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Editorial

Recurrence in the Conserved Breast: Why all this Fuss about Risk Factors?

J.M. Kurtz

University Hospital, Radiation Oncology Division, 24 rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland

In the almost 20 years that have elapsed since the first paper appeared on this subject [1], a growing literature has been dedicated to the phenomenon of local recurrence in the preserved breast. There is no denying the devastating effect that any disease recurrence, including local failure, is bound to have on the breast cancer patient. However, the extraordinary attention devoted to ipsilateral breast tumour recurrence (IBTR) might appear to be misdirected, considering that markedly different failure rates in this site have not clearly been shown to be associated with significant differences in patient survival [2]. The obsessive study of local failure is perhaps driven by the feeling that this represents a curable recurrence, or a preventable event caused by improper choice of initial therapy. Thus, it is not surprising that exhaustive research has been directed at identification of risk factors for IBTR [3], with the presumed intention of defining high risk groups that might benefit from more vigorous local treatment. A corollary to this notion of 'high risk' is the idea that mastectomy may be more appropriate therapy in such cases, despite a lack of evidence that more extensive surgery cures more breast cancer patients [4]. Although several patient- or tumour-related parameters have been identified that clearly relate to local recurrence risk [3], the clinical importance of these factors is considerably lessened by the impact of treatment, including extent of surgical excision, radiotherapy dose, and the local effects of chemotherapy and tamoxifen [2]. With current multidisciplinary approaches including careful attention to excision margins, use of re-excision, modern radiotherapy, and appropriate systemic treatment, IBTR rates should be below 1%/year [2].

In order to place risk factors in their proper perspective, it would be useful to have reliable data regarding their impact in terms of relative risk, i.e. the risk associated with the risk factor compared with the absence of that factor. The paper by Voogd and associates in the current issue of this journal represents an important effort in providing such data [5]. The use of the powerful case–control methodology, a prevalent technique in clinical epidemiological studies, was brought to bear on the analysis of the largest series of IBTRs yet published. The matching of cases and controls from the same participating institution minimised the potential biases resulting from inhomogeneities of treatment approach, which are likely to affect absolute recurrence rates but are assumed not to influence relative rates. Although inking of margins had not been carried out in all cases, excision specimens were reviewed in a standardised fashion by pathologists particularly interested in the local recurrence problem. The Dutch nested case–control study of Voogd and associates has several interesting aspects [5]. Firstly, the large size of the study population provides strong confirmation of the relative lack of importance of tumour size and tumour subtype in determining IBTR risk. Secondly, the analysis was carried out separately for premenopausal and postmenopausal patients, who may possibly be subject to different risk factors. Furthermore, a separate analysis was undertaken regarding different types of IBTR, namely those occurring in the vicinity of the index lesion, those located in other parts of the breast, and those that were diffuse or that involved the skin of the breast. As a result this study provides interesting new insights into the risk factors whose importance had already been established by prior research, in particular young age, extensive intraductal component (EIC), lymph vessel invasion and microscopic excision margins.

Young age is the most consistently demonstrated independent risk factor for IBTR [3, 6, 7]. The Dutch study suggests a continuous decrement in relative risk, which the authors calculated as 4% per year of advancing age. However, as in previous studies, the importance of the risk becomes most striking in premenopausal patients at a lower end of the age spectrum, i.e. age less than 35 years. Compared with older patients, patients in this age group more frequently have unfavourable prognostic factors [8], but it is unclear whether morphological features can be used to identify which young patients are at high risk for IBTR. Even young patients having tumours excised with clear margins [2], or those treated by quadrantectomy and radiotherapy have increased recurrence risk compared with older women [6]. However, satisfactory local control has been reported in this subgroup when adjuvant chemotherapy was given in addition to breast irradiation [7]. Interestingly, in an analysis of data from two randomised trials, patients younger than 35 years of age appear to represent the only subgroup for whom superior end results seem to have been achieved using total mastectomy [9]. Clearly breast-conserving treatment should be undertaken with particular caution in these patients.

E-mail: john.kurtz@hcuge.ch
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EIC is the most extensively studied tumour-related risk factor for IBTR. According to the Boston definition, based on small excisional biopsy specimens, EIC is considered to be present when at least 25% of the tumour mass comprises intraductal carcinoma, and *in situ* cancer is also present in the surrounding tissue. Using this definition, EIC has been demonstrated to be associated with a higher rate of positive margins, a greater frequency of residual cancer on re-excision specimens, and more extensive residual intraductal disease in mastectomy specimens [10]. Although not all groups have confirmed the importance of EIC, especially in the presence of negative excision margins [2], most studies show higher local recurrence rates at or near the original tumour site [3]. Alternative definitions of EIC have been proposed, including the one used in the Dutch study, especially in cases where wider excision specimens were available for analysis [5]. Basing the definition on the extent of intraductal involvement in ductulolobular units in peripheral tissues surrounding the tumour mass may be a more valid measure of the residual tumour burden remaining in the preserved breast. Using the Boston definition of EIC, recurrence risk appears to be significant only when excision margins are more than focally positive [11]. The Dutch study, however, implies that EIC (their own definition) remains a strong factor even in the face of negative margins, particularly in association with high nuclear grade [5]. A similar finding was published from Heidelberg using yet another definition of EIC [12]. These new data suggest that high grade EIC represents a risk factor that conveys high risk (RR = 4) of recurrence near the primary site in both pre- and postmenopausal patients, independently of resection margin status.

