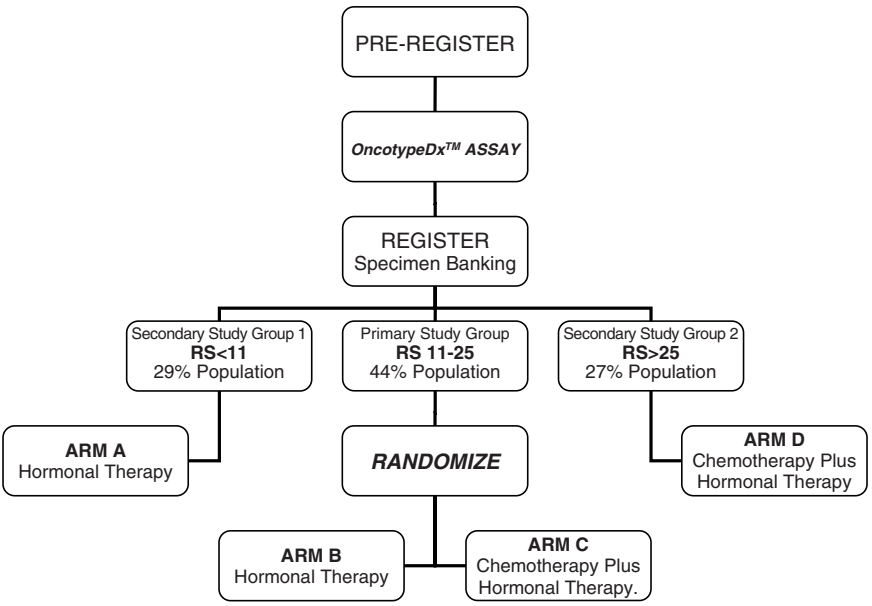

Figure 5. Schema of TAILORx.

samples will be collected and stored in a central and independent biological material bank. These biological materials represent an invaluable resource for future research and collaboration between the two trials is already ongoing.

CONCLUDING REMARKS / DISCUSSION

Given the clinical heterogeneity of breast cancer, the challenge that oncologists continue to face is that of matching the right therapeutic strategy with

the right individual, balancing benefit with risk to achieve the best favorable outcome. This ability to individualize patient treatment according to prediction of prognosis and treatment response is central to the evolution from empirical to molecular oncology.

Emphasis has previously been put on refining the traditional histopathologic criteria, on developing indices of proliferation (S-Phase fraction, Ki67), on understanding genomic instability (eg DNA ploidy) and on analyzing single gene expression profiles (p53 expression).[31] However, the results, so far, have not been as successful as hoped. More recently, gene expression profiling, enabled by microarray technology, has lead to multiple new gene signatures with prognostic and predictive potential which bear the promise of being better tools. However, several important issues should be noted.

Firstly, amongst the various gene signatures, there is very little overlap in the genes themselves. In fact, between the 70-gene and 76-gene signatures, only 3 genes overlap. This is not altogether surprising, because the process of choosing the genes is highly dependent upon the subset of patients used to develop the prediction model [44]. Furthermore, different platforms only partially interrogate overlapping gene sets[45] and they also have different sensitivity and dynamic range[46] to measure the expression of the same gene. As well, predictive non-overlapping gene sets can be identified from the same data because tightly co-expressed genes can give an equally good result regardless of which is selected.[47] It is thus, anticipated that many more prognostic signatures could emerge in the future.

However, even with the disparity within the gene lists, much of the prognostic information offered by the various signatures remains consistent. This may be explained by the fact that these signatures probably reflect similar oncogenic pathways where proliferation genes are central players. The challenge, therefore, is to somehow combine the different levels of information provided by these gene signatures into existing outcome prediction models to better refine treatment decision-making.

Secondly, by the very fact that microarray technology can allow for a simultaneous study of thousands of genes, this can also, on the flipside, bring about multiple biases especially because correlations are often made without a priori hypothesis. While the existing gene signatures show much promise, their clinical utility needs to be tested in large, prospective and randomized trials. Much of the studies to date have been small retrospective series with different patient populations, different microarray platforms and different statistical models.

Therefore, despite the fact that validation studies have been able to demonstrate an association between certain gene signatures and outcome, it will require trials such as MINDACT, testing the 70-gene Mammoprint^{R}, and TAILORx, testing the 21-gene OncotypeDX^{TM}, to prove that clinical benefit can be derived from the use of this new technology. Until such time when the necessary level of evidence is attained, the use of these new tools, outside the realm of clinical trials, can not be generalized.

Thirdly, a real prohibitive factor for current clinical application is the high cost of utilizing microarray technology or RT-PCR, and efforts to simplify both the cost and logistics of such technologies will be necessary after prospective validation. The recent ability to perform high-throughput, real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) on sections of formalin-fixed paraffin-embedded tissue,[20,43] has certainly made this technology more accessible to clinicians, but the cost of RT-PCR based signatures, such as OncotypeDx™ still remains high.

Despite all these issues, the shift in emphasis towards molecular profiling represents a significant revolution in the management of breast cancer patients. New prognostic tools, enabled by gene expression studies, will allow better tailoring of adjuvant treatment to individual patients, so that chemotherapy, with its potential side effects, is reserved for those patients most likely to benefit. Furthermore, the potential to predict for the response of an individual to a particular drug[37–42] or regimen, not only allows one to choose which patient should be treated with chemotherapy, but also with which agents that would best offer a chance of cure.

Even after positive validation in large prospective trials, it is unlikely that gene expression profiles will altogether replace existing clinico-pathological guidelines, but rather, they will become part of an integrative decision-making model based on multiple levels and sources of prognostic data. For now, treatment guidelines such as those of St Gallen[4] and NIH[14] as well as the NCCN,[3] having withstood both the test of evidence and time, will continue to be used widely.

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8. DEVELOPMENT OF NEW TARGETED THERAPIES FOR BREAST CANCER

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INTRODUCTION

Oncologists typically thought of systemic therapies for breast cancer as belonging to one of two categories: either cytotoxic chemotherapy or hormonal therapy. Though this simple approach served well for decades, the recent development of trastuzumab showed its inadequacies. Trastuzumab, neither broadly cytotoxic nor a classic hormonal manipulation, didn't fit. Thus, a third category, biologic therapy, or alternatively, targeted therapy, emerged. Targeted therapy is a type of medication which blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth, rather than by simply interfering with rapidly dividing cells.

Though we tend to think of targeting growth signals in cancer as recent developments, perhaps they are not so novel after all. First proposed as adjunctive therapy by Schinzinger in 1889, Beatson introduced ovariectomy into clinical practice in 1896[1]. While hormonal therapy is not traditionally categorized as targeted therapy, the estrogen receptor remains arguably the most important growth factor receptor identified for breast cancer, as adjuvant hormonal therapies have a bigger impact on recurrence and survival than any other treatment.

The growing complexity of cancer treatment, and more particularly of the biologic basis underlying these therapies, suggests we re-consider our conceptual approach to the treatment of breast, and indeed all cancer. Hanahan and Weinberg, in discussing "The Hallmarks of Cancer," provide a framework for approaching these novel therapies (Table 1).[2] This landmark review identified, in broad terms, seven critical features—the cancer cell's "tool kit"—responsible for the phenotype we recognize as cancer. Novel therapies for breast cancer can be viewed within

Table 1. The hallmarks of cancer

1. Self-sufficiency in growth signals
2. Insensitivity to antigrowth signals
3. Evading apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Tissue invasion and metastasis

SOURCE: From Hanahan, D and Weinberg, R.A.[2]

the framework of these hallmarks of cancer, and we will use this model to further discuss the development of new targeted therapies for breast cancer.

SELF-SUFFICIENCY IN GROWTH SIGNALS

During normal growth and differentiation, and throughout the life of the host, cell proliferation is rigidly controlled. Cancer cells escape the normal growth control and proliferate unchecked. This escape may occur via mutations that result in overexpression of differentially regulated growth factors or their receptors. Targeting self-sufficiency in growth signals has had profound effects in the development of new therapies for patients with breast cancer.

TARGETING THE EPIDERMAL GROWTH FACTOR RECEPTOR

The human epidermal growth factor receptor-2 (HER-2)/*neu* (c-*erbB*-2) gene is localized to chromosome 17q and encodes a family of four transmembrane tyrosine kinase receptor proteins that are members of the epidermal growth factor receptor (EGFR) or HER family (Figure 1).[3] Receptor tyrosine kinases such as these provide a binding site for various proteins, or ligands, which in turn, activate various downstream signaling pathways. These events are crucial for regulation of cell proliferation and survival.

Overexpression of HER-2 protein, amplification of the HER-2 gene, or both occurs in 20–25% of breast cancers and is associated with poor prognosis.[4–6] Several murine antibodies against the extracellular domain of the HER2 protein have been tested in human cancer cells that overexpressed HER-2 and have inhibited proliferation.[7–9] In order to minimize the immunogenicity, a humanized antibody called trastuzumab (Herceptin®) was created and shown to be effective in breast cancer cells.[10,11] Trastuzumab has been evaluated in phase III clinical trials in both the metastatic and adjuvant settings.

Trastuzumab in Metastatic Breast Cancer

Slamon and colleagues randomized 469 women with HER-2 positive metastatic breast cancer who had not received prior chemotherapy for metastatic disease to receive standard chemotherapy alone or in combination with trastuzumab.[12] The addition of trastuzumab to chemotherapy was associated with a longer time to disease progression (TTP) (median 7.4 months vs. 4.6 months, $p < 0.001$), a higher

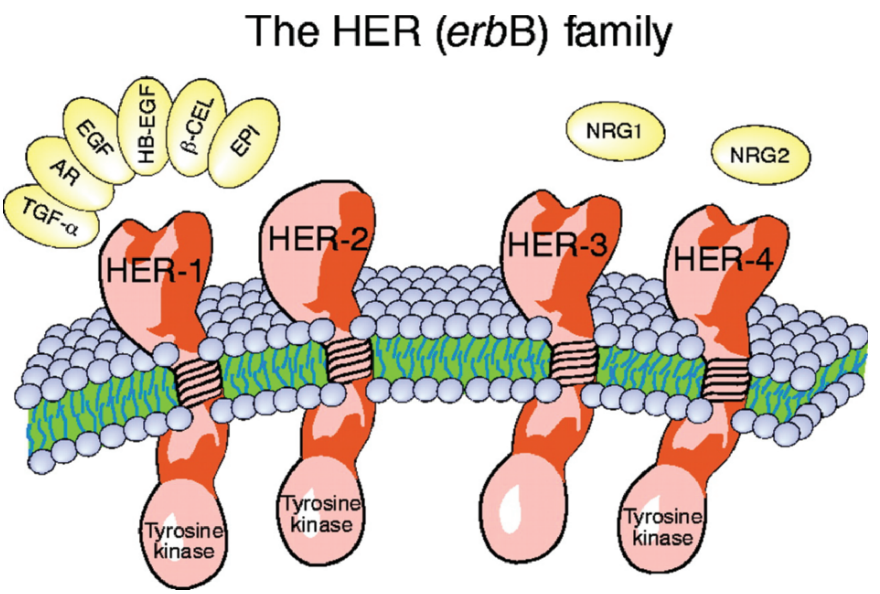

Figure 1. The HER (erb) gene family. Note that HER-2/neu has no known ligands and that HER-3 has no intrinsic tyrosine kinase activity. Abbreviations: TGF-α= transforming growth factor alpha; AR = amphiregulin; EGF = epidermal growth factor; HB-EGF = heparin binding EGF; β-CEL = beta cellulin; EPI = epinephrine; NRG1 = neuregulin 1; NRG2 = neuregulin 2. (By Permission of JS Ross3).

rate of objective response (50 vs. 32%, $p < 0.001$), and longer survival (median survival, 25.1 vs. 20.3 months; $p = 0.01$). With the overwhelmingly positive results of this trial, trastuzumab plus chemotherapy has become standard of care as first-line therapy for women with metastatic breast cancer that overexpresses HER-2.

