Preventing Overdiagnosis and Overtreatment: Just the Next Step in the Evolution of Breast Cancer Care

Rita A. Mukhtar, MD; Jasmine M. Wong, MD; and Laura J. Esserman, MD, MBA

Foreward

By William J. Gradishar, MD

Health care providers in the United States have the luxury (and perhaps curse) of having endless diagnostic tools and therapeutic interventions to offer their patients. In many situations, little scrutiny is given to how these tools are used. Cancer care is particularly relevant to this issue because of the increasing number of imaging tools, diagnostic molecular tests, and novel therapeutics that are emerging from clinical development and available to ordering physicians. Additionally, direct marketing to patients amplify the problem, because patients may then pressure their caregivers to order tests or request therapies with questionable added benefit.

All of these interventions have a cost, both economically and potentially as direct toxicity to the patient. Mukhtar and colleagues provide a thought-provoking discussion of these issues as they apply to breast cancer care. The overdiagnosis of breast cancers that may have remained indolent and have little clinical relevance to patient outcome is one end of the spectrum discussed. The other consequence of a diagnosis is overtreatment of a disease for which therapy offers little benefit to the patient. A better understanding of these clinical scenarios is a formidable challenge that clinicians must come to grips with to make the right decisions for their patients.

Abstract

The problem of overdiagnosis and overtreatment has been highlighted in breast cancer and many other cancer types, most notably prostate cancer. Addressing this problem presents an opportunity to continue the evolution of breast cancer care. Advances in technology, such as molecular subtyping, have increased the understanding of breast cancer biology and the range of associated behavior, and have provided tools that allow greater personalization of treatment. This article identifies 3 areas of breast cancer care where opportunity currently exists to refine management strategies and help decrease overtreatment and overdiagnosis: the use of adjuvant-external beam radiation in invasive breast cancer, the application of aggressive treatment for all ductal carcinoma in situ, and the authors' approach to breast cancer screening. Personalizing treatment based on patient and tumor characteristics holds promise for minimizing harms and maximizing benefits. This approach will allow continual improvement and ultimately result in providing the right treatment for each patient. (J Natl Compr Canc Netw 2015;13:737–743)

From the Department of Surgery, University of California, San Francisco, San Francisco, California.

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Correspondence: Laura J. Esserman, MD, MBA, UCSF Helen Diller Family Comprehensive Cancer Center, 1600 Divisadero, Box 1710, San Francisco, CA 94115. E-mail: laura.esserman@ucsfmedctr.org

Rather than denoting criticisms of breast cancer care, the terms *overdiagnosis* and *overtreatment* should represent opportunities to further refine the current state of the art. Overdiagnosis occurs when tumors that would otherwise not become symptomatic are identified. Overtreatment occurs when such a tumor is treated, often with surgery and adjuvant therapy in the case of breast

cancer.[1] As the ability to identify lesions of the breast improves, so must the ability to distinguish between lesions that require aggressive treatment and those that can be treated less aggressively. Breast cancer care has already undergone dramatic improvement, and this represents another step in its evolution.

In the past few decades, the surgical treatment of breast cancer has progressed from radical mastectomy to modified radical mastectomy, with the subsequent incorporation of breast conservation and oncoplastic techniques.[2,3] These advances have occurred simultaneously with improvements in multimodality therapy. More recently, the use of molecular tests in breast cancer have become part of the standard of care, and are included in the NCCN Guidelines.[4] Before 1980, most women with breast cancer were treated with radical mastectomy. In the 1990s, tumor size and stage essentially determined adjuvant therapy recommendations. Today, a wide array of patient and tumor features are used, including overall health status, and molecular tests, such as the 70-gene prognostic score and the 21-gene recurrence score, for determining optimal treatment strategies.[5,6]

This kind of evolution has also occurred in the management of other cancer types, in which what was once thought to be the standard of care is now considered unnecessary. In the 1960s, staging laparotomy and splenectomy were commonly performed in the treatment of lymphoma. These morbid procedures are now largely replaced with technology in the form of CT and PET scans.[7,8] In the treatment of squamous cell cancer of the anus, chemoradiation has replaced the surgical removal of the anus and rectum, providing equivalent survival but preserved sphincter function.[9] Epidemiologic data and advances in imaging, molecular subtyping, and genomics in breast cancer now present the opportunity to further evolve breast cancer care by preserving excellent outcomes while minimizing harms and unnecessary treatment.

