



# Calculation of recurrence risk of ductal carcinoma in situ: open questions, controversies and future perspectives

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*Comment on:* Van Zee KJ, Subhedar P, Olcese C, *et al.* Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ: Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years. *Ann Surg* 2015;262:623-31.

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Ductal carcinoma in situ (DCIS) of the breast is a heterogeneous group of lesions with diverse malignant potential and a range of treatment options (1). In the past, before the introduction of mammography for secondary prevention of breast cancer, diagnosis of DCIS was rare, representing less than 1% of all breast carcinomas. With the advent of mammography screening, its incidence rates rose rapidly, and this rise was seen consistently in different countries around the world (1-4). In the USA, according to SEER data, the incidence rates of DCIS for all women, irrespective of age and race, rose from 5.83 per 100,000 women in 1975 to 34.82 in 2013 (3). Likewise, in the UK, the incidence rates of DCIS for all women rose from 3.3 per 100,000 women in 1979 to 23.5 in 2013 (3). Recently, it has been estimated that in 2016, there will be 61,000 new cases of DCIS in the USA as compared with 246,660 new cases of invasive breast cancer (5).

Previous studies have shown that the majority of invasive breast cancer predisposition loci also predispose to DCIS (6-9), suggesting that DCIS is the precursor lesion for most invasive ductal carcinomas. However, it seems that not all DCIS lesions have the genetic ability or sufficient time during a patient's lifetime to progress to invasive disease (1). Thus, it has been widely debated whether DCIS detection with mammography screening represents overdiagnosis leading to unnecessary overtreatment (2,10). Especially in the era of breast conserving surgery (BCS) for invasive breast cancer, it seems paradoxical to continue treating less aggressive DCIS cases with mastectomy (1). Beyond possibly unnecessary surgery, overtreatment of DCIS might

also include radiation therapy and/or endocrine therapy, and potential adverse effects of these treatment modalities should not be overlooked.

Since DCIS per se is not a life-threatening disease, it is treated only because it is a major predisposing factor for the development of invasive breast cancer. It has been estimated that regardless of DCIS treatment, less than 2-3% of patients will ultimately die from breast cancer (10). According to previous studies, after breast conserving treatment for DCIS, 40-50% of local recurrences will be invasive and 10-20% of these patients will develop distant disease and die from breast cancer (1,11,12). Overall, mortality rates after diagnosis of DCIS according to treatment, have been estimated to be between 0% and 0.5% following mastectomy, between 1% and 2% after BCS followed by radiotherapy and between 2% and 3% for excision alone (1). Hence, the most important, clinically relevant question after diagnosis of DCIS has long been to find out which lesion will most likely recur.

Recently, an impressively large clinical study addressing the issue of DCIS recurrence has been published (13). Van Zee and colleagues, analyzed data from 2,996 women treated for DCIS with BCS for a period of 30 years, in a single institution, the Memorial Sloan Kettering Cancer Center, New York, USA. The focus of this study was on the relationship between margin width and recurrence of DCIS. In this study, 1,588 patients were treated with radiotherapy and 1,374 were not treated with radiation; there were 363 cases of recurrence, of which 159 were invasive, 192 were DCIS, 11 were cases of unknown types of breast

recurrence, and there was one case of distant metastasis without loco-regional recurrence; the median follow-up of patients was 75 months (range, 0–30 years); the median age of the entire population was 57 years (range, 20–92 years); the margin width was categorized as positive (tumor on ink), close ( $\leq 2$  mm), widely clear, i.e.,  $> 2$  and  $\leq 10$  mm and wider, i.e.,  $> 10$  mm. After controlling for different variables (age, family history, clinical presentation, number of excisions, radiotherapy, endocrine therapy, and year of surgery), wider margins were associated with lower risk of recurrence ( $P=0.0003$ ), with progressively lower hazard ratios associated with wider margins as compared with positive margins (0.78, 0.70, and 0.44 for negative margin widths of  $\leq 2$ ,  $> 2$  and  $\leq 10$ , and  $> 10$  mm, respectively). Moreover, an interaction between radiation therapy and margin width was found ( $P<0.03$ ); the association of recurrence with margin width was significant in those patients who did not receive radiation therapy ( $P<0.0001$ ), but not significant in those treated with radiotherapy ( $P=0.95$ ). The authors concluded that obtaining wider negative margins may be important in reducing the risk of recurrence in women who choose not to receive radiotherapy and may not be necessary in those who undergo radiation therapy (13).

This paper is indeed an important contribution to the literature, since it presents the large experience from a single institution with dedicated specialists (S. Klimberg, Little Rock AR) (13). As the authors state, “of the various risk factors for recurrence of DCIS after BCS, the only characteristic that is potentially modifiable by the clinician is width of margin” (13). It could be argued however, that additional modifiable risk factors might be the number of surgical excisions, the administration of radiotherapy and the administration of adjuvant endocrine therapy, especially since these factors were included in a nomogram for predicting the risk of local recurrence after BCS for DCIS, developed by some of the authors, in the same institution (14).