Trastuzumab in Early-Stage Breast Cancer—Use in the Adjuvant Setting

Five large trials have been conducted investigating the role of trastuzumab in the adjuvant setting for HER-2 positive early-stage breast cancers. Romond et al. reported results of two combined North American studies.[13] The North Central Cancer Treatment Group (NCCTG) trial N9831 compared three regimens: group A received doxorubicin and cyclophosphamide followed by weekly paclitaxel (AC→T); group B received the same regimen followed by 52 weeks of trastuzumab after paclitaxel (AC→T→H); and group C received the same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel (AC→TH). The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 compared doxorubicin (A) and cyclophosphamide (C) followed by paclitaxel (T) every 3 weeks (group 1) with the same regimen plus 52 weeks of trastuzumab (H) beginning with the first dose of paclitaxel (group 2). The studies were amended to include a joint

analysis comparing groups 1 and A (the control group) with groups 2 and C (the trastuzumab group). Group B was excluded from the joint analysis because trastuzumab was not given concurrently with paclitaxel. At a median follow-up of 2 years, the study was terminated early because of a 52% reduction in events (defined as recurrence, second primary, or death before recurrence) in the trastuzumab group. The primary endpoint of disease-free survival (DFS) at 3 years was 87.1% in the trastuzumab group and 75.4% in the control groups, an absolute difference of 12 percent. Major efficacy results are summarized in Table 2. Trastuzumab therapy was associated with a 33% reduction in the risk of death at 4 years, ($p = 0.015$). The three-year cumulative incidence of New York Heart Association (NYHA) class III or IV congestive heart failure (CHF) or death from cardiac causes in the trastuzumab group was 4.1% in the B-31 trial and 2.9% in the N9831 trial.

Similar results were seen in the HERA trial[14] (Table 3). This large (more than 5,000 women randomized), international, multi-center, randomized phase III trial compared one or two years of adjuvant trastuzumab therapy with observation in women with HER-2 positive early-stage breast cancer who had completed adjuvant or neoadjuvant chemotherapy, surgery, and/or radiation. In both treatment arms, trastuzumab was initiated at the completion of the adjuvant chemotherapy, radiation, or definitive surgery and was administered every 3 weeks. In contrast to

Table 2. Summary of efficacy data North American trials

	% Patients			
Endpoint	Control	Trastuzumab	Follow-up (years)	*p*-value
DFS	75.4	87.1	3	<0.0001
OS	91.7	94.3	3	0.015
DR	18.5	9.6	3	<0.001

DFS - disease-free survival
OS - overall survival
DR - distant recurrence

Table 3. Summary of efficacy data HERA trial

	% Patients			
Endpoint	Control	Trastuzumab (1y)	Median Follow-up (y)	*p*-value
DFS (2y)	85.8	77.4	2	<0.0001
OS (2y)	95.1	96	2	0.26
DFS (3y)	74	81	3	<0.0001
OS (3y)	90	92	3	0.0115

DFS (2y) - disease free survival at 2 years
OS (2y) - overall survival at 2 years
DFS (3y) - disease free survival at 3 years
OS (3y) - overall survival at 3 years

the North American trials, most women did not receive a taxane as a component of their adjuvant chemotherapy, and a larger percentage (approximately one-third) had node-negative disease. Early analysis after a median follow-up of one year revealed an absolute benefit in DFS at 2 years of 8.4% in the women treated with one year of trastuzumab (85.8 percent vs. 77.4 percent, HR 0.54, $p < 0.0001$). OS at 2 years was not statistically significant between the two groups. Updated results after an average of 24 months showed a 36% reduction in disease recurrence (HR 0.64, three-year DFS of 81% vs. 74%) as well as a significant improvement in overall survival (OS) (HR 0.66, 92% vs. 90% in the trastuzumab and nontrastuzumab groups, respectively).[15] Symptomatic CHF plus a decrease in left ventricular ejection fraction (LVEF) of ≥ 10 points to an LVEF <50 percent occurred in 2% of women on the trastuzumab arm compared to 0.1% in the control group. The only cardiac event occurred in the control group. Data have not yet been reported for the two-year trastuzumab group.

All of the aforementioned trials studied one year of adjuvant trastuzumab. Efficacy of shorter course trastuzumab was evaluated in the FinHer trial.[16] A total of 1,010 women with node-positive or high-risk node-negative breast cancer were randomly assigned to three courses of docetaxel or vinorelbine followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). The 232 women with HER2-positive breast cancer were randomly assigned to receive or not receive nine weekly trastuzumab infusions after completing chemotherapy. Within this subgroup, DFS was significantly better among those who received trastuzumab (89 % vs. 78%, $p = 0.01$), and there was a trend toward improvement in OS (96% vs. 90%, $p = 0.07$). These results are similar to those seen in women treated with trastuzumab for a year. No patient treated with short-course trastuzumab had decreased LVEF or heart failure.

Finally, in an attempt to maximize efficacy and minimize cardiotoxicity, Slamon and colleagues compared two anthracycline-containing regimens (AC followed by docetaxel [D] with or without trastuzumab) vs. a non-anthracycline arm (carboplatin plus docetaxel and trastuzumab, DCH) in 3,222 women with HER-2 positive, node-positive or high-risk node-negative disease in BCIRG 006 trial.[17] Preliminary results at a median follow-up of 23 months showed improved DFS in both traztuzumab-containing arms (HR 0.49 with AC→DH, $p = 0.00000048$ and 0.61 with DCH, $p = 0.00015$) with no statistically significant difference between the two regimens. Though there were fewer symptomatic cardiac events in the DCH arm as compared to anthracycline-containing arms, this was not statistically significant. While these early results suggest that DCH may represent a less cardiotoxic alternative to anthracycline-containing trastuzumab combinations, further maturation of the trial data is needed to know if the efficacy of DCH is sufficient to endorse it over AC followed by a taxane plus trastuzumab.

In summary, trastuzumab used in the adjuvant setting significantly prolongs both PFS and OS and has become standard of care for patients with HER-2 overexpressing breast cancer. The frequency of symptomatic cardiac events was similar in all the trials and ranged between 2–4%.

DUAL TYROSINE KINASE INHIBITION

Lapatinib is an orally active dual erbB-1/2 tyrosine kinase inhibitor that blocks signaling at both the epidermal growth factor receptor (EGFR, also called erbB-1) and HER2/neu (erbB-2), leading to cell growth arrest and/or apoptosis in ErbB1 and ErbB2 dependent tumors. Early clinical data in metastatic breast cancer suggested that combining two ErbB-targeted therapies (i.e., anti-ErbB2 antibody with small molecule tyrosine kinase inhibitor) that act at different sites of the receptor with distinct mechanisms of action may enhance the efficacy of both drugs.[18]

Lapatinib in Metastatic Breast Cancer

Lapatinib monotherapy has proven response in refractory metastatic breast cancer.[19] Two phase II trials of single-agent lapatinib in patients with refractory metastatic breast cancer have been conducted.[20–22] In the EGF20002 study, 78 patients with ErbB-2–overexpressing metastatic breast cancer, who progressed on prior trastuzumab-containing regimens, received lapatinib daily at a dose of 1,500 mg. In the EGF20008 study, metastatic breast cancer patients who developed progressive disease following prior treatment with anthracyclines, taxanes, and capecitabine received 1,500 mg/day lapatinib and were divided into cohort A (n = 140) and cohort B (n = 89). Cohort A included ErbB-2–overexpressing trastuzumab-refractory metastatic breast cancer patients, while cohort B included ErbB-2–non-overexpressing metastatic breast cancer with no prior trastuzumab. In the preliminary analysis, the clinical benefit rate (CBR = CR + PR + SD) was 22% in patients in the EGF20002 study and 14% in patients in the EGF20008 study.

A combined biomarker analysis was also conducted for these two studies, to determine the relevant tissue and serum biomarkers that would predict the response to single-agent lapatinib.[23] Preliminary data showed that metastatic breast cancer patients were more likely to respond to lapatinib if their disease was estrogen-receptor (ER) negative, progesterone receptor (PR) negative, and ErbB-2 overexpressing. Additionally, a decline in serum ErbB-2 extracellular domain after 4 and 8 weeks of lapatinib therapy correlated with clinical response.

In a phase II trial, lapatinib as a single agent was evaluated in inflammatory breast carcinoma (IBC). Patients were divided into two groups: those who overexpressed HER-2 and those who did not. There was a 72% RR in the group who overexpressed HER-2. There were no responders in the group that did not overexpress HER-2, thus demonstrating that ErbB2 overexpression, but not ErbB1 expression alone, predicts sensitivity to lapatinib.[24]

A randomized phase III trial (EGF 100151) was conducted that compared the addition of lapatinib to capecitabine with capecitabine alone in women with progressive, HER2-positive, locally advanced or metastatic breast cancer who had previously been treated with a minimum of an anthracycline, a taxane, and trastuzumab.[25] The combination regimen consisted of lapatinib at a dose of 1250 mg daily on a continuous basis, and capecitabine at a dose of 2,000 mg/m^2 in divided doses on days 1 through 14 of a 21-day cycle. The interim analysis showed that the

addition of lapatinib to capecitabine was associated with a 51% reduction in the risk of disease progression ($p < 0.001$). The median time to progression was 8.4 months with combination therapy and 4.4 months with monotherapy. CBR were 27% for the combination-therapy group and 18% for the monotherapy group. These results support the addition of lapatinib to capecitabine in patients with HER-2 positive breast cancer with disease progression after trastuzumab-containing regimens.

Currently, there are several ongoing phase III trials evaluating efficacy of combination therapy with lapatinib as part of the first-line treatment of metastatic breast cancer.

Lapatinib in Early Breast Cancer—Use in the Adjuvant Setting

Two large ongoing phase III trials evaluating the role of lapatinib in the adjuvant setting will be getting underway in the near future. In 2006, GlaxoSmithKline (GSK) and Breast Cancer International Group (BIG) initiated a cooperative group phase III adjuvant trial with lapatinib as the experimental drug in approximately 8,000 women. The study is a multi-arm design (trastuzumab vs. lapatinib vs. trastuzumab plus lapatinib vs. lapatinib followed by trastuzumab). Primary endpoints are OS, TTP, RR, and safety.[26]

TEACH (Tykerb® Evaluation After Chemotherapy) is a phase III, randomized, double-blinded, placebo-controlled trial using lapatinib in the adjuvant setting as the experimental drug. The objective is to determine whether adjuvant therapy with lapatinib for one year will improve DFS.[26]

SUSTAINED ANGIOGENESIS

Invasion and metastasis of breast cancer, and indeed of all solid tumors, depends on angiogenesis, the formation of new blood vessels to nourish the tumor.[27] Normal vasculature is quiescent in healthy adults with each endothelial cell dividing once every ten years; active angiogenesis is required only for wound healing, endometrial proliferation, postlactational mammary gland involution and pregnancy. In contrast, tissue remodeling and angiogenesis is crucial for the growth and metastasis of breast cancer and provides an attractive therapeutic target that may, theoretically, have limited toxicity.

TARGETING THE VASCULAR ENDOTHELIAL GROWTH FACTOR PATHWAY

Our growing understanding of angiogenesis has fostered the development of agents targeting specific steps in the angiogenic cascade, (Figure 2) many of which have entered the clinic. A detailed list of agents in clinical development can be obtained from the Angiogenesis Foundation (http://www.angiogenesis.org) or from the National Cancer Institute (http://cancernet.nci.nih.gov). Table 4 summarizes selected agents targeting the vascular endothelial growth factor (VEGF) pathway.