The opportunities for change in current breast cancer care need to be identified in order to reduce unhelpful and potentially harmful treatment. Making these advances will require a multifaceted and multidisciplinary approach, with roles for radiologists, pathologists, surgeons, medical oncologists, radiation oncologists, and geneticists in optimizing treatment recommendations. The heterogeneity of breast cancer has allowed the tailoring of specific treatments to specific tumor types. This not only improves outcomes but also reduces morbidity for women who potentially derive little or no benefit from receiving treatments designed for other tumor types.[10]

Although tailored treatment has improved outcomes in breast cancer,[10] the implementation of screening programs also bears some responsibility for increased survival.[11] However, one must recognize that screening itself impacts the disease in ways that should be considered when making management recommendations. Before the advent of screening in the 1980s, only women with clinically apparent, usually palpable, disease came to clinical attention. Since the institution of screening programs, the spectrum of breast cancer that comes to clinical attention has expanded. A large group of women have disease identified by screening only. Analyses of these screen-detected cancers show them to be very different from clinically detected cancers, with different grade and molecular subtypes.[12,13] Some may, in fact, be indolent lesions that would never impact a woman's life expectancy if left untreated, for which the authors have recommended the term *indolent lesion of epithelial origin* (IDLE).[1,14] If treatments designed for aggressive cancers are applied to screen-detected cancers that were never going to become clinically significant, this introduces the risk of overtreating. This is not an insurmountable problem. In fact, recognition of the differences between screen-detected and clinically apparent breast cancers provides the opportunity to better understand breast cancer biology and to tailor treatments even more specifically.

Several areas in breast cancer management currently exist in which changes can be implemented to reduce overtreatment. Three of these areas are (1) reducing the use of adjuvant radiation in some invasive breast cancers, (2) decreasing the morbidity of treatment for low-risk ductal carcinoma in situ (DCIS), and (3) changing the approach to breast cancer screening.

Adjuvant Radiation in Invasive Breast Cancer

For invasive breast cancer, new data allow us to better evaluate the benefit of external-beam radiation therapy (EBRT) and determine which patients will benefit, particularly those with competing causes of

morbidity and mortality. Radiation therapy is used to decrease locoregional recurrence typically in patients treated with breast-conserving surgery. Early studies comparing partial mastectomy alone versus partial mastectomy with EBRT demonstrated a significant reduction in the rate of breast recurrence with adjuvant radiation.[15] Several newer studies have now shown that in certain subgroups, radiation therapy can be omitted without a significant increase in local recurrence. In a randomized trial of women older than 70 years with hormone receptor–positive clinical stage I breast cancer, the addition of EBRT did not impact overall survival. Although EBRT did significantly reduce locoregional recurrence rates, these rates were reasonably low even without EBRT (90% vs 98% at 10 years; $P<.001$) and EBRT did not impact time to mastectomy or time to distant metastasis.[16] Because radiation does not impact survival in this age group, these data allow clinicians to offer patients the option of less aggressive treatment upfront, with the knowledge that if a local recurrence occurs, additional treatment can be offered at that time without an adverse impact on mortality.

In 2004, Fyles et al[17] reported randomized trial data for 769 women aged 50 years or older with node-negative T1 or T2 breast cancers treated with lumpectomy and tamoxifen with or without radiation. The radiation group was significantly less likely to experience local relapse at 5 years (0.6% vs 7.7%; $P<.001$) and axillary relapse (0.5% vs 2.5%; $P=.049$). However, no difference was seen in distant relapse or overall survival. Even though clinical features have traditionally been used to help identify patients likely to derive benefit from radiation, newer molecular tools provide opportunities for predicting treatment effect. The intrinsic molecular subtypes of breast cancer[18] may help predict response to radiation, with potentially less benefit seen in patients with luminal A tumors, and particularly in older women. Subset analysis of the Fyles randomized trial data[19] found no significant difference in local relapse in women with luminal A tumors (as approximated with immunohistochemical markers) with the addition of radiation. Among those with luminal A tumors, women who were treated with surgery and tamoxifen alone had a 10-year local recurrence rate of 6.9% compared with 4.5% in those who received radiation; in women older than 60 years, those who did not receive radiation therapy had a 10-year local recurrence rate of 5.4% compared with 6% in the group who received radiation. New treatment modalities, such as intraoperative radiation therapy (IORT), also provide alternatives with decreased morbidity. Five-year results from the TARGIT-A trial showed that in a correctly selected patient population, IORT offered similar local recurrence rates and overall survival as EBRT.[20]

