Overtreatment of DCIS: New Meta-Analysis Identifies Prognostic Factors

BY MICHELLE PERRON

Approximately 1 in 5 new breast cancers is diagnosed as ductal carcinoma in situ (DCIS), an early-stage cancer that is highly treatable. The number of cases of DCIS diagnosed in 2019 is estimated to be 62,930, while the number of new cases of invasive breast cancer is expected to be 268,600 (CA Cancer J Clin 2019;69:7-34). Without clear criteria to predict which women with DCIS will develop invasive breast cancer, it is common for patients with DCIS to receive aggressive treatment. More and more evidence is showing that this may not be appropriate.

“Since most DCIS lesions will never make it to breast cancer, it is urgent that we find out how to distinguish harmless from hazardous DCIS to spare many women the burden of needless treatment,” said Jelle Wesseling, MD, PhD, Professor of Breast Pathology in the Netherlands Cancer Institute and Leiden University Medical Center.

Wesseling and colleagues recently published a systematic review and meta-analysis summarizing current knowledge and prognostic factors for invasive disease after a diagnosis of DCIS. It identified six factors that may predict invasive breast cancer recurrence after DCIS (Cancer Epidemiol Biomarkers Prev 2019;28(5):835-845).

Study Background & Design

The natural course of DCIS is not well understood, Wesseling said, mainly because most women with it are treated with mastectomy or lumpectomy that is often complemented by radiotherapy. In addition, hormonal treatment is prescribed for a substantial number of women with DCIS.

“Current guidelines dictate surgical excision of DCIS, yet the majority of cases do not progress nor become life-threatening if left untreated. As a result, many women are overtreated,” Wesseling noted. Through the systemic review and meta-analysis, Wesseling and colleagues sought to examine past data in order to identify prognostic factors that may direct treatment.

The researchers performed a systematic search in Pubmed and identified 1,781 studies that had examined DCIS and the risk of invasive breast cancer recurrence. Forty met the team’s inclusion criteria, reflecting the small number of studies that specifically focused on invasive breast cancer recurrence after DCIS. Many studies did not specify recurrence type (in situ or invasive) and were excluded.

The sample size of studies included in the analysis ranged from 52 to 37,692 patients. The mean follow-up time ranged from 3.2 to 15.8 years. Seven studies included patients with DCIS who also had an adjacent invasive component or microinvasion, and seven other studies excluded such patients. Fourteen studies included patients representing all types of treatment modalities (breast-conserving surgery [BCS] alone, BCS + radiotherapy [RT] or hormonal therapy, mastectomy), while 16 other studies included only patients treated with BCS with or without RT. Ten studies included patients who underwent one treatment modality only: BCS with RT or BCS alone.

The data reported by all studies were collected retrospectively and represented patients diagnosed between 1960 and 2010. The studies were published between 1998 and 2018. Hospital registries, national registries, and data from clinical trials were used. Both cohort (80%) and case-control designs (20%) were used. Seventy percent were multicenter studies, and 30 percent involved only a single center.

To assess bias, the researchers used six Quality of Prognosis Studies (QUIPS) domains: study participation, study attrition, endpoint definition, prognostic factor measurement, confounding measurement and handling, and statistical analysis and reporting. In 39 of the 40 studies, they identified a high or moderate risk of bias in at least one domain. Twenty-two studies had a high risk of bias in at least one domain. The domains with the highest risk of bias were study participation and confounding measurement and handling.

Findings: 6 Prognostic Factors

Wesseling and colleagues performed meta-analyses on all data to estimate the average effect of the prognostic factors reported by more than one study, regardless of statistical significance. Most of the factors pointed to a higher relative risk of subsequent invasive breast cancer for patients with DCIS, but the effects were generally small. Six prognostic factors had a statistically significant pooled estimate:

1. Black race
2. Premenopausal status
3. Detection by palpation
4. Involved margins
5. High histologic grade
6. High p16 expression

The association between these six prognostic factors and subsequent risk for invasive breast cancer can be biologically explained, the
researchers wrote. “When DCIS has involved margins, this indicates that residual tumor cells are left behind at the resection site. These cells can subsequently grow out and form a recurrence, which could be invasive disease. Premenopausal status and African-American race are known independent predictors of worse breast cancer outcome. “The literature has shown that DCIS detected by palpation would be more aggressive than screening-detected DCIS, as these DCIS lesions are more often ER-negative and HER2-positive. The same holds true for DCIS lesions of high histologic grade. Lastly, p16 mediates cell cycle arrest through the p16/Rb signaling pathway. Disruption of the p16/Rb signaling pathway is an oncogenic event and results in sustained cellular proliferation, which can lead to DCIS progression to invasive breast cancer.”

Wesseling told Oncology Times that the findings of the meta-analyses were at once expected and unexpected. “It was already known to us that many different prognostic factors have been described … but the findings demonstrated a lack of robust data on validated prognostic factors,” he said, adding that his team is the first to perform bias assessment on prognostic factor studies for DCIS. “There is a high frequency of biases in previous studies,” he continued. “Some biases are inevitable, as it can be difficult to set up fully annotated cohorts. But other biases can be prevented easily. By mapping these, we aimed to increase awareness among researchers to help the community avoid these biases as much as possible.”

The Future
Wesseling recommends several next steps:
• analysis of unbiased cohorts rather than selected series;
• focus on the occurrence of subsequent invasive breast cancer rather than both DCIS and invasive breast cancer;
• increasing the availability of detailed information about treatment, pathology, and follow-up; and
• taking an integrated, comprehensive approach that involves new technologies and areas of research (e.g., detailed genomics and epigenomics analysis, the role of the microenvironment, and creation of a risk stratification tool to assess the likelihood of DCIS progression).

These steps have been incorporated into an international effort, spearheaded by Wesseling, that seeks to prevent unnecessary breast cancer treatment. The project, titled PRECISION (PREvent ductal Carcinoma In Situ Invasive Overtreatment Now) is funded by Cancer Research UK and the KWF Dutch Cancer Society. Experts from the U.S., U.K., the Netherlands, and other countries are involved. Learn more at the following websites: https://www.dcisprecision.org/ and https://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/grand-challenge-award/funded-teams-wesseling.

The goal of this research is to reduce overtreatment of DCIS. “I hope that oncologists will support all the efforts to learn how to distinguish harmless from hazardous DCIS,” Wesseling stated. “Together, we can save thousands of women from needless and burdensome treatment every year.”

Michelle Perron is a contributing writer.