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Breast Cancer Local Therapy: What Is Its Effect on Mortality?

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Abstract Until recently, the concept of biological predeterminism appeared pre-eminent and a worthy successor to the Halstedian doctrine of centrifugal spread of cancer. However, evidence has now emerged from clinical trials to cast doubt on the universal application of this concept to breast tumors. Prevention of local recurrence can save lives, local control does matter, and rates of local recurrence should be minimized in the first 5 years. In up to one quarter of cases of local recurrence the locally recurring disease will be a determinant and not simply a marker of risk for distant relapse and death. Both types of local recurrence are manifestations of the same biological processes and reflect intrinsic behavior of the tumor. This principle applies to reduction in local relapse from both adjuvant radiotherapy and surgical modalities.

Introduction

There is longstanding controversy over the significance of ipsilateral breast tumor recurrence following conservation surgery and whether rates of local recurrence affect overall survival. Of particular concern is the relationship to distant relapse and whether local recurrence within the conserved breast acts as a source of distant metastases or is a marker of risk for development of distant disease and de facto poor prognosis. Several studies have confirmed that local recurrence confers an increased risk of distant relapse of about 3–4-fold [1–4]. Nonetheless, for individual trials, this does not translate into survival differences, suggesting that no causal relationship exists between ipsilateral breast tumor recurrence (IBTR) and distant disease. These findings have promoted the view that recent falls in breast cancer mortality are largely attributable to a combination of screening and application of systemic therapies, with minimal contribution from any improvements in loco-regional breast treatments.

The most recent overview by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) revealed that moderate differences in rates of local recurrence at 5 years can have an impact on breast cancer mortality after more prolonged follow up of 15 years [5]. This suggests that local recurrence has a determinant role, with patients developing disseminated disease as a direct consequence of failure to remove residual, but viable cancer cells at the time of primary treatment. By implication, inadequate loco-regional treatment may compromise survival, and it is "important to distinguish local recurrences linked to increased risk of distant spread from those due to inadequate treatment" [2].

The variable natural history and enigmatic behavior of breast cancer at a clinical level has been recognized for many years. The development of molecular technologies with genetic profiling of individual tumors has emphasized the heterogeneous nature of breast cancer and the therapeutic challenges this heterogeneity presents [6]. A patient's clinical fate and overall survival are ultimately determined by the presence of distant metastases and their levels of dormancy. Competing sources of distant metastases are pertinent in some cases. If no distant micrometastases exist at

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presentation or have been obliterated with systemic therapy, then local treatments are relatively more important, as prevention of local recurrence avoids a potential source of distant metastases. In order to gain a survival benefit from local control, there must be no significant competing risk from uncontrolled distant disease arising either from activation of dormant micrometastatic foci present at the time of diagnosis or from innate biological properties of the tumor that confer a greater propensity of residual tumor cells to form distant metastases.

Biological paradigms in breast cancer

Two dominant biological paradigms have provided a conceptual rationale for management strategies in breast cancer over the past century. These two paradigms espouse opposing views on the significance of local recurrence and the influence of local treatments on mortality from the disease. With longer term follow-up of clinical trials and application of meta-analysis methodology, an intermediate paradigm appears to be more relevant. This encompasses elements of both the "centrifugal theory" (*Halstedian paradigm*) and the theory of "biological predeterminism" (*Fisherian paradigm*) and may better inform contemporary management of the disease.

Halstedian paradigm

According to the Halstedian paradigm, breast cancer is a localized disease at inception which commences as a single focus and spreads in a centrifugal manner, encroaching upon ever more distant structures with progressive and sequential spread along fascial planes and lymphatics [7]. Metastatic spread to distant organs by hematogenous dissemination is preceded by infiltration of lymph nodes, which provide a circumferential line of defense and initially serve as barriers but subsequently permit access of tumor cells into the circulation when their filtration capacity is exhausted (Fig. 1). Local recurrence is considered to be a cause of distant metastases, and the chance of cure relates to the extent of primary loco-regional treatment. At the extreme, mastectomy will minimize local recurrence, but acceptable rates of local control can be achieved with "adequate" wide excision and radiotherapy. Where local recurrence is a determinant of distant disease, treatment at relapse may prevent distant metastases, and the timing of diagnosis and initiation of treatment is critical. Though systemic treatment has been shown to be effective in prolonging overall survival of breast cancer patients, other modalities of treatment, such as surgery and radiotherapy, have until recently no proven benefit on long-term survival. Nonetheless, though more extensive surgery does not improve survival for the majority of patients, there