Despite these data, a large proportion of women older than 70 years with estrogen receptor–positive tumors continue to receive EBRT, with its associated morbidity.[21] After publication of cooperative group trial data showing little benefit of EBRT in women older than 70 years with stage I breast cancer, analysis of Medicare beneficiaries showed that EBRT use decreased, but only from 79% to 75%.[16,22] The data are now available to support omission of EBRT in women older than 60 years, with early-stage estrogen receptor–positive tumors, and the tools to evaluate intrinsic subtypes that narrow in even more on populations that are unlikely to benefit from EBRT. By applying available data to more patients, we could decrease morbidity, while maintaining the excellent outcomes we have achieved in breast cancer treatment.

Management of DCIS

Just as some patients with invasive breast cancer may not require EBRT, some patients with DCIS may not require the full scope of treatment that is currently used. We can better stratify DCIS lesions by risk and potentially identify those that would not impact mortality if left untreated; additionally, we can consider reflecting the wide spectrum of disease within DCIS by using more descriptive terminology.

Although some patients with DCIS quickly develop nodal disease and distant metastases, the overall survival for DCIS is very high, and even when untreated, most patients do not develop invasive breast cancer until many years after diagnosis. Although natural history data are sparse, a study of 28 women with low-grade DCIS and more than 30 years of follow-up showed that only 40% developed invasive breast cancer in the absence of any treatment other than biopsy, almost a third of which were diagnosed more than 2 decades later.[23] Other natural history studies report a broad range of risk, suggesting that 14% to 53% of DCIS lesions would progress to invasive breast cancer over 10 years if untreated.[24]

Given the broad spectrum of indolent versus aggressive disease in DCIS, clearly treatment should not be a one-size-fits-all model. More than 64,000 cases of DCIS were estimated to occur in 2013.[25] Using published estimates that 20% to 30% of diagnosed breast cancers would not have impacted mortality, between 12,000 and 19,000 women potentially underwent unnecessary treatment for a noninvasive disease found during screening.[26,27] Although overtreatment may not be able to be completely eliminated, its incidence can surely be reduced. Learning how other fields are dealing with the problem of overtreatment can help guide the approach. In prostate cancer, concerns about treating disease with a low potential for impacting life expectancy have led to efforts to avoid unnecessary treatment. Klotz et al[28] followed 450 men with favorable risk prostate cancer, showing 97% disease-specific survival at 10 years with no intervention at all. Surely for slow-growing DCIS with low progression potential and long latency periods, observational trials are justified.

Clinical, histological, and molecular tools already exist that can stratify DCIS lesions by risk. High-risk DCIS is more likely to present symptomatically instead of as a screen-detected lesion.[29] In a modern series of 375 women with DCIS, the prevalence of finding an invasive component within DCIS was 13% in the screen-detected group, but 43% in the symptomatic group.[30] It is known that DCIS lesions with high nuclear grade and comedonecrosis, and those affecting young women have a higher risk of recurrence.[31] These high-risk lesions represent a small proportion of all DCIS. Symptomatic or palpable DCIS represents only 10% of diagnosed DCIS lesions.[32] In 1980, DCIS with comedonecrosis represented approximately 40% of all DCIS compared with approximately 16% in 2001, a difference likely reflecting one of the impacts of screening.[33]

New molecular tests, such as the DCIS recurrence score, also stratify DCIS lesions according to risk of recurrence. The DCIS recurrence score is a continuous score based on the expression of 12 genes, and correlates with risk of ipsilateral breast events in patients who were treated for DCIS with lumpectomy alone as part of the ECOG E5194 study.[34] Just as molecular profiles to establish risk and response to therapy in invasive cancer have allowed more personalization of treatment,[5,6] applying these profiles to DCIS holds promise for identifying which DCIS lesions are unlikely to cause actual disease or will potentially benefit from surgery and/or radiation.

Current treatment of DCIS, including surgical resection and radiation, largely reflects the approach to invasive breast cancer. However, the lack of randomized trial data demonstrating actual benefit from surgery for DCIS combined with the mounting evidence of a wide spectrum of risk from different DCIS lesions have prompted the organization of both surgical and nonsurgical trials for its management. CALGB 40903 is a phase II study for postmenopausal women with nonpalpable hormone receptor–positive DCIS that is evaluating the response to 6 months of neoadjuvant letrozole via MRI, with subsequent surgical excision. This type of trial allows for correlative science between imaging and pathology findings, measuring changes in biomarkers such as Ki-67 before and after hormone therapy, and can be adapted to window trials in which new targeted agents are tried in the neoadjuvant setting.[35] In the United Kingdom, the LORIS trial is designed to randomize women with low-risk DCIS to surgery versus surveillance alone.[36] This study design acknowledges the importance of applying treatment to the right disease: clinicians must question why they treat low-risk and high-risk DCIS as if they are the same disease. Trials such as these and the availability of new molecular assays hold promise to dramatically change the way DCIS is treated, hopefully avoiding unnecessary interventions in women with low-risk disease.

