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Editorial Comment

# The weakest link

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The case-control study by Ringberg et al. in this issue[1] examined the impact of pathologic factors on the risk of local recurrence in patients with ductal carcinoma *in situ* (DCIS) participating in a trial which randomly allocated them to receive or not receive radiation therapy after lumpectomy. Their discussion ably compares their findings to those of others, which I will not repeat here. I must however point out that only 32% of the original pathology reports stated the tumour-free margin width in millimetres.[2] These investigators certainly should not be faulted too much for this failing – it was only well after their trial began in 1987 that the importance of margin width to the management of DCIS was generally appreciated.[3] (Such data are also unavailable for the other randomised trials of this issue.[4–6]) However, their article raises more general issues regarding how cooperative group trials should be performed, particularly ones examining the local therapy of breast cancer.

The randomised clinical trial has become the'gold standard' for comparing alternative treatment approaches. However, while randomisation eliminates bias in assigning treatment, it does not address other critical issues important to patient management, such as the intrinsic variability of the disease being studied.[7] The pathologic and clinical heterogeneity of breast cancer has been recognised for many years; recent genetic analysis has confirmed and amplified this understanding.[8] Perhaps the best example of the practical implications of such heterogeneity comes from studies of endocrine therapy – very effective in reducing the risk of relapse when used against tumours expressing hormone receptors, and useless for those which do not.[9] Hence, clinicians must examine results for separate patient subgroups defined by critical prognostic and predictive variables, whether or not treatment was assigned randomly.

Large randomised trials typically involve many different physicians and medical centres, sometimes spread across the world. Part of the mission of trial secretariats is thus to ensure that all the involved actors accurately and reproducibly describe patient and tumour characteristics. As anyone who has been involved in such efforts knows, this task is easier said than done, particularly when it comes to detailed pathologic diagnosis.

There can be substantial interobserver variability in distinguishing DCIS from microinvasion or atypical ductal hyperplasia.[10] For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial, the central reviewer considered the lesion to be atypical hyperplasia in 7% of cases and invasive cancer in 2% of cases.[11] In the European Organisation for the Research and Treatment of Cancer (EORTC) 10853 trial, central review found a benign lesion in 5% of cases, atypical hyperplasia in 7%, definite invasion in 3%, and a suspicion of invasion in 1%.[12] There were roughly similar rates in the Swedish trial (7% benign lesions,

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5% atypical ductal hyperplasia, and 4% invasive or microinvasive).[2] (However, it may perhaps be assuming too much to think that the central pathology review always represents the 'correct' diagnosis. I have seen many disagreements between well-known experts about individual cases, let alone about how best to define these entities. It is of note that when the three pathologists in the current study reviewed slides independently of each other, they disagreed about the diagnosis 21% of the time.[1])

There is also substantial variability between institutions and pathologists in margin assessment. For example, in the NSABP B-17 trial, the number of slides sent for central review ranged from 1–70 (median, 9 slides).[11] In the Swedish trial, 80% of patients were reported to have microscopically 'clear' margins by the original pathologist.[2] The report by Ringberg and colleagues does not state how often the central reviewer confirmed the original margin status.[1] However, in the NSABP B-17 trial, for which microscopically uninvolved margins (defined as no tumour at ink) was a condition of eligibility, 18% of 'eligible' cases were reclassified on central review as having involved or inevaluable margins. Even the interpretation of the original pathologist's written assessment can be confusing. As part of the early quality-control effort for the United Kingdom-Australia-New Zealand trial,[5] six coders independently reviewed the same hospital pathology and National Health Service reports for 50 patients.[13] All six coders agreed on margin status for only 16% of the study patients!

As a result of these problems, some patients may be erroneously entered on study, unless the trial requires biopsy material to be submitted for central review prior to enrolling patients. There are a number of understandable reasons why this is not routinely done, including the logistical difficulty and expense of conducting such review and the desire not to delay unduly the start of treatment. Feedback can be given to the original pathologist after the central review has been performed (as for example in the closed Eastern Cooperative Oncology Group trial 5914 of excision without radiotherapy for selected patients with DCIS), which will hopefully result in more accurate diagnoses from them in future patients entered. Nonetheless, this approach can clearly lead to many patients receiving inappropriate treatment. The risk of serious long-term complications due to breast irradiation is very small[14,15] – but it is too high for someone who has only benign breast disease.

Although pre-entry central pathology review might be the best way to prevent such problems, perhaps 'credentialling' local investigators prior to accepting patients into trials might work well enough. European groups have been leaders in requiring some proof of competency from centres wishing to participate in trials involving breast cancer radiotherapy.[16–18] This approach has become accepted on this side of the Atlantic Ocean, too, at least for some studies. For example, Radiation Therapy Oncology Group (RTOG) trial 0413 (also designated as NSABP B-39), comparing accelerated partial-breast irradiation to whole-breast irradiation, requires that each radiation oncology facility must undergo technical credentialling (including submitting a 'dry case' treatment planning) and each radiation oncologist must complete a 'knowledge assessment questionnaire' prior to entering patients. Similarly, surgeons have had to demonstrate their skill by performing a certain number of sentinel node biopsies followed by completion axillary dissection before being allowed to participate in randomised trials comparing the two approaches.[19,20]

Unfortunately, there has been reluctance or inability on the part of the cooperative groups to require the same advance demonstration of competency by institutional pathologists. For example, in the recently-closed RTOG trial 9804 comparing excision alone to excision plus radiation therapy for patients with low and intermediate-grade DCIS with minimum tumour-free margin widths of 3 mm, a 'teaching' set of photomicrographs illustrating key diagnostic features was made available on the RTOG website. However, mandatory credentialling of pathologists by testing (or even using this resource) was *not* a requirement for study participation. (Indeed, the National Cancer Institute was not even willing to support *post hoc* central pathology review for this trial when it began.) Whether such stop-gaps are sufficient to achieve adequate uniformity of diagnosis is unproven; frankly, I doubt it.

There are no professional societies or regulatory guidelines (at least in the United States) which set minimum standards for pathologists interpreting breast biopsies, comparable to those which exist for radiologists interpreting mammograms. The importance of histologic features and margin status to clinical decision-making, particularly for local therapy, cannot be overstated.[21] Ensuring the accuracy of pathologic interpretation is no less critical for patients on trials or in daily practice than is ensuring the accuracy of oestrogen-receptor[22] or HER2 status.[23]

I therefore challenge the cancer cooperative groups to extend their credentialling process to pathologists, making it a condition of patient study entry. This would strengthen greatly the validity of subgroup analyses of multi-institutional trial results. It also might well raise the standards of practice for all pathologists, and thus have a far wider impact than for just the small proportion of patients entered into clinical trials. I also challenge the governments which support the cooperative groups to fund such initiatives – besides, as my friend Michael Lagios has pointed out for many years,[24] in the long run they might save a lot of money by helping patients avoid the radiation oncologist's services.

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