Agents Targeting the VEGF Ligand

Invasive human breast cancers commonly express multiple angiogenic factors, with the 121-amino acid isoform of vascular endothelial growth factor (VEGF)

Table 4. Selected agents targeting the VEGF pathway

Class	Examples	Targets	Stage of Development
Agents targeting the VEGF ligand			
Antibodies	Bevacizumab	VEGF	Phase III
Soluble receptors	VEGF-TRAP	VEGF, PIGF	Phase II
Agents targeting the VEGF Receptor TK			
Small molecule inhibitors	Sunitinib	VEGFR-2, PDGFR, c-Kit	Phase II/III*
	Axitinib	VEGFR-2, PDGFR	Phase II
	SU14813	VEGFR-1,2, c-Kit	Phase I/II
	Pazopanib	VEGFR-1,2, PDGFR, c-Kit	Phase I/II
	Sorafenib	Raf, VEGFR-1,2, c-Kit	Phase II**
	PTK-787	VEGFR-1,2, PDGFR, c-Kit	Phase II/III
	AEE788	VEGFR-1,2, ErbB1,2	Phase II
	Vandetinib	VEGFR, EGFR	Phase II
	AZD2171	VEGFR, c-Kit	Phase II
	AMG706	VEGFR-1,2, PDGFR, c-Kit	Phase I/II

*Approved in RCC and GIST
**Approved in RCC

predominating[28].VEGF is a highly conserved, homodimeric, secreted, heparin-binding glycoprotein that stimulates endothelial cell proliferation and migration, inhibits endothelial cell apoptosis, and supports maintenance of the newly formed tumor vasculature (Figure 3). Additionally, VEGF induces proteinases that remodel extracellular matrix, increases vascular permeability and vasodilation, and inhibits antigen-presenting dendritic cells.[29]

Bevacizumab in Metastatic Breast Cancer

Bevacizumab is a humanized monoclonal antibody directed against all isoforms of VEGF-A. A phase II study of bevacizumab monotherapy in 75 patients with previously treated MBC reported a 9.3% objective response rate with 17% of patients responding or stable at 22 weeks; four patients continued therapy without progression for over 12 months.[30] The addition of bevacizumab to capecitabine significantly increased response rate (9.1% vs. 19.8%; $p = 0.001$) but not progression free survival (4.17 vs. 4.86 mos.; HR = 0.98) in patients with anthracycline- and taxane- refractory disease.[31]

The first positive phase III trial of antiangiogenic therapy in patients with metastatic breast cancer was an Eastern Cooperative Oncology Group (ECOG) study which compared the efficacy and safety of paclitaxel with or without bevacizumab as initial chemotherapy in 666 patients with metastatic disease (E2100).[32] Combination therapy significantly increased the response rates in all patients (35.8% vs. 20.9%; $p < 0.0001$) and in the subset of patients with measurable disease (47.2% vs. 25.2%; $p < 0.0001$). Paclitaxel + bevacizumab significantly prolongs PFS (11.3 mo vs. 6.0 mo; HR = 0.60, $p < 0.0001$). Overall survival was similar in both groups (26.6 mo vs. 25.2 mo; $p = 0.53$). Grade 3/4 hypertension (15% vs. 0%;

$p < 0.0001$), proteinuria (3.5% vs. 0%; $p = 0.0002$), headache (2% vs. 0%; $p = 0.009$) and cerebrovascular ischemia (2% vs. 0%; $p = 0.009$) were more frequent in patients receiving paclitaxel + bevacizumab. This trial represents an important proof of concept; antiangiogenic therapy now clearly has a role in the therapeutic arsenal for breast cancer.

The XCALIBr trial[33] is a phase II study that evaluated the combination of capecitabine and bevacizumab in the first-line treatment of metastatic or recurrent breast cancer. In the first phase of this trial, patients with HER-2 negative recurrent or metastatic breast cancer were given capecitabine 1000 mg/m^2 twice daily days 1–15 and bevacizumab 15 mg/kg on day 1 cycled every 21 days until progression. Upon progression, the bevacizumab was continued, and patients were given either weekly vinorelbine or paclitaxel in the second phase of the trial. In the first interim safety and efficacy analysis at a mean duration of follow-up of 6.1 months, the ORR was 34% and clinical benefit (response or stable disease) was 72%. There was no CHF or grade 4 diarrhea or stomatitis. The most common grade 3 adverse events were and-foot syndrome (HFS) (13%) and pain (10%). The only grade 4 adverse event was pulmonary embolism (2%). This trial shows that the combination of capecitabine and bevacizumab in the first-line treatment of metastatic breast cancer is active and well-tolerated. Mature efficacy results of TTP, PFS and OS have not yet been reported.

Currently enrolling, the Ribbon studies are investigating the combination of bevacizumab with standard chemotherapy for metastatic breast cancer. The Ribbon 1 study compares chemotherapy plus placebo to chemotherapy plus bevacizumab in previously untreated metastatic breast cancer, while Ribbon 2 compares the arms in patients who have previously received treatment for metastatic breast cancer. Bevacizumab in the Adjuvant Treatment of Breast Cancer.

The most successful use of anti-angiogenic therapy is predicted to be in the adjuvant setting, but large trials will be needed to prove this concept. Metastatic trials with bevacizumab have limitations. Firstly, it is evaluated as chronic therapy in only a few patients. Also, in the metastatic setting, there is different tolerance for toxicity and less concern for rare but potentially serious or fatal toxicities. Side effects of bevacizumab include hypertension, proteinuria, thromboembolic events, hemorrhage, and gastrointestinal perforation. CHF has only been reported with concurrent or prior anthracycline use.

Currently, there are two ongoing randomized clinical trials designed to evaluate the efficacy and toxicity of bevacizumab in combination with standard chemotherapy in the adjuvant treatment of early breast cancer. E2104, a phase II trial, has recently completed enrollment, with the primary objective of the study being incidence of clinical CHF. A future study E5103 is a large, three-arm phase III study comparing AC→T vs. AC→BT vs. BAC→BT→B (bevacizumab given for a total of one year) in women with node-positive or high-risk node-negative disease. The primary objective is DFS.

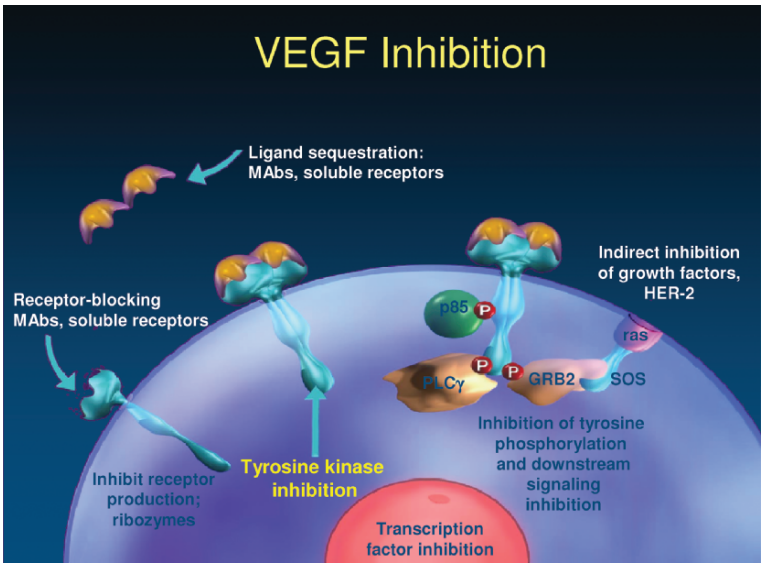

Figure 2. VEGF inhibition results from three main mechanisms: Ligand sequestration via soluable receptors or monoclonal antibodies (MAbs); receptor-blocking by soluble receptors or MAbs; or by indirect inhibition of growth factors (i.e. HER-2).

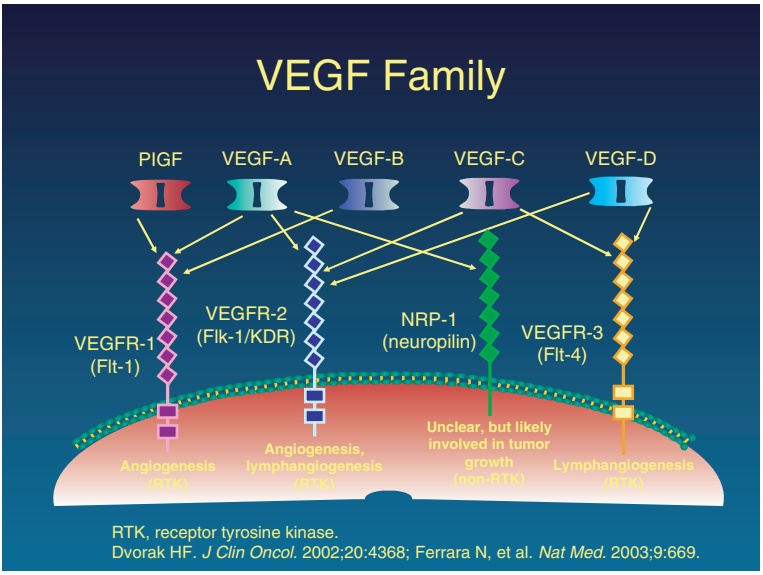

Figure 3. The VEGF family includes four receptor tyrosine kinases (RTK) with specific ligands that result in angiogenesis, lymphangiogenesis, and cellular proliferation. VEGFR-1 (flt-1) is a RTK that binds PIGF, VEGFA and VEGF-B and results in angiogenesis. VEGFR-2 (flk1/KDR) is a RTK that binds VEGF-A, VEGF-C, and VEGF-D and results in angiogenesis and lymphangiogenesis. NRP-1 (Neuropilin) binds VEGF-A, and its function is unclear but likely regulates tumor growth. It is not a RTK. VEGFR-3 (Flt4) is a RTK that binds VEGF-C and VEGF-D resulting in lymphangiogenesis. (Adapted from Dvorak, H. F. J. Clin Oncol. 2002, 20:4368; Ferrara, N., et al. Nat Med. 2003, 9:669.).

Agents Targeting the VEGF Receptor Tyrosine Kinase (TK)

Sunitinib (SU11248) is an oral tyrosine kinase inhibitor (TKI) that inhibits multiple signaling pathways including VEGFR, platelet-derived growth factor receptor (PDGFR), kit, and flt-3. Phase II data show activity of sunitinib monotherapy in previously treated MBC.[34] Patients ($n = 64$) in this trial with both HER-2 and ER positive metastatic breast cancer were treated with SU11248, 50 mg daily for 28 days followed by a 14-day break. Preliminary data show 7 (14%) patients with a PR and one patient with prolonged SD. The most frequently reported grade 2/3 non-hematologic toxicities were fatigue, diarrhea, anorexia, hypertension, mouth pain, and handfoot syndrome. Grade 3 neutropenia was reported by 39% of patients, but there were no neutropenic fevers. Grade 3 thrombocytopenia and anemia were less common (15% and 2%, respectively). Toxicity, albeit manageable, frequently necessitated dose reduction or delay with nearly half of patients requiring either dose-reduction or interruption for toxicity.

Since sunitinib has proven activity as monotherapy, it is now being studied in combination with other agents. Phase I and II studies with weekly paclitaxel plus sunitinib are nearly complete. A phase III study of paclitaxel plus sunitinib vs. paclitaxel plus bevacizumab is now enrolling. Other future trials with sunitinib in breast cancer include the addition of sunitinib with trastuzumab in previously untreated patients with HER-2 positive disease as well as evaluating sunitinib vs. standard chemotherapy in triple negative disease.

Another multi-targeted receptor TK currently in clinical trial is axitinib (AG013736). It has proven efficacy in renal cell carcinoma. A phase II study of docetaxel +/- axitinib in metastatic breast cancer is completed, but the results have not yet been reported.

EVADING APOPTOSIS

A tumor cell's survival is determined not only by the rate of proliferation but also by the rate of cell death. Apoptosis, or programmed cell death, is a physiologic response of normal cells to stressors. Programmed cell death machinery includes transmembrane death receptors (FAS ligand binding), bax (pro-apoptotic) and bcl-2 (anti-apoptotic) proteins, and p53 protein. The success of cancer cells, in part, is attributed to acquired resistance to apoptosis. One strategy includes alteration of the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway which is involved in mediating cell growth and proliferation. Signaling through this pathway regulates the serine-threonine kinase mammalian target of rapamycin (mTOR) which is important for regulation of the cell cycle. The PI3K/AKT pathway transmits anti-apoptotic survival signals and is likely involved in mitigating apoptosis in many human tumors. In a study of 70 primary breast cancer specimens, 40% had an activating mutation in the PI3KCA gene.[35]

MOTOR INHIBITION

Rapamycin is an antibiotic that has demonstrated anti-tumor activity through cell cycle arrest resulting from inhibition of mTOR.[35] Temsirolimus (CCI-779) is an

inhibitor of mTOR that, in preclinical studies, inhibited the proliferation of breast cancer cell lines that were estrogen dependent, overexpressed the HER2/neu receptor, or were deficient in the PTEN tumor suppressor.[36] Phase II clinical data suggested modest activity in previously treated patients with recurrent or metastatic breast cancer.[25] Because mTOR inhibition modulates resistance to endocrine therapy in breast cancer cell lines, it was postulated that the combination of CCI-779 with an aromatase inhibitors would improve RR and PFS. However, a phase III trial comparing letrozole alone vs. letrozole plus CCI-779 showed no difference in RR or PFS.[37] Thus, mTOR inhibitors have not yet entered into routine clinical use.