Even as new data emerge showing that tools for predicting response to therapy can help select patients who will not derive benefit, the relatively high threshold for withholding treatment relative to the evidence required to implement new treatment is well documented, leading to a risk of recommending unhelpful interventions.[37] One barrier to reducing interventions in even low-risk DCIS may be the terminology used to describe these lesions. Although encouraging the use of predictive assays and creating registries to follow patient outcomes can potentially mitigate this problem, we and others have acknowledged the impact of language for both providers and patients.[38,39]

Descriptors of breast lesions should better convey the risk associated with those lesions; whereas some DCIS are indolent, some will in fact progress to invasive breast cancer.[1,40] Pathology reports should use the available predictors, including traditional immunohistochemistry markers, and new molecular tests

when reporting the presence of these lesions.[38] Potential changes in terminology could eliminate the word *carcinoma*, use the IDLE nomenclature, or add more information to the current traditional descriptors, such as a risk assessment. The Athena Breast Health Network, a collaboration between the 5 University of California medical centers established to address issues in breast cancer screening, is starting a registry trial using the DCIS recurrence score to change the nomenclature for DCIS lesions, hopefully leading to more clarity in diagnosis and management.[41] Meanwhile, clinicians should acknowledge that low-risk DCIS (nonpalpable, screen-detected, low-grade, hormone receptor–positive) affecting older women likely does not warrant an aggressive approach to surgical resection and radiation, and communicate the spectrum of risk within DCIS to patients when discussing treatment plans. Alternatives to standard management include participation in clinical trials of observation or hormone therapy alone, and carefully weighing the morbidity of additional treatment, such as re-excisions, mastectomy, and radiation, against the benefit, particularly in patients with decreased life expectancy.

Risk-Based Screening

Lastly, screening healthy patients for breast cancer provides another area in which overtreatment can be impacted by pushing for personalized treatment. The goal of screening is to prevent late-stage cancer by identifying precursor lesions. In some tumor types, such as cervical and colon cancers, this goal has been achieved, and the incidence of invasive cervical and colon cancers has decreased since the implementation of screening programs.[42,43] In breast cancer, despite the increase in identification and treatment of DCIS, a concomitant decrease in invasive breast cancer has not occurred. Further, the increase in early-stage invasive cancers has not resulted in the expected decrease in later-stage cancers.[1,13,27] This suggests that the current approach to screening has not had as much impact on survival as was hoped. Additionally, normal- and low-risk women potentially stand to experience a higher rate of false-positive results, leading to increased morbidity in this population.[11] Just as the benefits of treatment would be diluted if applied to patients who did not have disease, the benefits of screening are diminished when applied to a population without sufficient risk. This concept is demonstrated in lung cancer screening programs, in which higher-risk patients derive more benefit from screening. When patients with heavier smoking histories are screened compared with lower-risk patients, the number needed to screen to save 1 life decreases from 3180 to 82.[44,45] Although lung cancer and breast cancer differ in biology, the principles of screening tests remain constant, and this dramatic difference illustrates the importance of screening the right population to reduce false-positives and potentially harmful interventions in patients with a low likelihood of having disease. In 2005 the Institute of Medicine issued a report advocating for the integration of technology, biology, and risk stratification in the development of screening models in breast cancer. This personalization could improve the positive predictive value of the screening test, and potentially lead to fewer unnecessary interventions.[46,47]

Although randomized trial data are currently lacking, 2 recent studies are among those that support the concept of risk-based screening in breast cancer as a way to mitigate harms of screening but still maintain the benefits. A recent analysis modeled the predicted risks and benefits of uniform screening strategies versus risk-based screening approaches. Using age, breast density, family history, and personal history of breast biopsies, risk categories were assigned. Various screening strategies that varied by starting age, frequency, and target risk group were tested using assumptions based on published data regarding false-positive rates and interval cancers, and risk-based strategies were found to have lower harm/benefit ratios and lower costs than uniform screening strategies.[47] Pace et al[11] recently published a review article focusing on meta-analyses of breast cancer screening trials, which highlights the reduction in breast cancer mortality associated with mammographic screening (15% for women in their 40s and 32% for those in their 60s), the high risk of a false-positive result with 10 years of annual mammogram (61%), and the potential overdiagnosis of 19% of cancers identified. Based on published estimates, they also conclude that the benefit of screening is highest in those with higher breast cancer risk.[11]

