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Personalization of Ductal Carcinoma In-Situ Management: Large Databases and an Emerging Role for Global Data Sharing

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We have read with great interest recent DCIS observational studies by Mannu et al.¹ and Giannakeas et al.² regarding invasive breast cancer risk and breast cancer mortality after ductal carcinoma in situ and the association of a diagnosis of ductal carcinoma in situ with death from breast cancer. In this paper, we explore some of the shortcomings of the current landscape of DCIS literature and make a call for global data sharing for sources of DCIS outcomes data.

I. Ductal Carcinoma in Situ Outcomes

A major challenge posed by ductal carcinoma in situ (DCIS) research is the significant heterogeneity of the disease coupled with the rarity of relevant outcomes of interest such as progression to invasive disease and breast cancer mortality (BCM). Several randomized controlled trials (RCTs) have been conducted on DCIS patients with lumpectomy-amenable disease to assess the effect of adjuvant radiation therapy (RT) and endocrine therapy (ET) on outcomes. These studies consistently demonstrated that while such adjuvant therapies reduced second breast cancer events (SBCE), they neither influenced BCM nor overall survival (OS).³⁻⁵

The full picture is more complicated. There is evidence that patients who suffer invasive SBCEs have higher rates of BCM⁶, a very rare outcome for DCIS patients. This suggests that either the previously mentioned RCTs were insufficiently powered to detect the impact of adjuvant therapies on BCM, or that the adjuvant therapies administered

are preferentially reducing rates of non-lethal invasive SBCEs, or that there is a small proportion of DCIS lesions that are associated with substantially high risk for a metastatic event, even when an invasive component has not been found.^{6,7} What we traditionally refer to as high risk factors for DCIS lesions are predominantly related to the risk of progression to invasive disease or recurrence. It is unclear, however, whether these factors are also associated with high risk of BCM. We anticipate that investigation of trends and patterns within subgroup analyses of large cohorts may shed light on the influences of such factors on these respective outcomes of interest.

II. Frequently Overlooked Covariates in DCIS Outcomes

Race

Black race has been repeatedly shown to be associated with increased risk of invasive progression and worse prognosis in DCIS patients in the US, which has been attributed to various causes, including delay in adjuvant therapy, biological differences such as differing rates of hormone receptor positivity, and, of relevance to the referenced studies, reduced access to high quality screening facilities.⁸⁻¹¹ In the study by Mannu et al., race was not incorporated into the outcomes analysis.¹ The proportion of black Britons relative to the overall UK population may be smaller than that in the US, but any information obtainable from the National Health Service Breast Screening Programme (NHSBSP) regarding the proportion of patients attending their invited screening mammogram would allow for a rough comparison of these numbers to the proportion of black Britons in the general population to help shed light on this question.

HER2 Overexpression

We recently showed that patients with HER2

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overexpressing DCIS had increased rates of ipsilateral invasive SBCE on an analysis of data from the Surveillance, Epidemiology and End Results Program (SEER), a large US cancer database, but the significance of HER2 overexpression on invasive recurrence has been debated, with some studies demonstrating increased, some decreased, and some no change in risk based on this marker.¹²⁻¹⁶ At most institutions, HER2 is not routinely assessed for DCIS; however, at one of the institutions represented by the authors, it has been routinely tested for DCIS patients in recent years, and at the other, it has been assessed for patients entering an active surveillance protocol due to the higher observed rate of invasive progression in patients declining surgical therapy at that institution. HER2 status was not accounted for in either of the referenced studies.

Microinvasion

Patients who received chemotherapy are frequently excluded from DCIS outcomes studies, as chemotherapy is not indicated for pure DCIS. One of the possible limitations of the referenced study by Mannu et al. is that it is unclear whether this was done with or without knowledge of microinvasion status. If this was done without the knowledge of microinvasive status, it is possible that a subgroup of patients with microinvasive disease would remain, because not all patients with microinvasive disease, or even those with triple negative microinvasive disease, are necessarily required to undergo chemotherapy. Microinvasion is associated with worse prognosis¹⁷, so an incomplete inclusion of these patients based on chemotherapy receipt may have unanticipated influences on outcomes analysis.

Surgical Laterality and Breast Reconstruction

Another concern particular to the study by Mannu et al. is that patients undergoing mastectomy were grouped together for analysis; we are interested in whether surgical laterality for mastectomy with unilateral DCIS was available, as this would be expected to significantly influence the results of the ipsilateral-contralateral rate comparison.

Furthermore, breast reconstruction may be associated with improved breast cancer specific survival in invasive breast cancers¹⁸⁻²⁰, though it is unclear whether this is secondary to biology or socioeconomic factors.¹⁹ However, it is possible that patients with DCIS may also have a survival benefit with reconstruction and represent an additional confounder.