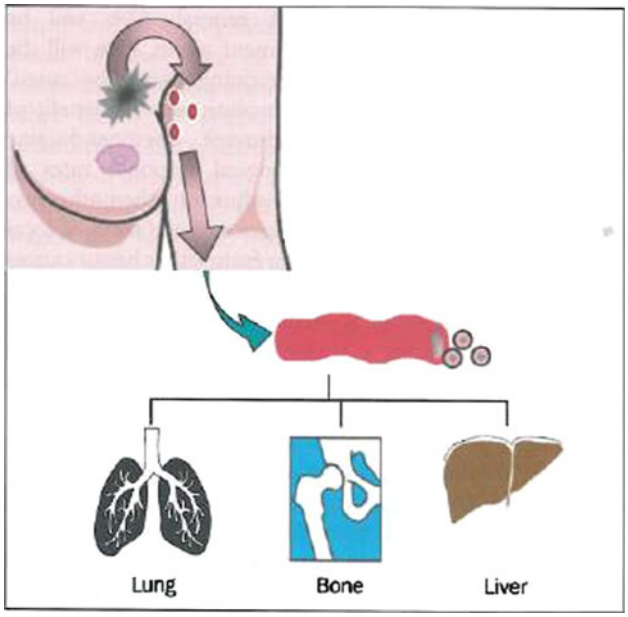

Fig. 1 Halstedian paradigm: sequential spread of breast cancer from single focus within the breast. Lymph node involvement is necessary for hematogenous dissemination [32]

may be a subgroup of patients with truly localized disease. For these patients, local therapy involving surgical excision (+ radiotherapy) might be curative and thus influence the natural course of the disease. Analysis of long-term survival of patients treated for stage I disease prior to the widespread use of adjuvant systemic therapy suggests that breast cancer is a loco-regional process in up to 75–80% of node negative cases, patients who may be considered statistically "cured" [8]. In a series of patients from Memorial Sloan-Kettering Cancer Center with node negative and node positive tumors less than or equal to 2 cm in size (T1N0 and T1N1), comparison of observed to expected survival at a median follow-up of 18 years revealed that 89% of patients with node negative tumors less than or equal to 1 cm were estimated to be cured, with survival curves becoming parallel or congruent during the second decade of follow-up (0.89; 95% Confidence Interval [95% CI] 0.80–0.98) [9]. For tumors between 1 and 2 cm, the figure was slightly lower at 77% (0.77; 95% CI 0.70–0.85). Though the time taken to attain parallelism was 13 years for tumors <1 cm and 18 years for tumors between 1 and 2 cm, there was no statistically significant difference between the observed and expected curves after 10 years. Any divergence of the curves beyond 20 years is unlikely to detract from the conclusion that a substantial proportion of patients will not die of breast cancer and are likely to have achieved a "personal cure" and will succumb from non-breast-cancer related causes (Fig. 2).

Patients with early stage breast cancer currently have 10-year survival rates in excess of 80% [10]. Although

