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Editorial

Can more breasts be saved if chemotherapy and radiotherapy are administered concomitantly?

Surgery and radiotherapy are local treatments, and their proponents rightly insist on the importance of their modalities in assuring loco-regional control in breast cancer. Since the local effects of systemic therapies are less marked than those of surgery and radiotherapy, the former are often not taken into account in planning local-regional treatment strategies. In particular, the decision regarding conservation *versus* amputation of the breast is frequently contingent upon obtaining microscopically negative lumpectomy margins, with little consideration of other parameters.

It is axiomatic that the risk of ipsilateral breast tumour recurrence (IBTR) is greater in the presence than in the absence of involved margins, as a somewhat greater percentage of margin-positive patients may have a residual tumour burden that is too extensive to be totally eliminated by radiotherapy. Thus it is not surprising that the recent literature regarding breast conservation has been dominated by the issue of resection margins. A cursory search of the English-language literature since 1994 reveals 152 publications devoted to some aspect of this problem, with fully 40 of them featuring 'margins' in their titles. This current 'margin mania' has both positive and negative consequences. On the one hand, it reflects a healthy concern for quality assurance in breast-conserving surgery and has probably contributed to a reduction in IBTR rates compared with those observed during the 1970s. On the other hand, margins are coming to be viewed as an end in themselves, resulting in patients undergoing questionably useful operations, including total mastectomy, simply to re-excise 'close' margins. It will be of considerable practical importance to define under what conditions excision margins status should legitimately influence clinical decision making.

The study of Assersohn et al. [1] in the current issue of this journal addresses the question as to whether or not lumpectomy margin status is clinically relevant in patients receiving breast irradiation concomitantly with chemoendocrine treatment. This paper analyses a subgroup of 184 conservatively-operated patients from a previously published trial comparing the results of eight courses of chemotherapy (mitozantrone and methotrexate, with inclusion of mitomycin-C in a minority of patients) given postoperatively with those of the same chemotherapy administered as a 'sandwich', half before and half following surgery. All patients received tamoxifen regardless of receptor status, and irradiation was started four to six weeks after surgery, concurrently with chemotherapy. After a median follow-up of 5 years the main findings of the study were, firstly, that local control was very high, with only 6 of 184 patients (3%) observed to have suffered IBTR (only 2 as first site of relapse), despite the fact that 38% of patients had microscopically positive excision margins. Secondly, although there were slightly more IBTRs when margins were involved, this difference was statistically insignificant and of little clinical importance. Only 2 of the 70 patients with positive margins had IBTR as first site of failure, a result that could hardly have been bettered by a more aggressive surgical approach. As might be expected in such a small study, there were no differences in outcome according to chemotherapy sequencing, nor did margin involvement seem to affect metastatic or survival rates.

Despite the small size of the study, these results from the Royal Marsden Hospital are provocative, especially in the light of the increasing use of chemoendocrine therapies and the importance attached to breast preservation in many Western countries. These data, along with those from other prospective trials, indicate that the question of systemic treatment, and possibly its sequencing with respect to radiotherapy, could be constructively integrated into decision making regarding surgical management. Data from randomised trials clearly indicate that IBTR rates are significantly lower when radiotherapy is associated with tamoxifen and/or chemotherapy. Under presumably optimal 'low risk' conditions of node-negative early breast cancer excised with microscopically clear margins, modern radiotherapy (even including a boost to the tumour bed) can *at best* achieve an IBTR rate of 1% per annum in the absence of systemic therapy [2, 3]. In oestrogen receptor-positive tumours long-term tamoxifen administration reduces this baseline IBTR rate, at least under these favourable conditions, to less than 0.5% per year [4, 5].