Some have argued that overtreatment, and not overdiagnosis, is the problem,[48] but the authors feel that there is room for improvement on all fronts. Clinicians should seek to improve the screening tests by

applying them to women with high enough pretest probability of having breast cancer that the positive predictive value of the test is improved.[11,12,49] The US Preventative Services Task Force (USPSTF) currently does not recommend routine screening for women in their 40s, but rather recommends a discussion of the risks and benefits. In this age group, the chance of absolute benefit is lowest and the chance of false-positives highest.[50] Applying a risk-based strategy could add value to making decisions about screening, because women in their 40s with a 1.9-fold risk of developing breast cancer are projected to derive the same benefit from screening as women in their 50s.[51] Several investigators are advocating a risk-based approach to improve the benefit and reduce harms of screening.[52] Such a model requires risk assessment and personalizing a screening program for an individual's risk profile. For example, instead of automatically starting annual screening for a 40-year-old woman, if the risk assessment tool found her to be low-risk, she might decide to hold off on screening and avoid the high chance of a false-positive result over the next 10 years of screening. Alternatively, a 30-year-old found to be high risk might be encouraged to consider starting annual screening with MRI. The available data suggest that in making screening recommendations based on risk, harms such as overdiagnosis will be minimized, and the potential benefit will be maximized. A randomized trial of personalized breast cancer screening versus annual screening (estimated accrual of 100,000 women) will open in the spring of 2015 across the University of California medical campuses through the Athena Breast Health Network. In this trial, women in the personalized arm will undergo comprehensive risk assessment combining genomic risk, breast density, family history, exposures, and overall health, which will be used to assign an age to start, an age to stop, and the frequency and modality of screening. No one will receive less screening than is recommended by the USPSTF breast cancer screening guidelines. The personalized screening arm will be compared with annual screening in all women aged 40 years and older.[53] This risk assessment also lends itself to personalized prevention strategies.

Although the authors feel that clinicians can decrease the effects of overdiagnosis and overtreatment by engaging patients in conversations regarding radiation for invasive breast cancer, management strategies for DCIS, and screening for healthy patients, and potentially decrease interventions in low risk cases, they acknowledge that these are complex issues with, at times, controversial data. There is a need for more long-term studies and randomized data. In particular, long-term studies evaluating the ability of the recurrence score to predict the benefit of radiotherapy in DCIS, observational trials in DCIS, and randomized trials of risk-based screening are needed.

In every aspect of breast cancer care, new epidemiologic data are being seen and new technology are help to determine which patients will benefit from particular types of screening and treatment. Although applying molecular tools to guide treatment decisions may be relatively new, the concept of evolution in cancer care is certainly old. The field is moving toward truly personalizing recommendations for individual patients, and this will no doubt result in some patients requiring more screening and others requiring less, and some patients with breast cancer may require more aggressive treatment, whereas others may be managed with surveillance or perhaps be reclassified as having an IDLE lesion. The solution to overtreatment is not less treatment, but rather finding the right treatment for an individual patient. Clinicians should welcome this challenge to continue to improve breast cancer care. Opportunities to advance the field of breast cancer care are listed in Table 1.

Table 1 Opportunities to Advance the Field of Breast Cancer Treatment

Reduce Overtreatment of Invasive Breast Cancer
• Discuss the option of lumpectomy without radiation in women >60 years with hormone receptor–positive breast cancer
Decrease Aggressive Treatment for DCIS
• Integrate new predictive tools, such as the DCIS recurrence score, in management decisions
• Work toward revising DCIS nomenclature to better reflect true risk
Risk-Based Screening
• Use available validated risk assessment tools
• Engage patients in risk/benefit discussions regarding when to start and stop screening, modality, and frequency of screening based on their risk profile and preferences
Generate Further Data to Decrease Overdiagnosis And Overtreatment
• Offer patients the opportunity to participate in observational and registry trials to increase opportunities for personalized screening, prevention, and treatment

Abbreviation: DCIS, ductal carcinoma in situ.

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