LIMITLESS REPLICATIVE ACTIVITY: TELOMERASE INHIBITION

In normal cells senescence is associated with progressive loss of telomeres, repetitive DNA sequences capping each chromosome. With each replicative cycle, telomeres become progressively shorter, eventually resulting in senescence and cell death. Tumors commonly express the enzyme telomerase, which protects the telomeres from shortening. In essence, tumors never grow old. Expression of hTERT, the human telomerase catalytic subunit gene, is common in breast cancers,[38] including preinvasive tumors.[39,40] Telomerase expression is associated with lymphovascular invasion, nodal metastasis[41], and a higher relapse rate following initial therapy.[42] Several factors affect telomerase expression in breast cancer. Estrogen[43] and progesterone[44] stimulate while tamoxifen[45] and wild-type p53[39, 46] inhibit telomerase activity.

Presently, it is not known whether we can target telomerase activity as a therapeutic intervention. Inhibiting telomerase would not lead to immediate tumor cell senescence and death. However, inhibition of telomerase in human breast cancer cells renders them more sensitive to topoisomerase inhibition,[47] suggesting the potential for combinatorial activity with standard agents such as doxorubicin. Specific telomerase-inhibiting agents are currently in development,[45,48] and should enter the clinic in the near future.

TISSUE INVASION AND METASTASES

Epithelial tumors such as breast cancer frequently derive from normal cells populating the inner lining of ductal structures surrounded by basement membranes. The ability to invade through basement membranes, which characterize the transition from a non-invasive to an invasive cancer, is a hallmark of the malignant phenotype. Metastasis is an extension of local invasion. Following invasion, cancer cells transit extracellular matrix, intravasate, and traverse blood vessels to lodge at a distant site, extravasate and grow as a metastatic focus.

METALLOPROTEINASE INHIBITION

Tumors secrete proteases such as the matrix metalloproteinases (MMPs) to degrade the basement membrane and surrounding stroma. Overall expression of MMP-2 and MMP-9 has been associated with grade and stage of breast cancer,[49, 50] and

increased serum levels are found in patients with metastatic disease.[51] Inhibition of the MMPs decreases metastasis and local tumor growth in mouse xenografts.[52] Several broad spectrum MMP inhibitors have entered (and exited) clinical trials when phase III trials failed to find a clinically meaningful improvement in outcome.[53–55] Chronic therapy with the broad spectrum MMP inhibitor marimastat failed to delay progression in patients responding or stable after initial chemotherapy for metastatic breast cancer.[56] Though theoretically use of the MMP inhibitors in the adjuvant setting would be expected to provide the greatest benefit, musculoskeletal toxicity prevents such use.[57]

Other Proteinases

Tumors may exploit other proteases besides the MMPs. Membrane-associated urokinase-type plasminogen activator (uPA) expression and the ratio of uPA to plasminogen activator inhibitor-1 (PAI-1) are associated with impaired survival or local relapse.[15,58,59] uPA inhibitors may have therapeutic potential, but clinical development has thus far been limited by toxicity.

CONCLUSION

As we acquire more knowledge about the molecular biology of cancer, we increase our potential arsenal for combating the disease in the clinical setting. Breast cancer treatment no longer consists only of traditional cytotoxic chemotherapy, but rather of a whole host of novel targeted agents with the promise of prolonging survival and even cure in patients with breast cancer. From targeting receptors to ligands to intracellular molecules, the number of potential targeted pathways now seems limitless. As we continue to translate what we know from preclinical models to the clinical setting, and as current ongoing clinical trials become more mature, the field of breast cancer research as well the treatment of the patient with breast cancer becomes even more exciting.

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9. NEW RADIATION TREATMENT STRATEGIES FOR EARLY STAGE BREAST CANCER

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INTRODUCTION

The development of breast-conserving therapy (BCT) using whole-breast irradiation (WBI) to eradicate residual disease following nonablative resection of breast cancer was one of the great success stories of twentieth-century oncology. Approximately 70-80% of patients with stage I or II invasive breast cancers are estimated to be potential candidates on technical grounds for BCT.[1, 2]

Despite this success, it seems likely that the role of radiation therapy (RT) in BCT will change substantially in future. Patients now present with smaller, more favorable cancers than when BCT was initially developed.[3] Systemic therapy has substantially decreased local tumor recurrence rates following BCT in patients receiving WBI.[4–7] Technologic advances, such as the use of computed tomography (CT) for RT treatment simulation and planning, now allow much more accurate localization of the tumor excision site and delivery of conformal and homogeneous radiation doses than was possible in the past.[8] Finally, molecular biology and genetics promise a far more sophisticated understanding of why some tumors are more responsive to RT than others, and why some patients are more likely to develop complications than others.

I will discuss some of the implications of these developments. First, can some patients with invasive cancer avoid having RT following breast-conserving surgery-and what are the consequences of having a local failure if RT is not given? Second, can partial-breast irradiation (PBI) substitute for WBI? Third, can the new RT technology reduce the duration, cost, and risk of complications associated with

WBI? And finally, what do recent studies suggest about whether we will really be able to practice "personalized medicine" with regards to breast cancer RT in the not too-distant future?

BREAST-CONSERVING SURGERY WITHOUT RADIATION THERAPY

Multiple randomized trials have shown that RT substantially reduces the risk of local recurrence following breast-conserving surgery (CS) in relatively unselected patients with early-stage invasive breast cancer.[8,9] However, RT is time-consuming, expensive, and may cause complications.[10] Further, some have argued that local failure is of only cosmetic or psychological importance, rather than affecting the ultimate chance of cure. Therefore, many investigators have tried with some success to identify patient subgroups with a low risk of local recurrence following CS without RT. Table 1 lists results in such studies with approximately 5-year median follow-up or longer.

It is not yet fully clear exactly what combinations of patient-, clinical-, and tumor-related factors are needed to yield such impressive results. Elderly patients may have especially relatively low risks of local failure after CS without RT, especially if tamoxifen is used.[11,14,15] In a trial conducted in Ontario and British Columbia in which the median patient age was 68 years, with a median follow-up of 94 months the 8-year actuarial local failure rates in unirradiated patients age 60 or older with hormone-receptor positive tumors 2 cm or smaller was 7%, and for those with tumors 1 cm or smaller 5%.[16,17]

In addition to patient age, tumor size, and hormone receptor status, features such as histologic subtype, grade, lymphovascular invasion, and margin width are probably also important to the risk of local failure after CS without RT. For example, a small prospective study of CS without RT or systemic therapy from the institutions affiliated with the former Joint Center for Radiation Therapy (Boston) found failure rates of 12%, 21%, and 50% in patients with grade 1, 2, or 3 infiltrating ductal carcinomas, respectively, with a median follow-up time of 86 months.[22] In series of patients older than age 70 treated in Nottingham, England, with a median follow-up time of 37.5 months (most of whom received tamoxifen), the risk of local failure was 33% (4/12) for patients with tumor-free margin width of less than 1 mm, 12% (2/17) for those with margins of 1-5 mm, and 2% (1/54) for patients with margins wider than 5 mm.[23] However, these factors have been very poorly studied, and little can be definitively stated about them.

Hormonal therapy may be needed to see low failure rates in patients treated without RT, even in highly selected populations. In the German Breast Cancer Study Group V trial, with a median follow-up time of 71 months, the rate of local failure in patients treated with CS without either tamoxifen or RT was 29% (23/79), compared to 3% (2/80) for patients treated with CS plus tamoxifen.[19] (Failure rates in the patients receiving CS plus RT were 5% for 94 patients not receiving tamoxifen and 3% for 94 patients who did.) In the BASO II trial, with a median follow-up time of 77 months, the risk of local failure in patients receiving neither tamoxifen nor RT was 14% (24/175); for patients receiving tamoxifen but

Table 1. Local failure rates for highly selected patient subgroups treated with conservative surgery without radiotherapy with median follow-up of approximately five years or longer

Study	Dates	Age	Nodes	Max size	Subgroup features	Margins	Tamoxifen used	FU (mo)	# Patients	Local failure
Milan III [11]	1987-1989	≥66	pN0/1	2.5	?	Neg	Optional (TAM or CT)	109	23	4%
Women's College Hospital [12]	1977–1986	≥65	pN0	?	ER+, LVPI−, no comedo DCIS	Neg	None	109	34	9%
Uppsala-Örebro [13]	1981–1998	≥56	pN0	2	No comedo or lobular features	Neg	None	103	84	11% (10-yr)
CALGB 9343 [14, 15]	1994–1999	≥70	pN0 or cN0	2	ER+	Neg	All	95	319	6%
Ontario-British Columbia Trial [16, 17]	1992–2000	≥60	pN0 or cN0	5	≤2 cm, ER+ or PR+	Neg	All	94	139	7% (8-yr)
NSABP B-21 [7]	1991–1998	Any	pN0	1	ER+	Neg	All	89	197	10%
BASO II [18]	1992–2000	≤69	pN0	2	HG 1	Neg	All	77	411	4%
GBSG V [19]	1991–1998	45–75	pN0	2	HG 1–2, EIC-, LVI-, ER+ or PRP+	Neg	All	71	80	3%
Boston-Providence [20]	1978–2003	≥51	cN0	1.5	HG 1–2	≥10 mm (gross)	Some	61	80	6%
Vienna [21]	1983–1994	≥61	pN0	4	ER+	Neg	Some	60	83	1%

Note: Crude local failure rates are given, unless a time is given in parentheses, in which case the results are actuarial.
Symbols/Abbreviations:?: unknown or not stated; CALGB: Cancer and Acute Leukemia Group B; cN0: clinically-uninvolved axillary lymph nodes; CT: chemotherapy; EIC-: no extensive intraductal component; ER+: positive for the estrogen-receptor protein; FU: median length of follow-up (in months); GBSG V: German Breast Cancer Study Group Trial V; HG: histologic grade; LVI-: lymphovascular invasion; LVPI-: no lymphovascular or perineural invasion; Neg: "negative" margins, not otherwise defined in the study; NG: nuclear grade; NSABP: National Surgical Adjuvant Breast and Bowel Project; pN0: pathologically-uninvolved axillary lymph nodes; PR+: positive for the progesterone-receptor protein; SPF: S-phase fraction.
Adapted from: Recht A. 2005. Lessons of studies of breast-conserving therapy with and without whole-breast irradiation for patient selection for partial-breast irradiation. Semin Radiat Oncol 15:123–132[9]; with permission of the publisher.

not RT, the rate was 4% (17/421).[18] (The rates in patients receiving RT but not tamoxifen were 5%, or 9/182 patients, and 1% or 3/380 patients, for those receiving both RT and tamoxifen, respectively.)

The physical and psychological implications of local recurrence must also be considered before deciding whether patients should be treated with CS without RT. First, salvage CS has been performed in only 30–70% of patients initially treated with CS alone following local relapse.[8] It rarely seems that the extent of the recurrence prevents further BCT; rather, I believe the psychological trauma of relapse pushes patients and physicians to prefer mastectomy. Second, the Early Breast Cancer Trialists' Collaborative Group 2000 overview demonstrated that improvements in initial local control obtained by giving RT increase breast-cancer specific and overall survival rates.[24] For patients with histologically-uninvolved axillary nodes, the 10-year actuarial local failure rates in the unirradiated and irradiated patients were 29.2% and 10.0%, respectfully; the 15-year breast cancer-specific mortality rates were 31.2% and 26.1%, a statistically-significant improvement of 5.1%; overall mortality rates were 36.0% and 31.4%, respectively, or a differences of 4.6%, which was almost significant ($p = 0.06$). If one assumes that RT reduces the 10-year local failure rate from 10% to 5%, then (since the degree of benefit of RT is roughly proportional to this difference) RT will likely yield about a 1% or smaller increase in breast cancer-specific mortality. Further, using the Oxford overview as a guide, this difference will not begin to appear until 5–10 years after initial therapy. The recent randomized trials comparing CS with and without RT for selected patients are too small to reliably show such differences, even with adequate follow-up. Finally, even patients with a such a "low" risk of local failure may prefer to reduce this risk yet further by being irradiated.[25, 26]

PARTIAL BREAST IRRADIATION

Patients undergoing BCT traditionally have been irradiated to the entire breast. However, the majority of tumor cells in the breast are found quite close to the primary tumor in most patients. A recent study examined tumor distribution in 134 patients with Stage I or II cancer (most of whom had screen-detected lesions) undergoing reexcision at William Beaumont Hospital near Detroit, after an initial excision showed uninvolved margins.[27] This found residual disease in 51 patients (38%), all of which was within 15 mm of the initial margin in 90% of patients. Multiple synchronous cancers are also rare for patients with clinically unicentric cancers (for example, only 3 of 183 patients in a study from Tokushima, Japan).[28] Finally, whether or not radiotherapy is given, 70-90% of recurrences are at or near the original tumor bed in the first 5–10 years after BCT,[8] suggesting regrowth of tumor cells not destroyed by the initial therapy.