III. Additional Analyses for Consideration

Breast Cancer Mortality without an Intervening Invasive Lesion

In Steven Narod's 2015 analysis on BCM among DCIS patients, roughly half of patients who suffered

BCM after an initial diagnosis of DCIS did so without documented evidence of an intervening SBCE.⁶ In the study by Mannu et al., it would be intriguing to see whether this trend was also present among the cohort in this study, as it is possible that Narod's observation could have been related to one of the many sometimes rather opaque abstracting guidelines for tumor registrars, or it could be secondary to biology, in which case, learning more about these types of high risk DCIS would be very important.

Molecular Phenotype Changes after Adjuvant Endocrine Therapy

If data regarding the molecular phenotype of invasive recurrences were available, it would be interesting to investigate whether RT or ET influence rates of changes in molecular phenotype from the initial lesion to the invasive recurrence. And in particular, if a subset of HR- patients were identified who are more likely to have a HR+ invasive recurrence, it may be possible that these patients could benefit more from adjuvant or prophylactic ET.

IV. Point of Interest

Contralateral Invasive SBCE Rates

One of the most interesting findings to us in the study by Mannu et al. was the association of BCS without adjuvant RT as well as involved margins with invasive contralateral SBCE, where BCS without RT reduced contralateral invasive risk, and involved margins increased contralateral invasive risk.¹ Involved margins are classically thought of as conferring risk of local recurrence, and adjuvant RT has only been shown to influence ipsilateral recurrences. There are many possible explanations for this interesting finding. It is possibly as simple as exposure to less intense radiation in the contralateral breast predisposing to a new focus of disease in that breast, though at least for invasive lesions, this does not appear to be a significant influencer.²¹ Alternatively, the presence of involved margins may represent some lesion related factor suggestive of a predisposition to further disease at other sites.

V. Minor Clarification

Tumor size

One issue we have noted in DCIS registry data in the US, including the SEER based study by Giannakeas et al., pertains to the method by which lesion sizes are coded when there is more than one focus of disease.² In our local tumor registries, DCIS size may be abstracted as either the largest contiguous focus of disease or as the overall extent of disease. This could have a significant impact on the outcomes analyses performed. For example, a tumor coded as one centimeter, due to the pathologist stating the largest contiguous focus of disease, when that disease actually extends over a much larger area



of breast tissue, could result in an inappropriate proxy for tumor size. If tumor size reporting is inconsistent in the UK as it seems to be here in the US, a better surrogate may be the lesion size on screening images, assuming the entire lesion is mammographically visible or otherwise that the patient's lesion was appropriately characterized by adjunct imaging methods such as ultrasound or magnetic resonance imaging.

VI. A Call for Global Data Sharing

In the US, there are two large publicly available cancer databases that can be readily queried for the purposes of BCM analysis. Both have advantages and disadvantages.²²⁻²⁴ The previously mentioned SEER database allows for analysis of invasive SBCE, BCM, and OS, but does not include data on ET and captures a smaller percentage of DCIS patients. The National Cancer Database (NCDB), on the other hand, includes a larger sampling of patients and offers a better characterization of treatment related factors including ET and immunotherapy, but problematically the only outcome made available is OS, not BCM or invasive SBCE.

An equally important limitation from the data science standpoint pertains to the relationship between these two databases. While many patterns may be identified within a given individual dataset, not all of them are necessarily of clinicopathologic consequence. We recently showed, for example, that a coding idiosyncrasy within SEER guidelines results in its underestimation of breast cancer mortality, even though it has previously been used to estimate this outcome.^{6,25} Another possible source of error is that some patterns may be identified due to confounding variables that are either not available within a given dataset or not utilized within a particular analysis. Ideally, to combat such unanticipated influences, one of these sources could be used as a discovery database, analogous to the training datasets utilized in machine learning techniques, and the other could be used to verify these findings, analogous to validation datasets. This is unfortunately unrealistic with respect to outcomes analysis using the current publicly available datasets because of the lack of overlap between endpoints such as SBCE and BCM, as well as the fact that there are shared patients between some datasets such as SEER and NCDB.

The two University of California institutions representing our authors have been in the process of making a publicly accessible DCIS resource. This dataset will obviously be smaller in size than such national datasets as SEER and NCDB. However, it will incorporate not only clinical, histopathologic, and outcomes data, but also curated data on exposure to hormone therapy and findings from our molecular biology and imaging studies on these deidentified patients. This will allow data scientists interested in

subgroup analyses to investigate trends that may be missed in more comprehensive analyses. We are planning a system whereby any researcher or data scientist with a legitimate question can gain access through us to this database, similar to the systems utilized by SEER and NCDB.

We wish to invite all researchers with access to such unique DCIS datasets to work to make deidentified, publicly available versions. Such publicly accessible versions of these datasets would be highly valuable from the standpoint of outcomes analysis, as it would allow for validation of hypotheses generated regarding BCM from other large, public datasets which may be more limited with respect to characterization and outcomes.

Translational scientists may someday provide the medical community with the tools to provide truly individualized patient care for DCIS patients. In the interim, we believe that more can be done to personalize management for the hundreds of thousands of women diagnosed with this condition each year by more carefully elucidating the relevance of different clinicopathologic features to different possible outcomes.

Conflict of Interest

None.

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