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Review

Precision surgery and avoiding over-treatment

A. Hosseini [a], A.L. Khoury [b], L.J. Esserman*

University of California, 1600 Divisadero, 2nd Floor Box 1710, San Francisco, CA 94115, USA

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Abstract

Over-diagnosis and over-treatment are consequences of greater awareness about breast cancer, more intensive screening, and the resultant identification of more cases of breast cancer that are low or ultralow risk. This area represents an important opportunity to optimize the delivery of appropriate targeted therapy for breast cancer patients. Despite the evolution of breast cancer care over the last few decades and our ability to tailor treatment to biology, a one-size fits all approach is still prevalent in the local and regional management of and screening for breast cancer, failing to reflect the unique biology and tumor characteristics of each patient. In this review, we explore how we can use new tools to better define tumor biology and also how we can change current clinical practices based on already available data. Every surgeon should be knowledgeable about how to craft personalized breast cancer care in the areas of systemic therapy, adjuvant radiation therapy, management of ductal carcinoma in situ (DCIS), precision surgery, and breast cancer screening.
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Keywords: Medical overuse; Breast neoplasms; Precision medicine

Introduction

It is widely accepted that breast cancer is a heterogeneous disease with varying risk for metastatic progression and death. The spectrum of breast cancer ranges from indolent to rapidly progressive. For the former, over-diagnosis and over-treatment have emerged as important issues for providers that care for breast cancer patients. Despite the mounting evidence on over-diagnosis, we continue to follow local therapy guidelines that predated widespread screening, and our screening guidelines are the same for all women even though there must be varying risk for the different types of breast malignancies.[1] Those who are diagnosed with in-situ or early invasive disease are often offered local treatments that are the same as for those with locally advanced disease. Better precision and the ability to characterize the lowest risk patients will provide greater health care value: similar or better outcomes with less morbidity and associated costs.

Great advances in the management of breast cancer patients have been achieved over the last few decades. These include smaller surgeries, less axillary surgery, vastly improved reconstructive techniques saving skin and optimizing cosmesis, moving from size or stage-based to biology-based decisions for adjuvant chemotherapy, and the introduction of systemic targeted treatments. Some of the greatest strides have been made in identifying molecular markers and other tumor characteristics to help predict which patients would benefit from systemic and/or local adjuvant therapy.[2,3] However, there is greater opportunity to use evidence to further optimize clinical practice. Precision surgery and further tailored treatment are the means by which we can begin to address these issues plaguing providers and more importantly our patients.

Biology of breast cancer

Understanding the biology of breast cancer is the key to precision surgery and avoiding over-treatment. Over the last decade, the classification of breast cancer has evolved

* Corresponding author. Fax: +1 415 353 9651.
E-mail addresses: Ava.hosseini@ucsf.edu (A. Hosseini), amal.khoury@ucsf.edu (A.L. Khoury), laura.esserman@ucsf.edu (L.J. Esserman).
[a] Fax: +415 353 9651.
[b] Fax: +415 353 9651.

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from clinical parameters, such as size and grade, and receptor status to include the molecular biology of the disease. Tumors are now classified according to subtype: Luminal A and B, Her2 positive, basal-like, Claudin-low, and normal breast.[4] These subtypes have different prognoses and responses to therapy. Gene expression profiles such as Oncotype Dx®, Prosigna®, and MammaPrint® further stratify tumors according to risk of recurrence on the basis of genomic make-up. This additional information helps personalize breast cancer treatment and determine which women need aggressive systemic treatment for high-risk cancers versus close surveillance for indolent tumors. It also has helped pave the way for targeted therapies, such as endocrine therapy and herceptin.