In detail, the Memorial Sloan-Kettering Cancer Center DCIS nomogram integrated the following ten clinico-pathological variables in order to calculate the risk of recurrence for DCIS: age at diagnosis, family history (yes *vs.* no), initial presentation (clinical *vs.* radiological), administration of radiation therapy (yes *vs.* no), administration of adjuvant endocrine therapy (yes *vs.* no), nuclear grade (low *vs.* intermediate/high), necrosis (absent *vs.* present), margins (negative *vs.* positive/close), number of excisions ( $\leq 2$  *vs.*  $\geq 3$ ) and year of surgery ( $\geq 1999$  *vs.*  $\leq 1998$ ). The development of this nomogram was based on data from 1,681 patients and later it was validated in three

independent populations, in Singapore (15), Belgium (16) and the USA (17). For comparison, the initial Van Nuys Prognostic Index (VNPI) combined three variables: tumor size ( $< 15$ , 16–40 and  $\geq 41$  mm), margin width ( $\geq 10$ , 1–9 and  $< 1$  mm or involved margins) and pathologic classification, as determined by the nuclear grade and the presence or absence of comedo-type necrosis; its development was based on data from 333 patients, of whom 195 were treated by excision only and 138 by excision followed by radiotherapy (18); later on, age was added as an extra variable in the updated University of Southern California (USC)/VNPI, based on data from 706 patients with pure DCIS treated with BCS (19,20). It is noteworthy, that tumor size, one of the four USC/VNPI variables, was not included in the Memorial Sloan Kettering nomogram, which however included two other variables reflecting disease extent, i.e., the number of excisions and clinical *vs.* radiological initial presentation of DCIS.

It is also noteworthy, that as commented by Wood from Atlanta, GA, tumor size was also not included in the recent study by Van Zee and colleagues analyzing 2,996 cases of DCIS over a period of 30 years (13). As the first author answered, tumor size was not included in their study, since in the 1980s and 1990s it was not routinely reported, in contrast to present day practice; if these cases were excluded, then the total number of cases in their study would “go way down”. Furthermore, it was emphasized that even in the overview of four prospective randomized trials tumor size was missing in the majority of the patients (13,21). A second, critical, clinically relevant question asked by Wood to Van Zee and colleagues was what this study leads to do for a patient with a 1-mm clear margin or a 3-mm clear margin. The answer to this question was that in such cases, there are different options, ranging from mastectomy or even bilateral mastectomy, to lumpectomy with radiation or lumpectomy alone, that discussing the pros and cons of those different options is time-consuming, and that the online DCIS nomogram might be helpful (13).

The study of Van Zee and colleagues is indeed “a superb addition to our knowledge about DCIS” (Wood) (13) and brings up two questions regarding future research on calculating the risk of DCIS recurrence. First, is there a way forward on research regarding traditional clinico-pathological factors? Second, is there a role for translational research beyond the use of traditional clinico-pathological factors? Similar questions, with different wording, were asked to Van Zee and colleagues, by P. Borgen from Brooklyn, NY, USA (13).

To address the first question first: it is reasonable to expect that the Memorial Sloan-Kettering Cancer Center DCIS nomogram will eventually need to be updated, since one of its variables, i.e., the year of surgery ( $\geq 1999$  vs.  $\leq 1998$ ) will no longer be relevant; it might be probably replaced by the period of follow up since the initial diagnosis of DCIS. Furthermore, since tumor size is now being routinely reported, one would expect that this variable would be eventually added; however, given the lack of strong evidence from prospective studies to support the impact of tumor size and given the confounding with two other variables (initial DCIS presentation and number of excisions) this might not be that simple. In essence, a synthesis of existing algorithms might prove to be a more robust approach. Nevertheless, Van Zee expressed her willingness to do a study combining and comparing the DCIS score and a combination of multiple different available clinical variables (13).

Regarding the second question, translational research in this field has been conducted for quite a long time now. Lari and Kuerer conducted a systematic review of biological prognostic markers for DCIS recurrence (22), in which the following factors were included: steroid receptors, proliferation markers, cell cycle regulation and apoptotic markers, angiogenesis-related proteins, epidermal growth factor receptor family receptors, extracellular matrix-related proteins, and COX-2. The authors found that common limitations of published studies were that patient cohorts were small, with variable treatment approaches and variable methods of determining biomarker expression, and no prospective validation studies (22). Pang and colleagues (23) reviewed the landscape of genomic alterations in DCIS and their potential as prognostic biomarkers and concluded that so far, none of these alterations is a reliable indicator of in situ recurrence or invasive progression. Recently, the Oncotype DX DCIS score was developed in order to quantify the risk of DCIS recurrence, by using seven cancer-related and five reference genes (24). It should be emphasized, that this 12-gene assay should be used cautiously, since “no single test, especially one in which other prognostic factors are ignored, can validly estimate the risk of local recurrence among patients with DCIS” (25). The Oncotype DX DCIS score should only be used for women with DCIS who strictly meet the Eastern Cooperative Oncology Group (ECOG) E5194 trial criteria, i.e., size of  $\leq 25$  mm for low-to-intermediate grade tumors and  $\leq 10$  mm for high-grade tumors and those with margin widths of  $\geq 3$  mm (24,25). Taken together, future research

should aim at combining traditional clinico-pathological and novel molecular factors in prospective validation studies, in order to calculate the risk of recurrence in different subgroups of patients. Besides genomics, future studies should also integrate epigenomic, and transcriptional data, which might prove to be more informative of prognosis, by using novel technologies (23). However, this is not as simple as it may seem, since (as Van Zee notes) “it is very difficult to get the archival material and it would be very expensive” (13).

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