Partial breast irradiation in principle has several potential advantages compared to WBI.[29,30] Such an approach may allow much shorter ("accelerated") treatment schemes, so that irradiation could be completed in a single day or one week. This would be more convenient for the patient, perhaps allow easier integration

of RT with chemotherapy, and potentially decrease the overall cost of treatment. By reducing the irradiated volume of the lungs, heart, and ribs, PBI might reduce the risk of long-term complications. Further, most physicians believe that a second course of irradiation cannot be safely given to the ipsilateral breast should the patient develop a new primary tumor; initial use of PBI might allow another chance at preserving the breast.

A number of different approaches to PBI have been described. These include: temporary brachytherapy using interstitial implantation[31–33] or a "balloon" device (MammoSite™, Cytec Corporation, Palo Alto, California)[34]; permanent implants[35]; intracavitary single-dose therapy[36,37]; and external-beam therapy using photons (with or without electrons)[38–40] or protons.[41]

Only a few modern studies of PBI (all using interstitial implantation) have had a median follow-up of 5 years or longer (Table 2). Their results have generally been excellent. For example, at William Beaumont Hospital near Detroit, 120 patients were treated from 1993–2000 with low-dose rate and 54 with high-dose rate brachytherapy.[32,42,46] All had tumors smaller than 3 cm in size, 0–2 positive axillary nodes, and nearly all had margins of excision wider than 2 mm. Most of the high-dose rate patients received 32 Gy in 8 fractions given twice daily, except for 8 patients treated with 34 Gy in 10 fractions; the low-dose rate patients received 50 Gy. Implants included a margin of 1–2 cm of normal tissue around the excision cavity. With a median follow-up for surviving patients of 103 months, there were 6 ipsilateral breast failures (2 of which were clinically located in another area of the breast and were thought to represent a new primary cancer, although one had the same pattern of loss of heterozygosity as the initial tumor). In an earlier analysis, local control and cosmetic results were identical to those of patients treated with conventional whole-breast irradiation in a matched-pair analysis.[32] Serious complications were rare, with an 8% incidence of grade 2–3 fibrosis by 5 years and 14% of patients developing (usually) asymptomatic fat necrosis.[47]

Three of the randomized trials comparing PBI to conventional WBI have been completed and reported to date. The first was conducted from 1982–1987 at the

Table 2. Local failure in series of accelerated partial-breast irradiation using interstitial implantation with median follow-up of 5 years or longer

Institution	# Patients	Follow-Up (months)	Local Failure
William Beaumont Hospital [42]	199	103	3%
London Regional Cancer Center [43]	39	91	16%
Budapest [33]	45	81	7%
Radiation Therapy Oncology Group Trial 95-17 [44]	99	74	6%
Ochsner Clinic [45]	163	65	3%

Christie Hospital in Manchester, England.[48,49] Axillary dissection was not performed, and systemic therapy was not used. Most patients did not have pre- or postoperative mammographic evaluation, and specimen margins were not evaluated microscopically. Patients received radiotherapy either of the entire breast and supraclavicular and axillary nodes (40 Gy in 15 fractions over 21 days, delivered on a 4-megavolt linear accelerator without the use of wedges) or of only the affected quadrant (40–42.5 Gy in 8 fractions delivered over 10 days, typically using 10-megavolt electrons, prescribed to the 100% isodose line, delivered to an average field size of 8 × 6 cm). With a median follow-up of 65 months in 708 evaluable patients, the 7-year actuarial rates of breast relapse were 11% and 20% in the whole-breast and PBI arms, respectively.[49] A more recent abstract confirmed these results.[50]

A small trial conducted from 1986–1990 at the Cookridge Hospital, Leeds, England randomly allocated 174 patients to receive either 40 Gy in 15 fractions to either the entire breast plus a boost dose of 15 Gy in 5 fractions to the area of the tumor bed plus an unspecified margin, or 55 Gy in 20 fractions to this tumor bed area.[51] The tumor bed location and extent were determined by palpation. With a median follow-up of 96 months, the local failure rates in the two arms were 4% and 12%, respectively.

A much more sophisticated approach was used in the trial conducted from 1998–2004 at the National Institute of Oncology in Budapest.[33,52] Patients with pathologic T1N0-1mic breast cancers, histologic grade 1 or 2 without an extensive intraductal component, with microscopic resection margins wider than 2 mm, received either whole-breast irradiation without a boost (50 Gy in 25 fractions) or PBI (high-dose rate interstitial brachytherapy of 7 fractions of 5.2 Gy each, or 50 Gy in 25 fractions using electrons for patients not technically suitable for implantation). At a median follow-up of 60 months, the 5-year actuarial failure rates in the two arms were 4% and 6%, respectively. There were no significant differences between the two treatment arms in the incidence of radiation side effects or cosmetic outcome.

Additional randomized trials are in progress. These include: the "TARGIT" trial, in which patients with uninvolved margins or limited margin involvement receive either conventional WBI with or without a boost (as per institutional policy) or a single intraoperative dose of 5 Gy delivered to 1 cm from the edge of the excision cavity using the 50 keV Intrabeam™ device (Carl Zeiss Surgical GmbH, Oberkochen, Germany)[36]; a trial the European Institute of Oncology, Milan which randomizes patients to conventional treatment or a single intraoperative electron treatment of 21 Gy delivered to the tumor bed[37]; a joint trial of the National Surgical Adjuvant Breast and Bowel Project and Radiation Therapy Oncology Group (B-39/0413) comparing PBI (using interstitial implantation, balloon brachytherapy, or external-beam therapy) to conventional whole-breast radiotherapy for patients with either invasive breast cancer or ductal carcinoma in situ, which opened in November 2004[29,30]; an trial in Europe only allowing interstitial implantation[53]; and trials in the United Kingdom[54] and Canada[55] allowing only external-beam techniques.

There are few data suggesting the optimal selection parameters for PBI. In the Christie Hospital trial, a striking difference was seen in the risk of breast recurrence

in relation to the histology of the tumor.[49] Actuarial 7-year breast recurrence rates for patients with infiltrating ductal carcinomas in the whole-breast arm and in the PBI group were approximately 11% and 15%, respectively. For patients with infiltrating lobular tumors the respective recurrence rates were 8% and 34%. In the PBI arm, 64% of the breast failures in patients with infiltrating ductal carcinomas were in the same quadrant as the primary tumor, compared to only 38% for patients with infiltrating lobular carcinomas. (The failure rate outside the quadrant of the original tumor for patients with infiltrating ductal carcinomas was 5.5%.)

The minimum microscopic tumor-free margin width needed to achieve excellent results with PBI is not known. In the London, Ontario study, there were 2 failures in 12 patients with margin widths of 2 mm or less, none among 13 patients with margins of 3–9 mm, 1 among 8 patients with margins of 10 mm or more, and 3 failures among 6 patients with unknown margin width or no tumor in a reexcision specimen.[43] In the William Beaumont Hospital study, the failure rate was 36% (4 of 11) for patients with margins less than 2 mm, 1% (1/77) for patients with margins 2–10 mm wide, and 1% (1/111) for margins wider than 10 mm or with no tumor on reexcision.[42]

Technical parameters of PBI and the use of adjuvant therapy may also affect the risk of relapse. In the London, Ontario study, the volume of treatment was much more limited than in the other implantation studies discussed above, encompassing only the surgical clips delineating the excision cavity, without an additional margin.[43] In the William Beaumont Hospital experience, the only correlate of an increased risk of failure elsewhere in the breast was the nonuse of tamoxifen.[32]

There are also few data regarding the correlates of complications following PBI. A recent dose-escalation study using low-dose rate brachytherapy conducted at Massachusetts General Hospital, Boston found that the rebiopsy rate (due to fat necrosis or fibrosis) was 11% for 19 patients receiving a dose of 50 Gy, 20% for 15 patients receiving 55 Gy, and 25% for 12 patients receiving 60 Gy.[56] The rates of moderate or severe fibrosis in these patients were 0%, 7%, and 25%, respectively. A study from Tufts-New England Medical Center, Boston using high-dose rate implantation (34 Gy in 10 fractions) found that the incidence of clinically-apparent fat necrosis (27%, or 8/30 patients) increased with the volume of the breast receiving doses of 3.4, 5.1, and 6.8 Gy per fraction.[57] In a large registry study of balloon brachytherapy, cosmetic results were superior in patients when the skin-applicator distance was larger than 7 mm than when this distance was narrower.[58] Finally, several studies have found that giving chemotherapy following interstitial PBI substantially increased the incidence of fat necrosis and poor cosmetic outcomes.[59,60]

HOW NEW RADIATION TECHNOLOGIES MAY REDUCE COMPLICATION RATES

A number of investigators have reported using three-dimensional physical compensators[61,62] or intensity-modulated radiation therapy (IMRT) to treat the entire breast,[63,64] with or without delivering simultaneous boost treatment of the excision site,[65,66] with or without treating regional lymph nodes.[67–69] Dose delivery

is substantially more homogeneous than with conventional two-dimensional "wedged" compensation techniques.

Prospective single-arm[64] and randomized trials[70,71] have shown that three-dimensional compensation decreases acute skin toxicity. However, there are only limited data on whether three-dimensional approaches confer long-term advantages. A randomized trial conducted from 1997–2000 at the Royal Marsden Hospital in the United Kingdom treated 306 moderate- or large-breasted patient with either standard two-dimensional or three-dimensional techniques (either physical compensation or static-field IMRT).[70] At two years, a change in the appearance of the breast was apparent in 52% (60/116) evaluable patients treated with the conventional technique, compared to 36% (42/117) of those treated with three-dimensional ones.

While these results are promising, these approaches take considerably more time to design and deliver than the traditional approaches. Simple maneuvers, such as using 10 MV or higher-energy photons, reduced fraction sizes (1.8 Gy per day, rather than 2 Gy), and/or adding few additional "segments" to conventional treatment fields using forward planning[72] may be able to achieve much the same results more easily and cheaply.

Breast irradiation may cause cardiac disease, though its overall incidence fortunately appears quite small with modern treatment techniques.[10,73] Respiratory gating or breath-hold techniques have been described which, by treating patients only during moderate or deep inspiration, often substantially reduce the irradiated amount of heart treated compared to giving treatment during the entire respiratory cycle.[74–76] However, such techniques may increase the dose given to the contralateral breast (for patients receiving nodal irradiation) and the volume of lung irradiated to doses above 20 Gy (for patients treated to the breast alone), compared to tangential fields. Also, not all patients are able to cooperate with this approach.[77]

Although patients are ordinarily treated in the supine position, using the lateral decubitus[78] and prone positions[79,80] may substantially reduce the volume of heart and lung irradiated. They also improve the homogeneity of the deposited dose by decreasing the thickness of the traversed tissue. This may be especially helpful in decreasing the risk of radiation-induced fibrosis, especially for large-breasted women. However, these positions are less reproducible than the conventional supine position, and they may be difficult for some patients to lie in comfortably.

MOLECULAR BIOLOGY AND GENETICS AND BREAST IRRADIATION

The last few years have seen an explosion of information about the molecular biology and genetics of breast cancer. As yet there has been relatively little work using these approaches to predict the risk of local recurrence after BCT. The most successful attempt to date to use "genetic profiling" for this purpose was conducted by a group at the Netherlands Cancer Institute, using fresh-frozen tissue obtained from 161 patients age 53 or younger at diagnosis.[81] The "wound signature" profile allowed them to divide their validation set into two subgroups of patients,

with 10-year risks of local failure of 5% and 29%, respectively. However, to do this required setting a *different* threshold dividing "quiescent" from "activated" tumors than was used in the original study of this profile, where the endpoints were freedom from distant metastases and overall survival.[82]

There has also been considerable interest in how host genetic factors may affect response to treatment, particularly with regards to development of long-term complications after breast RT. However, this topic is difficult to study for a number of reasons. One is the relatively small incidence of such complications (particularly severe ones), which means that large numbers of patients must be studied. Second, long follow-up is needed to assess their incidence. Third, toxicity endpoints are often difficult to assess in an objective, reproducible manner, requiring substantial effort to establish acceptable metrics. Finally, RT needs to be delivered homogeneously in order to be able to distinguish the effects of genetic factors from other potential variables, such as systemic therapy.

