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## Editorial

# Clinical and Biological Implications of the Milan Breast Conservation Trials

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THE MATURE data from the Milan II trial reported in this issue [1] (pp. 1156–1162) which compared tumorectomy with quadrantectomy clearly demonstrate that wider excision reduces the risk of local recurrence of cancer from 18.6 to 7.4% over 10 years. The one-line message from this paper could be ‘the wider you excise, the lower the chance of local failures’. If only it were that simple! First of all there is the danger of overinterpreting the results to advocate ‘quadrantectomy for all’. Quadrantectomy fares quite poorly in its main objective i.e. cosmesis. It removes a quarter of a breast and even in women with large breasts, it would still cause asymmetry. In Japan, the cosmetic outcome after quadrantectomy was found to be poor and most patients expressed greater satisfaction with transposition of a latissimus dorsi muscle flap to fill the defect left following a quadrant excision [2]. Another study from Italy, albeit non-randomised, found that quadrantectomy gave a much poorer cosmetic outcome than a wide local excision [3]. In the present Milan trial, if we assume that tumorectomy does give a significantly superior cosmetic outcome, then although 11% fewer women suffer local recurrence in the QUART group, it is at the expense of a poor cosmesis in most, if not all women (see Table 1).

While applying the results of this trial to clinical practise, the surgeon must discuss with the patient the relative benefits and harms of the two treatments, bearing in mind that survival is not jeopardised in any way. Data from the Milan group about the comparative cosmetic outcomes and patient satisfaction in the two arms of this study would throw considerable light on this issue and would make our decisions even more informed.

The other important observation in this study is the fact that most local recurrences occurred in the surgical bed but paradoxically did not correlate with pathological status of the resection margins. Furthermore, even more surprising is the observation that, in tumours less than 5 mm where complete excision would be judged facile, recurrence was seen in 5 out of 15 in the QUART group and 11 out of 13 in the TART group. Not only do these findings challenge the obsession about positive margins but also open several biological

questions about the origins of local recurrences and suggest that they do not simply arise out of tumour cells left behind in the cavity wall. One possibility could be multicentric cancers within the diseased breast. The classic whole organ pathological study by Holland in 1985 [4] suggested that most multicentric cancers are in close proximity of the primary tumour leading to the concept that these are responsible for local recurrence. A recent study [5] analysed the spatial distribution of multicentric cancers in two- and three-dimensions within each affected breast. This found that multicentric foci are present beyond the index quadrant in 80% of those cases which harbour multicentric cancers, which accounts for half of all cases. This suggests that recurrences probably do not arise from multicentric cancers, *de novo*. If local recurrences do not arise from residual disease in the tumour bed or other more distant foci then it takes a leap of imagination to postulate another mechanism for this event. It is known that the aromatase activity of the quadrant harbouring the primary tumour is considerably higher than the other quadrants [6, 7]. Aromatase converts androgens to oestrogens; its high local concentration could thus be favourable for mutagenesis and growth. The question whether the chicken or the egg came first has been asked and it appears that aromatase most likely arises from the primary tumour because the aromatase production in the tumour tissue is much higher than normal breast parenchyma. The tumour cells may also induce aromatase activity in surrounding cells via production of IL-6 [8, 9]. It appears that once a malignant process goes beyond a certain threshold, it is self-perpetuating and not only do the tumour cells multiply but also recruit surrounding cells by making the milieu favourable for mutagenesis. Spectacular support for this hypothesis came from a recent report in the *British Journal of Cancer*. A human prostatic cell line when injected in athymic nude mice produced tumours which contained both human tumour cells and murine stromal cells and most remarkably, the murine stromal cells had specific chromosomal abnormalities, in the absence of human DNA [10]. These results suggest that cancer cells are capable of inducing neoplastic transformation in stromal cells of the host organ. An even more radical explanation to account for the paradoxes of local recurrence is the suggestion that they result from the transfection of normal host cells in the vicinity

Table 1. Calculations of harm versus benefit of QUART versus TART

Treatment	No local recurrence	Local recurrence	Re-excision	Mastectomy	Deaths/10 years
TART (100 cases)	72 enjoy good cosmesis	18 suffer the distress of LR	10 suffer poor cosmesis	8	21
QUART (100 cases)	93 suffer the distress of poor cosmesis	7 suffer the distress of LR	2 suffer even poorer cosmesis	5	21

of the tumour by subcellular nuclear particles shed from the tumour [11]. Recently, loss of heterozygosity has been demonstrated in morphologically normal breast tissue adjacent to breast cancer [12]. Either or both of the above proposed mechanisms, could account for this finding. It appears that although the margins of excision of morphologically clear they are genetically unstable and that this genetic instability is induced by the milieu surrounding the original tumour. The change in surrounding normal cells could be mediated through an agent that could be nucleic acid, cytoplasmic or paracrine secretion from the cancer cells and IL-6 and aromatase are some of these agents already identified. It is likely that the interaction of these agents with the surrounding breast tissues is complex and dynamically linked to the general hormonal milieu of the patient. The appearance of local recurrence is probably triggered by an imbalance in these interactions. Hypothesis of such a complex system working dynamically within the breast is also very compatible with the observation of a remarkable non-linear clinical phenomenon: namely the hazard of local recurrence does not follow a linear path, but occurs in two peaks, one at 2–3 years and the other less pronounced at 7–10 years [13]. Radiotherapy probably helps because it ablates most of the epithelial cells capable of mutagenesis. But targeted therapy with specific agents like aromatase inhibitors introduced locally via a slow release pellet might be worth a clinical trial. Whatever the truth there are no simple answers to breast conservation and the origin of local recurrence.

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