However, further work can be done to improve local-regional and systemic management. Despite the growing research on tumor biology, women with low-risk tumors still receive aggressive local-regional therapy. Over time, this has become a more significant issue because of the initiation of widespread screening, which has changed the distribution of breast cancers that present today. Specifically, screening has increased the detection of biologically low-risk tumors, which fit the category of indolent tumors of epithelial origin (IDLE), and there is increasing evidence that a meaningful proportion of tumors truly have indolent behavior even when followed.[5] Therefore, we should work to translate this knowledge into changes in breast cancer treatment: from a local management perspective, low-risk biology should not be treated as aggressively as high-risk biology. Another important change in management is the increasing use of neoadjuvant therapy. This allows not only the incorporation of tumor biology, but also the ability to alter local management strategies based on response to therapy. Better understanding and incorporating the information we now have regarding tumor biology will allow us to develop a more personalized approach and avoid over-treatment; this can be achieved specifically in the areas of chemotherapy, adjuvant radiation, management of ductal carcinoma in situ (DCIS), surgical management of locally advanced tumors, and screening practices.

Systemic therapy

With improved knowledge of the biology of disease, indications for systemic therapy in the management of breast cancer have evolved in the last few decades. Initially, recommendations for systemic therapy were based on clinical stage. Women with any tumor greater than 1 cm (even in the absence of nodal involvement) were given chemotherapy based on any absolute benefit $\geq$1–2%. Loprinzi, Ravdin and colleagues determined that communication between providers and patients regarding prognosis often lacked a discussion of the absolute benefit with the addition of adjuvant therapy, and was often confusing or inaccurate.[6] Ravdin et al. went further to help both patients and providers understand quantitative risk and absolute additional benefit of adjuvant therapy by creating ADJUVANT!, a computer-based tool that incorporates tumor characteristics including size, grade, nodal and receptor status in addition to other patient characteristics such as age, menopausal status. This online application allows patients and providers to enter their specific data into the system to generate their baseline prognosis as well as expected improvement with the addition of adjuvant endocrine and/or chemotherapy. This tool has been validated and is used frequently to aid in decision-making about adjuvant systemic therapy.[7,8] At the time this tool was developed, we did not have data on Her-2 receptor status or multi-gene tests, which have now provided new information on the impact of adjuvant treatment.

Development of multi-gene tests have given us further insight in predicting those patients who will benefit from adjuvant endocrine and chemotherapy. Oncotype Dx® is a 21-gene assay which provides a recurrence score in women with ER+, node-negative Tamoxifen-treated breast cancer.[2] Patients are categorized into low, intermediate and high-risk based on recurrence score and patients who are low-risk do not benefit from systemic chemotherapy. Appropriate management of those with intermediate-risk of recurrence is controversial and awaits the results of the TAILORx trial. Although the original study demonstrated that these patients did not benefit from chemotherapy, high-risk women had a large absolute benefit (20%) from chemotherapy. This tool is only validated in women with ER+ node negative breast cancers. The MINDACT Trial, however, included women aged 18–70 with primary invasive (T1-operable T3) breast cancer of all types, with size up to 5 cm, who had up to 3 positive lymph nodes. This trial evaluated the clinical utility of the MammaPrint® 70-gene breast cancer assay in women who had scores discordant with the clinical risk score provided by the ADJUVANT! online clinical risk tool in guiding systemic management. Subjects with low clinical and genetic risk avoided chemotherapy and those with concordant high-risk scores received chemotherapy. Those with discordant clinical and genetic scores, on the other hand, were randomized to chemotherapy vs. none. The primary outcome, which was met, was that 5-year distant disease-free survival for women with the 70-gene low-risk profile would be above 92% even without chemotherapy. The result for women without chemotherapy was 94.5% and was not inferior to the outcome of women with chemotherapy. They found that among women with high clinical risk factors and low MammaPrint® scores, 46% could have avoided adjuvant chemotherapy.[3] These findings validate that we may be over-treating some patients with unfavorable clinical risk factors, giving toxic drugs that provide little or no improvement in disease-free survival and that molecular profiling is a replicable and reliable test that provides assurance that less can be more.

There is also data demonstrating that molecular tools can be used to identify ultralow-risk or indolent cancers,[9] which pose almost no risk of death from breast cancer at

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