One of the few studies so far in this area meeting these criteria consists of 319 women treated with postmastectomy RT in Aarhus, Denmark from 1978–1982.[83] Skin fibroblasts were harvested before treatment and are still available for research. Forty-one patients whose samples had been used in a prior study by the Aarhus group were reexamined by a sensitive liquid chromatography method for detecting mutations in the ATM gene developed by researchers at Mount Sinai and New York University Medical Centers in New York City.[84] They found that a G-to-A base mutation (resulting in asparaginine being substituted for aspartic acid) at nucleotide 5557 (in codon 1853) was associated with an increased risk of fibrosis.[85] They then created a model looking at the estimated dose needed to cause 50% of the population to develop grade 3 fibrosis as a function of how many "risk" polymorphisms they had in genes for which prior evidence suggested some role in repair of radiation damage (XRCC1 codon 399, XRCC3 codon 241, SOD codon 16, and TGFB1 codon 10, in addition to ATM codon 1853). This estimated dose decreased as the number of risk alleles increased. Of note, none of these polymorphisms individually was significantly associated with the risk of subcutaneous fibrosis in a separate study they performed on a different group of 120 patients in the Aarhus study population.[86]

Despite the relative homogeneity of the population and its long follow-up, this study has methodological problems that make its interpretation more complex. Though most patients received prescribed doses of 36.6 Gy in 12 fractions, 7 patients (17% of the study population) received 40.9 Gy in 22 fractions. These two groups were not analyzed separately. Further, the first fractionation scheme is not in widespread use today. Their analyses combined calculated doses at a reference point 4.1 mm deep to the skin surface in three different regions, creating a "common denominator," then converted it to a "biological equivalent dose" in 2-Gy fractions by using an alpha-beta ratio of 1.9. (Patients were treated with a technique that used photons to cover nodal areas and electrons to cover the chest wall, with bolus placed along the surgical scar in the photon field.) This approach is debatable, especially as a recent randomized trial of differing fractionation

schemes found that the alpha-beta ratio for telangectasias was 5.1 and that for induration was 3.1.[87]

CONCLUSIONS

The role of RT in treating patients with early-stage invasive breast cancer seems likely to undergo substantial changes over the next ten years. Fewer patients will receive RT in any form. However, while BCT without RT appears to be a viable alternative for a substantial minority of patients, we do not yet know the optimal selection parameters for it. Omitting RT clearly increases the risk of local recurrence, and hence some of these patients will prefer having RT as "insurance". Therefore, the decision to omit RT should be made by the patient and her physicians together, not unilaterally.

More patients will receive PBI instead of WBI, but as yet we know very little about patient selection for PBI, the advantages and disadvantages of different RT modalities, and the optimal technical parameters of PBI. I do not believe that it is necessary to have completed the randomized trials comparing PBI to WBI before new technologies can enter widespread use. (Certainly, this was not the case for prostate seed implants, IMRT, or indeed BCT with WBI.[88]) However, women who wish to be treated by PBI must be formally and candidly informed of the potential increased risks (even if small) of complications, local failure, loss of the breast, and death due to breast cancer if PBI is not ultimately found to be as safe and effective as conventional WBI.

The great majority of patients treated with conventional approaches already have low local failure rates, excellent cosmetic results, and few complications. The trials in the United Kingdom and Canada may help delineate the proper place of three-dimensional compensation and IMRT in breast RT. Some patients may benefit from respiratory gating and alternative positioning techniques, but these are not always feasible and have their own drawbacks.

Finally, it seems likely that useful clinical assays of tumor radioresistance and normal-tissue sensitivity can be created. However, these will need to examine multiple genes, not just a single one. Further, there are enormous methodological obstacles to conducting sound studies in this area. It will probably be even more difficult to convince investigators to perform adequate (and expensive) validation studies on independent patient populations. Nonetheless, such studies must and (I hope) will be done.

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10. BREAST CANCER PREVENTION

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INTRODUCTION

Breast cancer is a devastating illness that affects tens of thousands of American women each year. Although it is impossible to predict who will develop breast cancer, clinicians can identify women who are at increased risk for breast cancer and provide them with options to reduce their risk. A number of validated, quantitative risk-assessment models incorporate features of a patient's medical and family history to help women more accurately estimate their individual risk and thus aid them in decision-making. Over the years, research has focused on the development of both surgical and medical methods for breast cancer risk reduction in high-risk women. This chapter will emphasize the importance of identifying and educating women at increased risk for breast cancer, and then providing them with a comprehensive breast cancer risk management plan. We will also discuss the surgical and medical options available and offer a management summary for breast cancer risk reduction.

IDENTIFYING HIGH-RISK WOMEN

Studies indicate that most women overestimate their risk of developing breast cancer by an order of magnitude or more.[1] Women need a validated model that accurately assesses their risk so that they do not make decisions about their health based on faulty assumptions. A number of factors that have the most significant impact on a woman's risk are summarized here.

Age and Ethnicity

The single most important risk factor for the development of breast cancer is age.[2] A woman's risk of breast cancer increases throughout her lifetime. The

annual incidence of breast cancer in American women ages 80–85 is fifteen times higher than that in women ages 30–35. Ethnicity also modifies the effect of age on breast cancer risk. For example, African-American women under age 50 have a higher age-specific incidence of breast cancer than American white women of the same age. However, African-American women over age 50 have a lower age-specific incidence than their Caucasian counterparts. Hispanic women living in North America have only a 40–50% incidence compared to non-Hispanic white women. Asian women residing in Asian countries have a very low lifetime risk of breast cancer, but Asian women who are born in North America have the same lifetime risk of breast cancer as American white women. No adequate explanation for these differences has yet been proposed, even when dietary issues are considered.[3]

Ovulatory Cycles

Events in a woman's life that alter her number of lifetime ovulatory cycles appear to correlate with her risk of breast cancer. Early menarche and late menopause equate to more total lifetime menstrual cycles and result in a 30–50% increase in breast cancer risk.[3] Similarly, late menarche and early menopause lead to an equivalent reduction in breast cancer risk. Nulliparity and age over 30 years at first live birth are also associated with nearly a doubling of the risk of breast cancer. Pregnancy before age 20 significantly reduces the incidence of subsequent breast cancer. Interestingly, only pregnancies that result in a live birth reduce the risk of breast cancer.

Family History

A family history of breast cancer, especially in first-degree relatives, is a well-known risk factor for breast cancer. About 70–80% of breast cancer is sporadic and occurs by chance. Another 15–20% of breast cancer is familial and occurs within the context of a positive family history. These cancers are likely the result of a combination of genetic and environmental factors that cause acquired genetic mutations over time.[4] While members of these families are clearly at higher risk, they do not have a specific known genetic mutation and their risk rarely exceeds 30% over a lifetime.

Only 5–10% of all breast cancers are related to known genetic mutations.[5] Two autosomal-dominant gene mutations have been identified so far, *BRCA1* and *BRCA2*. Carriers of these genes have a 50–85% lifetime risk of developing breast cancer and a 45% risk of developing ovarian cancer by age 70[6–8]. Characteristics of an individual's history that are concerning for these mutations include age <50 at diagnosis, breast cancer in two or more relatives of the same lineage, multiple primary tumors in a single individual (either bilateral breast or breast and ovarian cancer), a family member with a known predisposing cancer gene, breast cancer in a male relative, and Ashkenazi Jewish ancestry. Any of these features should lead a clinician to consider genetic testing.

Benign Breast Disease

Benign breast disease can be non-proliferative, proliferative, or proliferative with atypia. Non-proliferative lesions such as normal cysts, duct ectasia, mild hyperplasia, and fibroadenomas are not associated with increased breast cancer risk.[9,10] However, proliferative disease such as papillomas and sclerosing adenomas can increase risk by as much as 70%.[11,12] Only 5-10% of proliferative lesions that are biopsied show atypical hyperplasia, but atypia confers the highest risk, increasing the risk of breast cancer fivefold.[13]

The Breast Cancer Prevention Trial was a large prospective trial studying the effects of tamoxifen on women at increased risk of breast cancer. Analysis of the data from women taking placebo revealed that certain types of benign breast disease did confer increased risk. Specifically, women with a history of lobular carcinoma in situ (LCIS) were found to have a 100% increase in the rate of invasive breast cancer compared with women who did not have a history of LCIS (12.99 vs. 6.41 cancers per 1000 women, respectively).[14] Women with a history of atypical hyperplasia had a 57% increase in the rate of breast cancer compared to those who had no atypical hyperplasia (10.11 vs. 6.44 per 1,000 women). These data indicate that women with a history of LCIS or atypical hyperplasia are among those with the highest risk and should be encouraged to undergo counseling regarding their risk management options.

QUANTITATIVE RISK ASSESSMENT

All of the factors discussed above have led to the development of validated, quantitative risk-assessment models that allow for the rapid identification of women at high risk. The model developed by Gail, et al.[15] quantifies a woman's lifetime risk of developing breast cancer by incorporating current age, age at menarche, number of breast biopsies, age at first live birth (or nulliparity), family history of breast cancer in first-degree relatives, and race. Several other models have been developed as well which give varying weight to the different risk factors, but the Gail model has been used most often as the definition for eligibility in the risk reduction trials. The Food and Drug Administration has defined increased risk as a 5-year risk of ≥1.66% which equates to the 5-year risk of an average 60 year-old North American white woman.

COUNSELING, SCREENING, AND GENETIC TESTING

Criteria for patients who should be considered for individualized management of their breast cancer risk include women with first-degree female relatives with breast cancer, women with a history of LCIS, ductal carcinoma in situ (DCIS) or atypical hyperplasia, and women with relatives having either a known *BRCA1* or *BRCA2* mutation or features of the family history suggestive of predisposing genetic mutations (discussed above). Women who present with any of these criteria should undergo quantitative risk assessment followed by counseling. Counseling is important to help educate each patient about breast cancer risk, to assess and manage her anxiety and concerns about her risk, and to prepare her to discuss risk

reduction options. Because an individual's preferences and risk status can change substantially during a lifetime, it is important that decisions about risk management not be regarded as either urgent or irreversible.

Until recently, screening recommendations for high-risk women over age 40 have been the same as those for average-risk women. However, a recent study of high-risk women found that screening MRI at the time of initial breast cancer diagnosis identified occult breast cancer in the unaffected breast in 3% of patients.[16] This study has led the American Cancer Society to recommend yearly breast MRI in addition to yearly mammography in certain high-risk women, including women with *BRCA1* and *BRCA2* mutations, a first-degree relative with a *BRCA* mutation, a lifetime breast cancer risk of 20–25% or greater, or a history of radiation to the chest. There is not yet sufficient evidence to recommend MRI screening in other high-risk women.

Indications to consider genetic testing have been previously discussed. Patients should undergo pre-test counseling to ensure understanding of the implications of a positive test. Counseling should also include the risks and benefits of early cancer detection and the prevention modalities that are available. Post-test counseling should be available to help patients cope with their test results and to review prevention modalities. Women who have been advised of their risk and decide that they want to pursue risk reduction therapy can then be presented with the management options that are most appropriate for them.

SURGICAL MANAGEMENT

Prophylactic Mastectomy

Prophylactic mastectomy is an option for breast cancer risk reduction in high-risk women. Because of the significant physical and psychological burden that accompanies the procedure, prophylactic mastectomy is generally reserved for women whose lifetime risk of developing breast cancer is very high, specifically *BRCA* mutation carriers. A full discussion of the procedure and its consequences must be provided in pre-surgical counseling. Although there has not been a large, prospective trial to assess the efficacy of prophylactic mastectomy, the data available indicate that the procedure is highly effective. In one retrospective study, bilateral mastectomy was associated with a greater than 90% reduction in the risk of breast cancer in high-risk women (as determined by features of the family history).[17] A small prospective study was conducted to investigate the efficacy of prophylactic mastectomy in *BRCA1* and *BRCA2* mutation carriers.[18] Although the number of patients was small and the mean follow-up was only 3 years, women who underwent mastectomy had a significant reduction in the incidence of breast cancer (0 of 76 women) compared to those who underwent surveillance only (8 of 63 women).

