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Editorial Comment

Should patients with lobular carcinoma *in situ* be irradiated? – not yet, but...

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Lobular carcinoma *in situ* (LCIS) is the neglected step-child of breast cancer research. This is due in part to its rarity, but also in no small measure due to complacency: we thought we knew what to do about it. The consensus view for many years has been that LCIS is a marker of elevated risk of subsequent breast cancer development which is roughly equal in the ipsilateral and contralateral breast [1]. Most invasive cancers that will develop on either side will have ductal histology. Hence, the only local treatment required is a biopsy sufficiently large and well-examined by the pathologist to be certain that there was no ductal carcinoma *in situ* (DCIS) or invasive cancer present. Chemoprophylaxis has been shown to be effective in reducing the risk of future cancers in patients with LCIS [2], but certainly radiation therapy was not felt to play a role in their treatment. In recent years, ''pleomorphic'' LCIS and carcinomas *in situ* with mixed ductal and lobular features have been recognised as being separate entities from ''classic'' LCIS; they behave like DCIS and should be treated accordingly [3,4]. Still, LCIS *sensu strictu* remained boring.

This idea that the index LCIS can basically be ignored has been challenged intermittently. A study by the Danish Breast Cancer Group found that 17% of 88 patients with either LCIS or mixed LCIS–DCIS developed ipsilateral invasive cancer or mixed DCIS–LCIS with a median follow-up time of 61 months; no contralateral cancers occurred [5]. Further, there were no differences in the ipsilateral breast tumour recurrence (IBTR) risk between the 69 patients with pure LCIS and the 19 patients with mixed lesions. The National Surgical Adjuvant Bowel and Breast Project (NSABP) conducted a registry study for patients with a biopsy showing LCIS as an adjunct to protocol B-17 [6]. The 12-year results for these 180 patients were very recently published [7]. If one removes ''recurrences'' that were actually LCIS, then (in contradiction to the Danish study) the numbers of ''real'' cancers eventually appearing were similar for the ipsilateral and contralateral breast (9 invasive cancers and 4 DCIS in the ipsilateral breast, and 10 and 4 of each type, respectively, in the contralateral breast). However, 8 of 9 patients with invasive IBTR for whom material was available for central pathology review had infiltrating lobular carcinomas (ILC), as did 6 of 8 patients with contralateral invasive breast cancers. (It should also be noted this study defined atypical lobular hyperplasia as ''grade 1'' LCIS, a system which is not commonly used. Only 1 of 63 patients in this group developed an IBTR that was invasive or DCIS, which was much lower than the 13% rate among patients with grade 2 or grade 3 lesions).

A different line of inquiry should also serve to shake us from our slumbers. Investigators at the University of California San Francisco examined the genetic relationships between LCIS and ILC which were found simultaneously in the ipsilateral breast of 24 patients, using random primer-amplified microdissected DNA hybridised onto bacterial artificial chromosome arrays [8]. Fourteen samples of LCIS were related more to their paired samples of ILC than to any other ILC, suggesting a clonal relationship, in turn implying that LCIS may indeed be a precursor to invasive carcinoma.

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Finally, we now have an outstanding contribution from Cutuli and colleagues [9] finding a 4% risk of IBTR in 25 patients with LCIS following treatment with radiation therapy with a median follow-up of nearly 13 years. Because of the small number of patients in this series, it is quite possible that this failure rate is due to chance, rather than the use of radiation therapy. In addition, 12 of their patients received tamoxifen for 2 years, which muddies the waters somewhat. (Interestingly, the rate of subsequent contralateral breast cancer development was also low, only 1 of 23 evaluable patients. However, two patients also underwent contralateral mastectomies for cancers found at the same time as discovery of the index LCIS.)

The three recent clinical studies hardly seem definitive, due to their small numbers of patients, their conflicting findings regarding the ipsilateral-to-contralateral breast cancer ratios, and their conflicts with other studies which Cutuli and colleagues very ably review (see their Table 2). These new studies also have other problems which make their interpretation more difficult, such as it not being clear whether cases of pleomorphic LCIS were included or not in the studies of Hwang or Cutuli.

Nonetheless, these studies forcefully raise the disquieting thought that classic LCIS may not be so harmless as generally believed. If LCIS is really an entity to be treated in its own right, then it seems to me that the appropriate analogy is to low-grade DCIS, for whom the risk of breast-cancer death after initial treatment with excision alone appears minimal [10]. Hence, I feel it premature to recommend that all patients with classic LCIS should be irradiated, or even that the excision margins need to be ''negative'' for patients to be treated with conservative surgery alone – but I won't be too unhappy if they are.

Conflict of interest statement

None declared.

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