Given the multiplicity of cytotoxic regimens and their potential interactions with radiotherapy, the situation regarding the effects of chemotherapy on IBTR is more complex. Factors that potentially modulate the inherent risk of local failure in patients receiving a given chemotherapy regimen include the delay in starting radiotherapy imposed by chemotherapy administration, and the timing of radiotherapy with respect to systemic treatment. This can be illustrated from the trails of the National Surgical Adjuvant Breast and Bowel Project (NSABP), whose data most clearly show the impact of chemotherapy on IBTR rates (Table 1). In the early NSABP trials, breast irradiation was begun after the first cycle of chemotherapy and further chemotherapy was not delayed during the five weeks of radiation treatment [2]. Despite chemotherapy regimens that might be considered sub-

Table 1. Ipsilateral breast tumour recurrence (IBTR) in trials of the National Surgical Adjuvant Breast and Bowel Project in patients receiving 50 Gy breast irradiation after breast-conserving surgery, according to the sequencing of adjuvant chemotherapy

Sequence	Trials [references]	*n*	IBTR rate
No chemotherapy	B-06, B-13, B-14 [5–7]	1008	1.5%–2%/year
Sequential	B-15, B-18, B-22 [2, 8, 9]	1764	> 1%/year
Concomitant	B-06, B-13, B-15, B-19 [2, 6,7]	903	~ 0.5%/year

standard today, these studies were distinguished by very low IBTR rates. In the B-06 Trial the 12-year IBTR rate was 5% in 192 node-positive patients receiving melphalan and 5-fluorouracil concomitantly with 50 Gy breast irradiation [6]. Similarly, in node-negative, oestrogen receptor-negative patients 50 Gy breast irradiation started just after the first cycle of chemotherapy led to an eight-year IBTR rate of 3% in 116 patients receiving methotrexate, 5-fluorouracil, and leucovorin, and to a five-year IBTR rate of 1% in 194 patients receiving CMF [7]. Such low IBTR rates were never observed in NSABP patients having the same local treatment without systemic therapy (Table 1). In later studies by the same group, the introduction of doxorubicin and cyclophosphamide (AC) led to a change in the timing of breast irradiation, which was not only delayed, but was no longer administered during chemotherapy [2]. In these studies the observed IBTR rates once again increased to 1% per annum or more, even though some of the patients in these later studies also received tamoxifen [2, 8, 9]. Interestingly, in the arm of the B-15 Trial in which patients received CMF without delaying breast irradiation, the IBTR rate was about half of that observed in the other two arms in which radiotherapy was given after completing anthracycline-containing chemotherapy [2]. Although some of the apparently poorer local control observed in the AC studies might be attributed to the inclusion of higher-risk tumours, these results nevertheless raise intriguing questions regarding the temporal relationship between the treatment modalities.

Radiation oncologists have long been dismayed by the practice of delaying radiotherapy in patients receiving chemotherapy after breast-conserving surgery. The only randomised trial addressing the question of treatment sequencing, though of insufficient statistical power to be considered definitive, suggests that delaying breast irradiation until after chemotherapy results in some decrease in local control [10]. The degradation in IBTR rates observed in NSABP studies since the introduction of AC chemotherapy may simply be related to an increased interval between surgery and radiotherapy. However, the additional delay occasioned by the sequential administration of four cycles of AC is relatively short, generally about five weeks [2]. Consequently the observed effect may more plausibly be related to the fact that radiotherapy was administered sequentially rather than concomitantly with chemotherapy as in the earlier studies.

The paper of Assersohn et al. adds to the growing body of studies of various tumour types [11, 12], suggesting that the simultaneous administration of radiotherapy and chemotherapy leads to superior local control. Although simultaneous radio-chemotherapy may pose problems of logistical organisation and acute tolerance, breast irradiation is feasible in conjunction with CMF regimens, and does not appear to lead to increased late effects [13]. Although there is understandable reluctance to use radiotherapy concomitantly with anthracyclines in breast cancer, particularly regarding the potential for increased cardiac toxicity, improvements in radiotherapy technology [14] should allow safe and effective combinations to be developed, even if they require a modest reduction in radiation dose or dose per fraction. Concomitant combined treatment strategies should be the object of future prospective trials, with the intention of both improving breast preservation rates and shortening the oppressively long treatment programmes to which patients are sometimes subjected. Moreover, as the Royal Marsden experience suggests, the methodology as well as the clinical usefulness of microscopic resection margin assessment require serious re-evaluation in the setting of concomitant treatment approaches.

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