Prophylactic Oophorectomy

The surgical removal of the ovaries has also been shown to reduce the lifetime breast cancer risk in *BRCA* mutation carriers. This procedure is generally considered

more acceptable to patients, presumably because oophorectomy is a "hidden" procedure. In one prospective study, 170 women with *BRCA* mutations who had not yet undergone surgery were followed for 6 years and were given the option to undergo prophylactic oophorectomy.[19] Although the number of participants in this study was also small, the data suggest a large benefit for women with *BRCA* mutations who choose prophylactic oophorectomy (HR for combined endpoint of breast or gynecological cancer = 0.25; 95% CI, 0.08–0.74). Another small case-control study was done in *BRCA* carriers (n = 241) who did not have breast cancer and had not yet undergone mastectomy. The incidence of breast cancer was much lower in those women who had undergone oophorectomy than in those who had not (HR = 0.47; 95% CI, 0.29–0.77).[20]

CHEMOPREVENTION

Unlike the surgical options which are primarily recommended for *BRCA* mutation carriers, chemoprevention provides a non-invasive option for breast cancer risk reduction for many high-risk women. The selective estrogen-receptor modulators (SERMs) were chosen to investigate for chemoprevention given their well-known estrogen antagonist effects in breast tissue. Tamoxifen was the first agent recommended for breast cancer risk reduction after it was found to reduce the incidence of all breast cancers by 38% and estrogen-receptor (ER) positive tumors by 48%.[21] Raloxifene, a second-generation SERM that was originally studied as an osteoporosis agent, was then thought to be a possible alternative to tamoxifen. In the Study of Tamoxifen and Raloxifene (STAR) trial, raloxifene was compared directly with tamoxifen and has indeed been found to be as effective as tamoxifen in reducing the risk of invasive breast cancer. Additionally, raloxifene has a more favorable side effect profile with fewer thromboembolic events and less uterine malignancies than tamoxifen. Chemoprevention is now more feasible than ever with the addition of raloxifene to the options for high-risk women.

Tamoxifen

Tamoxifen was introduced into clinical use as a chemopreventive agent based on its now well-known ability to inhibit the binding of estrogen to estrogen receptors in breast tissue.[22] Although tamoxifen is an estrogen antagonist in the breast, it acts as an estrogen agonist in other parts of the body including on clotting factors and in the uterus. This effect leads to the major side effects of tamoxifen which include an increase in thromboembolic events and uterine malignancies. Several large, prospective trials have compared tamoxifen with placebo for breast cancer risk reduction in women at increased risk for breast cancer. The trials are listed in Table 1 and summarized briefly below.

The Royal Marsden Hospital Prevention Trial

The Royal Marsden Hospital Prevention Trial began in 1986 with 2,494 women who were randomized to receive either tamoxifen 20 mg daily or placebo for up to 8

Table 1. Summary data of clinical trials using tamoxifen for breast cancer risk reduction*

	Royal Marsden		NSABP P-1		Italian		IBIS-I	
	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo	Tamoxifen	Placebo
Number 1238 **randomized**	1233	6681	6707	2700	2708	3573	3566	
Breast cancers								
Invasive	54	64	89	175	28	40	64	85
DCIS	7	7	35	69	5	4	5	16
Unknown	1	4	-	-	1	1	-	-
Total	62	75	124	244	34	45	69	101
ER status (invasive)								
Positive	31	44	41	130	19	30	44	63
Negative	17	10	38	31	14	12	19	19
Breast cancer								
Age <50 years	36	44	38	68	7	8	25	39
Age >50 years	26	31	51	107	27	37	44	62
Odds ratio for risk reduction of total breast cancers (95% CI)	**0.83** (0.58–1.16)		**0.51** (0.39–0.66)		**0.76** (0.47–1.60)		**0.67** (0.49–0.91)	
Odds ratio for risk reduction of ER-positive cancers in follow-up study (95% CI)	**0.48** (0.29–0.79)		**N/A**		**N/A**		**0.66** (0.50–0.87)	

*Adapted from Cuzick et al[21]

years.[23] Hormone replacement therapy (HRT) was permitted during the trial. When the data from this trial were first released in 1998, the authors did not find a statistically significant reduction in the incidence of breast cancer, even when the tumors were divided by estrogen receptor status. However, when patients were followed beyond the initial treatment period for a median of 13 years, there was a highly statistically significant reduction in ER-positive breast cancers in the tamoxifen group (HR = 0.48; 95% CI, 0.29–0.79).[24] The authors concluded that the preventive effect of tamoxifen on breast cancer lasts well beyond the active treatment phase.

The National Surgical Adjuvant Breast and Bowel Project (NSABP)

The NSABP Breast Cancer Prevention Trial (BCPT; NSABP P-1) commenced in 1992 and represents the largest, prospective randomized-controlled trial evaluating the risks and benefits of tamoxifen in high-risk women. The primary goal of the BCPT was to determine whether tamoxifen, administered for at least 5 years, prevented invasive breast cancer in women at increased risk, as determined by the Gail model. These high-risk women were randomized to receive either tamoxifen 20 mg daily or placebo. The study was terminated early at a median of 48 months

when tamoxifen was shown to reduce the risk of invasive breast cancer by 49% ($p < 0.00001$)[14]. The decrease in breast cancer incidence was accounted for entirely by a decrease in ER-positive tumors, with no significant change in the occurrence of ER-negative tumors. While tamoxifen was beneficial in all age groups, older women appeared to gain the most benefit in respect to breast cancer risk reduction.

The Italian Tamoxifen Prevention Study

The Italian Tamoxifen Prevention Study was another randomized-controlled study beginning in 1992 that was designed to determine whether tamoxifen would prevent breast cancer in healthy women who had undergone hysterectomy.[25] Participants were not required to undergo risk assessment. At a follow-up of 81 months, there was no significant difference in the incidence of breast cancer in the treatment groups. However, further analysis of the data revealed that the initial results may have been confounded by the fact that 48.3% of the study population had already undergone bilateral oophorectomy at the time of entry into the study and another 18.6% had undergone a unilateral oophorectomy.[26] As previously discussed, oophorectomy reduces the risk of breast cancer, and thus these women would be considered low to normal risk. The authors reanalyzed the data by sorting participants into high-risk and low-risk categories, with all women who had undergone prior oophorectomy being excluded from the high-risk group. Based on these criteria, the high-risk group had an overall risk of breast cancer that was three times that of the low-risk group. The high-risk women had a decreased incidence of breast cancer of 82% when treated with tamoxifen compared to high-risk women treated with placebo.

The International Breast Intervention Study-I

The International Breast Intervention Study-I (IBIS-I) began in 1992 and was a randomized placebo-controlled study in which patients received either tamoxifen 20 mg daily or placebo for 5 years.[27] Women were at moderately increased risk, based upon a published model of breast cancer risk assessment[28] and were permitted to use HRT during the study. The primary outcomes were frequency of invasive and *in situ* breast cancer. After a median follow-up of 50 months, tamoxifen was shown to reduce the overall risk of breast cancer by 32%. Women were then followed beyond the initial 5-year treatment period to determine if any of the risks and benefits of tamoxifen lasted beyond the active treatment period.[29] Indeed, the benefit of tamoxifen remained apparent for up to at least 8 years after randomization (RR = 0.73; 95% CI, 0.58–0.91). Interestingly, the benefit of tamoxifen for chemoprevention was only seen in patients who were not taking concurrent HRT, demonstrating that HRT may negate the beneficial effects of tamoxifen.

Meta-Analysis of Tamoxifen Chemoprevention Trials

A meta-analysis of tamoxifen breast cancer risk reduction trials was published in 2003[21]. All together, the trials demonstrated that tamoxifen decreased breast

cancer incidence by 38% ($p < 0.0001$), and ER-positive tumors by 48% ($p < 0.0001$). Again there was no decrease in the incidence of ER-negative tumors. Age had no apparent effect on the degree of breast cancer reduction in the meta-analysis.

Raloxifene

Raloxifene is a second-generation SERM with characteristics similar to, but distinct from, the first-generation SERMs such as tamoxifen. Raloxifene has estrogen antagonist effects on breast and endometrial tissue and estrogenic effects on bone, lipid metabolism, and blood clotting.[30–32] This indicates that raloxifene should have a similar preventive benefit in the breast tissue, but perhaps fewer or more acceptable side effects than tamoxifen. Raloxifene was initially studied as an osteoporosis drug, but was later found to also decrease the incidence of invasive breast cancer. The trials that led to the development of raloxifene as a chemopreventive agent are summarized in Table 2 and will be reviewed below.

Fracture Risk

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial was conducted to determine whether women taking raloxifene would have a lower risk of vertebral fractures than those taking placebo.[33–38] Participants were postmenopausal women with a known diagnosis of osteoporosis who were randomly assigned to take either 60 mg or 120 mg of raloxifene daily or placebo. The results of the MORE trial showed that vertebral fracture risk was reduced in both the 60 mg and 120 mg raloxifene groups after a median of 40 months (RR = 0.7; 95% CI, 0.5–0.8 and RR = 0.5; 95% CI, 0.4–0.7, respectively). The authors also found, as a secondary outcome, that raloxifene appeared to decrease the incidence of invasive breast cancer. In order to further study this effect on breast cancer incidence, participants in the MORE trial were asked to continue in the study for an additional 4 years which became known as the Continuing Outcomes Relevant to Evista (CORE) trial.[39,40]

Table 2. Clinical raloxifene trials reporting endpoint of invasive breast cancer

Study	MORE[34]	CORE[39]	RUTH[43]	STAR[44]
Number of women taking raloxifene	5129	3570	5044	9745
Number of women in the comparison group	2576	1703	5057	9726
Comparison drug	Placebo	Placebo	Placebo	Tamoxifen
Average follow-up time	40 months	48 months	67 months	47 months
No of breast cancers in the raloxifene group	13	40	40	168
No of breast cancers in the comparison group	27	58	70	163
Event rate in the raloxifene vs. comparison group (per 1000 woman-years)	0.9 vs. 3.6	1.4 vs. 4.2	1.5 vs. 2.7	4.4 vs. 4.3
Risk reduction (i.e. hazard rate or risk ratio) (95% CI)	**0.24** (0.13–0.44)	**0.34** (0.22–0.50)	**0.56** (0.38–0.83)	N/A

Cardiovascular Risk

The effect of raloxifene on the incidence of cardiovascular events in postmenopausal women was first reported in the MORE and CORE trials.[41,42] Over the 8-years of the combined trial, the incidence of serious cardiovascular adverse events did not differ significantly between the raloxifene and placebo groups (HR = 1.16; 95% CI, 0.86–1.56). These results remained consistent when coronary and cerebrovascular events were analyzed separately.

The Raloxifene Use for The Heart (RUTH) trial was conducted with two primary outcomes: coronary events (i.e., death from coronary causes, myocardial infarction, or hospitalization for an acute coronary syndrome) and invasive breast cancer.[43] In the RUTH trial, 10,101 postmenopausal women with coronary heart disease (CHD) or multiple risk factors for CHD were randomly assigned to receive either raloxifene 60mg daily or placebo. Raloxifene had no significant effect on the risk of primary coronary events when compared to placebo (HR = 0.95; 95% CI, 0.84–1.07), even when women with established CHD were considered separately. There is no evidence, therefore, for either a beneficial or harmful effect of raloxifene on cardiovascular events in postmenopausal women.

Invasive Breast Cancer Risk

Raloxifene was found to have a significant effect on invasive breast cancer risk on secondary analysis of each of these raloxifene trials (Table 2). In the MORE trial, raloxifene decreased the risk of ER-positive breast cancer by 90% (RR = 0.10; 95% CI, 0.04–0.24), but had no significant effect on ER-negative breast cancer. This trend continued over the 8-year course of the combined MORE and CORE studies with a 76% reduction in the incidence of invasive ER-positive breast cancer in the raloxifene group and no significant difference in the incidence of ER-negative breast cancer.[41,42] In the RUTH trial, raloxifene reduced the risk of invasive breast cancer in this population of lower risk, older women by 44% (HR = 0.56; 95% CI, 0.38–0.83).[43] Again, the risk reduction was accounted for entirely by ER-positive breast cancers.

Raloxifene vs. Tamoxifen

To compare the relative safety and efficacy of raloxifene and tamoxifen on the risk of developing breast cancer, the NSABP conducted a prospective, randomized-controlled trial, known as the STAR trial.[44] Participants were 19,747 postmenopausal women who had a 5-year predicted breast cancer risk of ≥1.66% based on the Gail model. They were randomly assigned to receive either tamoxifen 20 mg daily or raloxifene 60 mg daily for 5 years. Outcomes of interest were incidence of invasive and noninvasive breast cancer, thromboembolic events, uterine cancer, and cataracts.