Another interesting finding stemmed from the analysis of 71 diffuse or skin recurrences [5], which are those that are associated with the most serious consequences for the patient regarding both metastatic risk and uncontrolled local disease [13, 14]. It is logical that tumours recurring diffusely within the breast will often be found to have been excised with positive margins, as cancer at the edge of a specimen may not simply reflect incomplete excision of a localised tumour, but may less commonly be a clue to widespread involvement within the retained breast. Classification of margin involvement as focal or extensive may prove to be useful in this regard [11]. Voogd and associates observed that the association of lymph vessel invasion with positive margins appears to carry a very strong association with diffuse or skin recurrence [5]. This has been alluded to by other authors [14]. Whether more extensive surgery might improve local control in such patients is unknown. Retrospective analysis of randomised data suggests that local control in patients with lymph vessel invasion is not improved by mastectomy alone [9]. In patients with diffuse margin involvement with lymphatic invasion, aggressive multimodality therapy should be considered (e.g. chemotherapy, followed by mastectomy and postoperative irradiation).

The Dutch study failed to provide convincing evidence for significant risk factors related to recurrence elsewhere in the breast [5]. Although this is disappointing, it is not unexpected, since these remain uncommon events, into which the literature provides little insight [3]. The authors' very plausible hypothesis that ipsilateral new tumour formation may relate to factors known to be associated with contra-lateral breast cancers (e.g. young age, lobular histology) could not be confirmed by their analysis.

This leaves us with excision margins, which are unique among risk factors in that they can be modulated by further surgical intervention. Obtaining microscopically negative inked excision margins assures that few patients will have residual tumour burdens that cannot be effectively dealt with by radiotherapy. However, although negative margins are desirable, if radiotherapy is to be given there is little scientific basis for insisting on negative margins as an indispensable condition for breast conservation [15]. The oncological equivalence between breast-conserving therapy and total mastectomy was established by several randomised trials [4], in only two of which [2] were negative margins a prerequisite for inclusion. Although patients with tumour involvement at resection margins are generally at higher risk of IBTR, positive margins are often confounded by the presence of morphological risk factors such as EIC and lymph vessel invasion, and in some multivariate analyses, including that of Voogd and colleagues, margins lose their significance [5, 12]. Nonetheless, debate continues in the literature regarding how to best define negative ('truly negative' versus 'close'), and positive ('focally' versus 'diffuse') margins [11, 15, 16]. Although this 'margin mania' has certainly led to the unnecessary loss of many a breast in the name of 'high risk', continued study of the interplay between margins and other risk factors is justified in order to determine under which conditions negative margins are truly important. Moreover, the benefits of obtaining somewhat better initial local control should take into account the possible disadvantages, cosmetic and otherwise, of 'prophylactic' re-operation, as well as the overall metastatic risk to which the patient is exposed.

The big fuss about risk factors for IBTR should not obscure the fact that, with current surgical techniques, modern radiotherapy, and appropriate systemic therapies, the local results of breast-conserving treatment are very satisfactory for the great majority of patients [2]. In fact, in recent randomised clinical trials IBTR rates in patients receiving tamoxifen or chemotherapy have been much lower than the (at best) 1% per annum universally seen in older series (Table 1). The very high recurrence rates associated with certain risk factors and based on patients treated during the 1970s may thus no longer be relevant for decision-making today. As a consequence, the usefulness of currently recognised risk factors for IBTR, including microscopic excision margins, merits re-evaluation in the context of contemporary multidisciplinary treatment practises.

Table 1. *Data from randomised trials demonstrating the effect of systemic therapy on the risk of local recurrence (IBTR) in node-negative patients after conservation surgery and* 50 *Gy breast irradiation*

Author	*n*	IBTR (%)	Follow-up	*P* value
Dalberg and colleagues [17]				
without tamoxifen	219	12%	10 years	0.02
with tamoxifen	213	3%		
Fisher and colleagues [18]				
without tamoxifen	532	10%	10 years	0.0001
with tamoxifen	530	3%		
Fisher and colleagues [19]				
without chemotherapy	119	13%	8 years	0.001
with chemotherapy*	116	3%		

*Methotrexate and fluorouracil.

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