Mitigating Overdiagnosis and Overtreatment in Breast Cancer

What Is the Role of the Pathologist?

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fter decades of experience with breast cancer screening programs in the United States and other countries, recent attention has focused on balancing the benefits and harms of screening for breast cancer.1 In a Viewpoint article entitled “Overdiagnosis and Overtreatment in Cancer: An Opportunity for Improvement” in the August 28, 2013, issue of the Journal of the American Medical Association (JAMA), Esserman et al2 summarized recommendations from a working group charged with improving the current approach to cancer screening and prevention. The JAMA Viewpoint is generating considerable debate in the medical community and was widely reported in the national media. The working group evolved out of a National Cancer Institute meeting convened to evaluate the problem of “overdiagnosis” or overdetection, most often defined as the detection of tumors by screening that, if left unattended, would not become clinically significant or cause death.3 The treatment of all such screen-detected tumors potentially results in overtreatment of a subset of patients whose tumors may be indolent, unlikely to affect their well-being or mortality. For some tumors, including breast cancer, the significant increase in the detection of early-stage disease, in the absence of a commensurate decline in more advanced disease, may lead to overtreatment of more patients.4 The working group offered 5 recommendations: (1) recognize that overdiagnosis is common and more frequent with cancer screening, (2) change cancer terminology based on companion diagnostics, (3) create observational registries for low malignant potential lesions, (4) mitigate overdiagnosis, and (5) expand the concept of how to approach cancer progression. This editorial will review key ideas in the overdiagnosis and overtreatment debate from the perspective of practicing pathologists. We will highlight 3 areas in which we believe pathologists can and should participate: the classification of potential precursor lesions for breast cancer, clear communication of their cancer risk implications, and participation in multidisciplinary studies to better define the risk of recurrence and progression for those lesions in individual patients.

CANCER TERMINOLOGY AND COMPANION DIAGNOSTICS

Most screening programs began with the assumption that an ideal program would detect all cancers and allow treatment at an early stage. But it has become apparent that a better goal would be selective early detection of aggressive tumors or their precursors, allowing intervention before progression, metastasis, and death. For cancers with diverse biologic behavior, a highly successful screening program would require the ability to distinguish indolent from aggressive disease and the use of terminology that clearly conveys the risk associated with a given lesion. Promising developments in the molecular characterization of invasive breast cancer include the definition of clinically relevant intrinsic molecular subtypes5,6 and the estimation of the risk of distant recurrence during the next 10 years for estrogen receptor–positive, lymph node–negative tumors.7 However, work remains to be done to identify indolent invasive tumors with companion diagnostics that could be appropriately classified or treated as anything other than an invasive cancer. Among invasive (or potentially invasive) breast tumors, small (pT1a-pT1b) pure tubular carcinomas and encapsulated papillary carcinomas may be candidates for a change in terminology based on their excellent prognosis and indolent behavior. Given the uncertain risk of local and distant recurrence for most invasive mammary carcinomas and many physicians’ (and patients’) fear of not doing enough, any change in terminology for indolent types of invasive carcinomas could be met with anxiety and resistance. The question is: How can we ensure that in all cases these low-risk lesions are clearly identified and separated from other, similar-appearing lesions that may have significant metastatic potential? A more complete understanding of the biology of the screen-detected cancers is required to estimate the efficacy of screening, including women in the 40- to 50-year age group. Retrospective studies have shown that many of the women younger than
50 years who died from breast cancer did not participate in screening programs. However, the current approach to breast cancer screening may be most effective in detecting indolent tumors and least effective in detecting aggressive tumors in this age group. Ongoing multi-institutional research studies will continue to refine molecular tests to more accurately quantify the risk of metastasis of a particular invasive tumor at the time of diagnosis, and pathologists will have a role in analyzing and applying the data from those studies. Ideally, future studies would help identify new approaches to screening that maximize the benefit of detecting a tumor. Going forward, effective screening for breast cancer will almost certainly combine both diagnostic and prognostic tests. Pathology reports will eventually need to integrate traditional pathologic data with companion diagnostic molecular information to provide a comprehensive report that quantitates the risk associated with a particular breast carcinoma.

**DUCTAL CARCINOMA IN SITU**

**Cancer Terminology and the Concept of Progression**

When patients better understand the risk associated with their particular breast cancer precursor lesion, they can more carefully weigh the risks and benefits of interventions designed to prevent a future invasive carcinoma. As pathologists, how do we do a better job of conveying the risk associated with a particular lesion? As recently pointed out by Esserman et al, the term “ductal carcinoma in situ” (DCIS) may be a good place to start. The high survival rates of 98% to 99% for DCIS suggest that we may be overtreating some patients with DCIS. Treatment for DCIS, including radiation and mastectomy, and subsequent follow-up imaging and procedures can have a substantial impact on the patient’s quality of life. Patient decisions regarding treatment of DCIS are influenced by the terminology used for this precursor lesion. When DCIS is framed as a high-risk condition rather than as cancer, more women may opt for nonsurgical treatment. Pure DCIS does not metastasize or cause mortality. It is treated because it is associated with a very high risk of the patient subsequently developing invasive carcinoma. There is increasing agreement that the label of “carcinoma” or “cancer” for DCIS overestimates the risk of recurrence. We would support the emerging multidisciplinary recommendation to remove the term “carcinoma” from DCIS, with the hope that surgical pathologists will have a central role in revising the classification for carcinoma in situ.