After a median of 3.2 years, there was no significant difference in the incidence of invasive breast cancer in the tamoxifen and raloxifene groups (RR = 1.02; 95% CI, 0.82–1.28) (Figure 3). The pattern of no differential effect by treatment

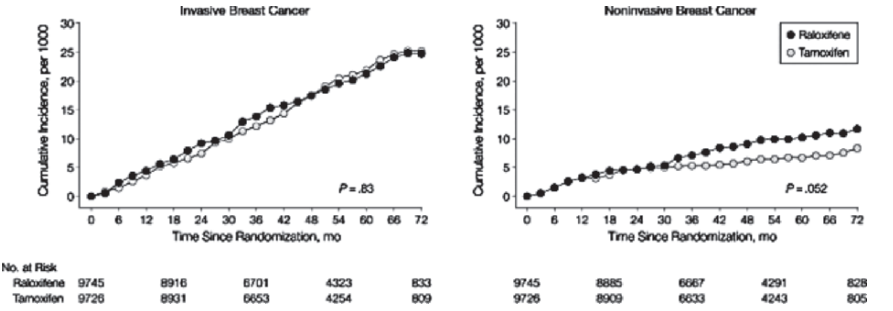

Figure 1. Cumulative incidence of invasive and noninvasive breast cancer in women treated with tamoxifen and raloxifene in the STAR trial.*
*From Vogel, VG, et al. JAMA 2006; 295:2727-41. *Copyright © (2006), American Medical Association*. All Rights reserved.

assignment remained consistent when the treatment groups were compared by baseline categories of age, history of LCIS, history of atypical hyperplasia, Gail model 5-year predicted risk of breast cancer, or the number of relatives with a history of breast cancer. Additionally, there were no differences between the treatment groups when comparing tumor size, nodal status, or estrogen receptor status.

In contrast to the findings for invasive breast cancer, there was a trend toward fewer cases of noninvasive breast cancer in the tamoxifen group compared to the raloxifene group, although this did not reach statistical significance (RR = 1.40; 95% CI, 0.98–2.00) (Figure 1). The pattern of fewer cases among the tamoxifen group was evident for both LCIS and DCIS. No adequate explanation for this trend has yet been proposed, and its significance remains unclear.

The major side effects of the SERMs include venous thromboembolic events, uterine malignancies, and cataracts. Many women are also concerned about changes in quality of life, including vasomotor symptoms, sexual side effects, and mood changes. A complete understanding of these side effects is critical for patients and their physicians when considering these medications for breast cancer prevention. The careful selection of patients to exclude those at higher risk of blood clots and uterine malignancies can greatly reduce the risks associated with these agents.

Menopausal Status

A woman's menopausal status is perhaps the most important factor to consider when discussing chemoprevention. There are no data on the safety or efficacy of raloxifene in premenopausal women, and thus its use in this population is not recommended. On the contrary, the risk-benefit ratio of tamoxifen in premenopausal women is extremely favorable. In the BCPT, thromboembolic events and uterine malignancies were much less common in women <50 than in women ≥50 years old (Table 3), indicating that premenopausal women have significantly fewer risks in taking tamoxifen than

Table 3. Adverse events associated with tamoxifen use in the BCPT*

	Age	
	<50	≥50
Relative risk of invasive endometrial cancer (95% CI)	**1.21** (0.41–3.60)	**4.01**(1.70–10.90)
Relative risk of deep vein thrombosis (95% CI)	**1.39** (0.51–3.99)	**1.71** (0.85–3.58)
Relative risk of pulmonary embolism (95% CI)	**2.03** (0.11–119.62)	**3.19** (1.12–11.15)

*Adapted from data from Fisher et al.[14]

postmenopausal women.[14] The side effect profiles of tamoxifen and raloxifene in postmenopausal women are more complicated and will be reviewed below.

Thromboembolic Events

As mentioned above, both tamoxifen and raloxifene are believed to have an estrogenic effect on clotting factors that leads to thromboembolic events. In the BCPT, women ≥50 years old who were taking tamoxifen experienced increased rates of pulmonary embolism (PE), stroke, and deep vein thrombosis (DVT) (Table 3).[14] Interestingly, in the IBIS-I follow-up data, the incidence of DVT and PE was statistically higher during the active treatment period (RR = 2.26; 95% CI, 1.36–3.87), but not in the post-treatment period.[29] The authors concluded that although the breast cancer risk reduction appears to be a lasting effect, the risk of thromboembolic events returns to baseline after the tamoxifen treatment is completed. In the MORE, CORE, and RUTH trials, raloxifene was also found to increase the incidence of thromboembolic events. However, when tamoxifen and raloxifene were compared directly in the STAR trial, thromboembolic events occurred significantly less often in the raloxifene group than in the tamoxifen group (RR = 0.70; 95% CI, 0.54–0.91) (Figure 1),[44] showing a benefit for choosing raloxifene over tamoxifen for chemoprevention.

Endometrial Cancer

In the BCPT, women ≥50 years old who were taking tamoxifen experienced an increase in localized, non-fatal endometrial cancer (RR = 4.01; 95% CI, 1.20–10.90).[14] Unlike tamoxifen, raloxifene has anti-estrogenic effects in the endometrium which should theoretically lead to fewer endometrial cancers than those seen with tamoxifen. The results from both the MORE and RUTH trials showed that indeed there was no statistical difference between the rates of endometrial cancer in the raloxifene and placebo groups. When tamoxifen was directly compared to raloxifene in the STAR trial, there was a trend toward fewer cases of uterine cancer in the raloxifene group (Figure 2), although this did not reach statistical significance (RR = 0.62; 95% CI, 0.35–1.08). These data indicate that use of raloxifene for breast cancer risk reduction may avoid some of the uterine cancers associated with tamoxifen use.

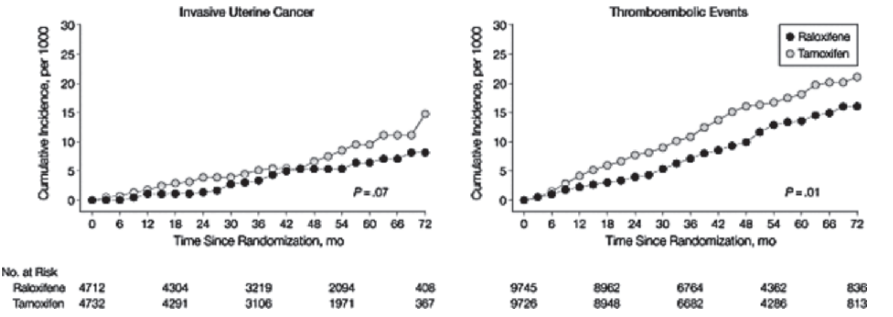

Figure 2. Cumulative incidence of invasive uterine cancer and thromboembolic events in women treated with tamoxifen and raloxifene in the STAR trial.*
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Cataracts

Tamoxifen also increases the incidence of cataracts. There was a 14% increase in the development of cataracts in the tamoxifen group in the BCPT[14] and a nonsignificant increase in cataracts in patients taking tamoxifen (1.9% vs. 1.5%) in the IBIS-I study.[27,29] By comparison, in the STAR trial, there were fewer cataracts (RR = 0.79; 95% CI, 0.68–0.92) and cataract surgeries in the women taking raloxifene than in those taking tamoxifen.[44]

Quality of Life

Patients have been reluctant to take tamoxifen routinely for breast cancer risk reduction because of the perception that tamoxifen may lead to a worsened quality of life. Some concerns include vasomotor symptoms, gynecologic complaints, joint pains, and mental health. In order to get an overall assessment of quality of life, the BCPT surveyed patients using the Center for Epidemiological Studies-Depression Scale (CES-D) and found that there were no consistent differences between the tamoxifen and placebo groups.

To compare the quality of life experienced by women on tamoxifen and raloxifene, data was collected every 6 months during the STAR trial using a 36-item symptom checklist for patient-reported symptoms.[46] Quality of life was measured using several established outcomes surveys[47–52] including the CES-D and the Medical Outcomes Study Short-Form Health Survey (SF-36), in a sub-study of 1,983 participants over 5 years. Primary quality of life end points were the SF-36 physical (PCS) and mental (MCS) component summaries. Mean PCS, MCS, and CES-D scores worsened modestly throughout the study with no significant difference between the tamoxifen and raloxifene groups (Figure 3). Sexual function was slightly better for participants assigned to tamoxifen. Although mean symptom severity was low among these postmenopausal women, those in the tamoxifen group reported more gynecological problems, vasomotor symptoms, leg cramps,

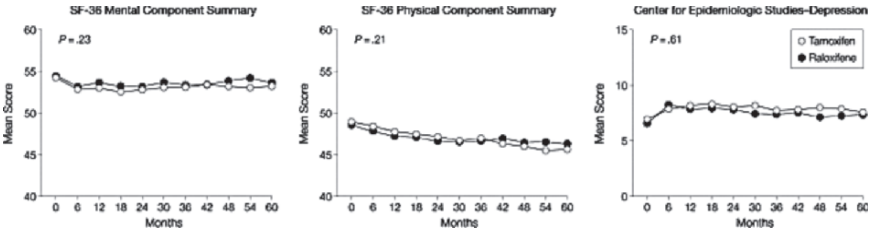

Figure 3. Quality of life data reported from the STAR trial as determined by SF-36 mental and physical health component summaries and the CES-D over time in the tamoxifen and raloxifene groups.*
*From Land SR et al. JAMA 2006; 295:2742–51. *Copyright © (2006), American Medical Association.* All Rights reserved.

and bladder control problems. Women in the raloxifene group reported more musculoskeletal problems, dyspareunia, and weight gain. No significant differences existed, however, between the tamoxifen and raloxifene groups in patient-reported outcomes for physical health, mental health, and depression.

MANAGEMENT SUMMARY

The new advances in risk reduction management presented here demonstrate that all women should be considered for routine breast cancer risk assessment. The development of quantitative risk models such as the Gail model allows a woman's risk to be easily calculated. The information needed for these models can readily be obtained from a basic intake questionnaire during yearly health maintenance exams in the primary care setting. Risk assessment is the starting point for counseling women about risk and leads to discussions about screening, prophylactic surgery, and chemopreventive agents. Clinicians can now create an individual management plan for each woman based on her level of risk and her current health status. The steps to create this management plan are summarized in Table 4. Physicians should continue to readdress breast cancer risk reduction over time as a patient's quantitative risk will change and her feelings about risk reduction may change accordingly.

CONCLUSION

Comprehensive breast cancer risk management is an important and necessary component of women's health. Risk assessment tools, such as the Gail model, allow for rapid risk calculation which provides women with an accurate estimate of their risk. Women with predisposing genetic mutations should be identified early and counseled appropriately. All women at increased risk should be educated about their risk and the options available to them. Surgical options remain an effective risk-reduction method for those women with hereditary cancer syndromes who have an extremely high lifetime risk of developing breast

Table 4. Management summary

Step 1: Determine if the patient is an appropriate candidate for risk reduction.

Women who are likely to derive net benefit:

- Premenopausal women with predisposing genetic mutations (*BRCA*)
- History of atypical hyperplasia
- History of ductal carcinoma in situ (DCIS)
- History of lobular carcinoma in situ (LCIS)
- Women aged ≥35 years with Gail model 5-year probability of breast cancer ≥1.66%

Women in whom caution should be used when considering risk reduction:

- History of stroke, transient ischemic attack, deep vein thrombosis, or pulmonary embolus
- Age greater than 65 years
- Current use of hormone replacement therapy
- History of cataracts or cataract surgery
- Obese women

Step 2: Determine which method of risk reduction is most appropriate.

Women with a known or suspected *BRCA* mutation:

- Counseling and genetic testing, when appropriate
- Prophylactic mastectomy (after discussing risks/benefits with patient)
- Prophylactic oophorectomy (after discussing risks/benefits with patient)
- Chemoprevention (in women who prefer not to undergo surgery)

Premenopausal women:

- Tamoxifen 20 mg PO daily for 5 years

Postmenopausal women:

- Raloxifene 60 mg PO daily for 5 years – appears to have the same clinical efficacy with fewer or more acceptable side effects than tamoxifen, indicating that raloxifene may now be the first choice for high-risk postmenopausal women
- Tamoxifen 20 mg PO daily for 5 years – an effective means of reducing breast cancer risk, but currently appears to have no clinical benefits over raloxifene

cancer. For other high-risk women, chemoprevention is a safe and effective non-invasive alternative. Tamoxifen remains the chemopreventive agent of choice for premenopausal women. For postmenopausal women, raloxifene is as effective as tamoxifen with fewer adverse events and no difference in overall quality of life. Routine breast health should now include periodic risk assessment, patient education, and risk management as appropriate. With the advent of raloxifene as a chemopreventive agent, comprehensive breast care is poised to move into the primary care setting.

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