Changing the nomenclature of DCIS is likely to be controversial, if not impossible, in the absence of a reliable companion diagnostic test to predict the risk of progression. To date, studies have not been able to consistently identify the cases of DCIS with the lowest and highest likelihoods of progression to invasive carcinoma. Results from the ECOG 5194 trial indicate that traditional pathologic criteria alone may be insufficient to identify a low-risk population. Given the issues related to reproducibility and standardization in classifying DCIS, evaluating margins, and estimating size (extent), additional tools are needed to better stratify risk for a particular patient with DCIS. There is a relative paucity of molecular studies on large numbers of patients evaluating the risk of progression associated with DCIS. The Oncotype Dx test (Genomic Health Inc, Redwood City, California) for DCIS to predict local recurrence risk is the first commercially available assay designed to help individu-
starded terminology with specific implications for cancer risk and patient management. The diagnostic categories that we use as pathologists should give patients and their physicians an accurate impression of the threat the lesion poses to the life or well-being of the patient. Based on model diseases like colorectal carcinoma, patients and physicians may overestimate, perhaps more than they realize, the risk of progression of putative precursor lesions. A model of stepwise, linear progression through well-defined lesions with increasing atypia and risk seems intuitive. But it may be inappropriate to apply the lessons from nonmammary tumors to breast cancer. Conveying the concept of epithelial atypia as a marker of risk, or nonobligate precursor, is a difficult but essential undertaking.

As pathologists we need to use uniform criteria and terminology in the diagnosis of atypical ductal hyperplasia, atypical lobular hyperplasia, and FEA. It is essential that we communicate in our reports the specific type(s) of atypia we have diagnosed. Our clinical colleagues may not always understand the different risk implications of atypical ductal hyperplasia and FEA. Avoiding the generic use of the term “atypia” for complex lesions or for cellular patterns of usual-type hyperplasia should reduce overdiagnosis. And educational comments for low-risk lesions, such as pure FEA, may help mitigate overtreatment.

Just as some authors may argue that the term “cancer” is too broadly applied to the lesions detected in population-screening programs, we might argue that “atypia” in the breast may be too broadly defined and applied. If the word “atypical” or “atypia” in any diagnosis triggers a surgical excision and more frequent follow-up visits and imaging studies, we may need to reexamine the terminology we use. The long-term risk of subsequent carcinoma after a diagnosis of pure FEA in an open biopsy appears to be significantly lower than that for ADH and ALH. The lower risk associated with FEA and the available data on the laterality of subsequent invasive carcinomas raise questions about the role of local surgical excision in the management of FEA diagnosed on core biopsy. It may be prudent to have discussions about removing the word “atypia” from FEA because the term leads to confusion and overestimation of the risk of developing cancer. One specific example that we have observed is clinicians entering FEA as a form of ADH when using the Gail model to assess risk. Even if one believes that FEA “progresses” along the low-grade pathway of carcinogenesis, the carcinomas most often associated with FEA are indolent hormone receptor–positive tumors that represent a low threat to the mortality of the patient.

STUDY DESIGN

Designing and conducting better protocols to individualize patient management of atypia on core biopsy is another opportunity for mitigating overtreatment. Most studies evaluating the upgrade rate for FEA and lobular neoplasia on core biopsy are retrospective studies from single institutions with widely varying upgrade rates. Many of these studies suffer from absent or inconsistent clinical and radiologic data, lack of central pathology review by dedicated breast pathologists, and small sample size. In other words, the published data do not provide a sufficient level of evidence to inform our daily practice. Also lacking from most of these studies are the details of the cancers that are detected. Many of the nonobligate precursors to breast cancer that are detected by screening mammography are part of the low-grade breast neoplasia pathway. When we evaluated the upgrade rate at our institution for 73 cases of pure FEA on core biopsy, we detected 2 pT1a low-grade invasive tumors and 3 cases of estrogen receptor–positive grade 2 DCIS (overall upgrade rate of 6.8%). It is unclear whether any of these upgrades would have ever become clinically relevant for the patients. Prospective studies with central pathology review, detailed molecular correlation, and long-term follow-up data would improve risk assessment for patients in the future. Collecting an adequate number of well-defined cases remains a significant challenge and will only be achieved through multi-institutional collaboration and pathologist participation.

CONCLUSION

Although several of these discussion points are controversial, there is clear evidence that there are many opportunities for pathologists to participate in the process of improving breast cancer screening. It is essential that, as active participants, pathologists share their unique perspectives and knowledge on the diagnosis and classification of breast disease as efforts evolve to improve breast cancer screening.

References