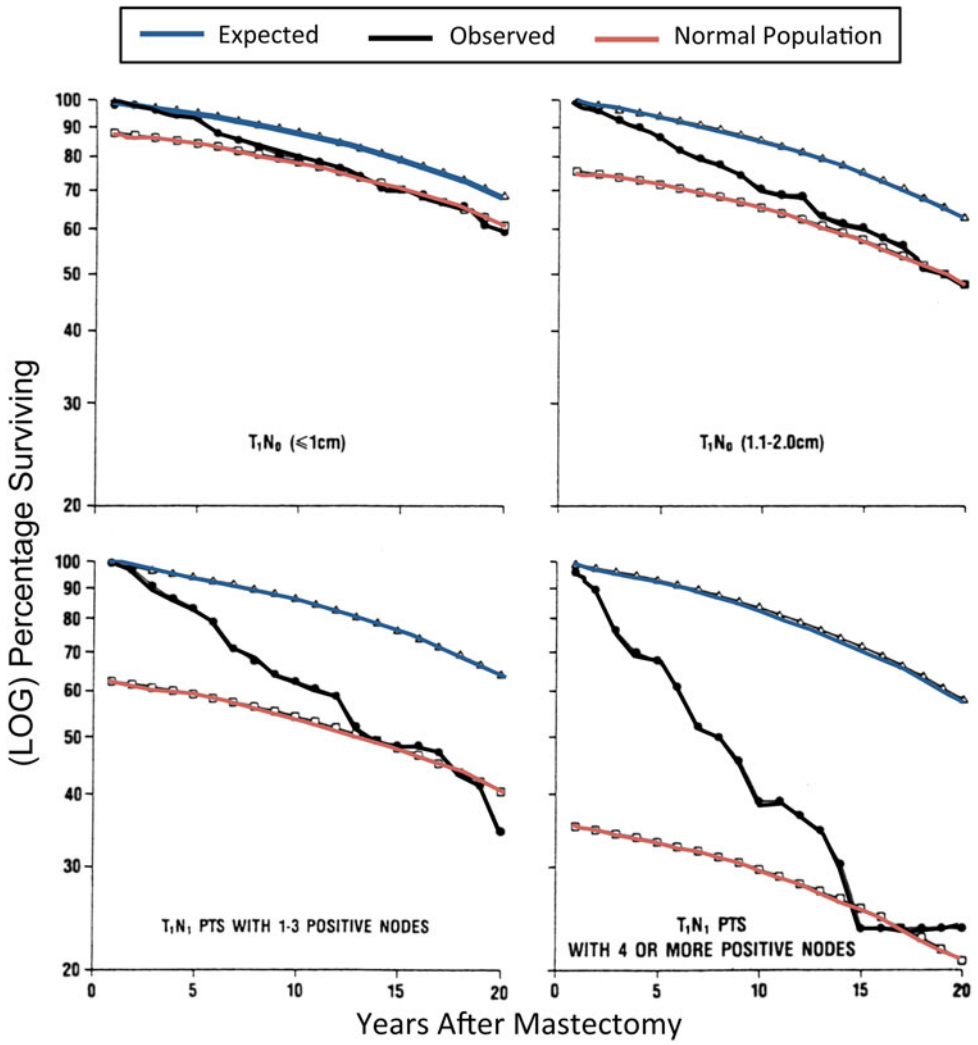

Fig. 2 Observed and expected survival curves for T1N0 and T1N1 patients with tumors measuring either 1 cm (group A) or 1.1–2 cm (group B) [8]

improved outcomes are largely attributable to adjuvant chemo-hormonal therapies, about 50–60% of breast cancer patients would survive for this period with loco-regional treatments only. This implies that disease is confined to the breast and lymph nodes and is adequately managed with local treatments or that some tumors possess low innate biological aggressiveness with stringent dormancy. William Halsted commented that "the efficiency of a breast cancer operation is measured truer in terms of local recurrence than of ultimate cure…." [7]. Treatments that allowed en bloc resection of tumor together with adjacent loco-regional tissues offered the best chance of "cure" and minimized local recurrence. In 1952, in an attempt to increase cure rates, Urban proposed an extended radical mastectomy involving partial removal of the chest wall and internal mammary nodes. Though this reduced rates of parasternal recurrence for inner quadrant tumors, there was no difference in overall survival [11, 12]. These findings have been confirmed with 30-year follow-up of the Milan randomized trial of radical mastectomy versus extended radical mastectomy (737 patients).

These results support the Halstedian paradigm, as does the reduction in mortality from breast cancer screening, which aims to detect cancers during the preclinical phase, when they remain localized without micrometastatic dissemination [13]. Between one third and one half of documented mortality reductions for breast cancer are attributed to screening [14], but a recent analysis from Norway suggests that only 10% of the decrease in breast cancer specific mortality results from screening per se, with the remainder due to improvements in systemic treatments and the formalization of multidisciplinary care [15].

Fisherian paradigm

The Fisherian paradigm presupposes that breast cancer is a predominantly systemic disease at the outset, and it challenges the concept of progressive centrifugal spread according to anatomical, mechanical, and temporal criteria. Thus cancer cells can enter the bloodstream at an early

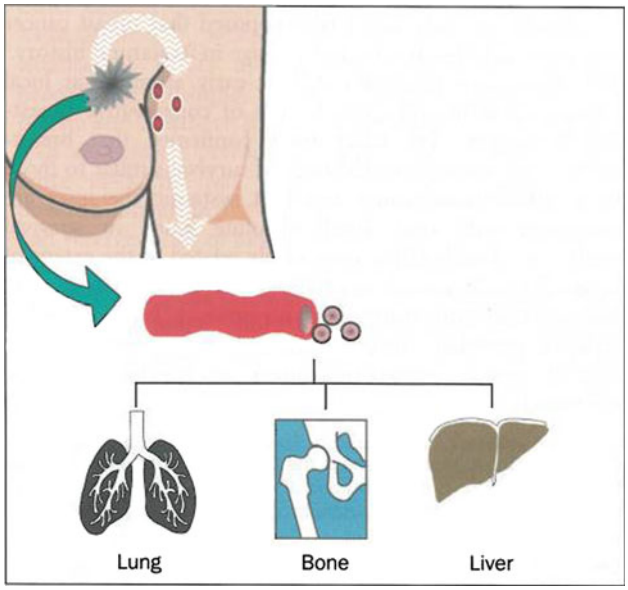

Fig. 3 Fisherian paradigm: spread of tumor cells into the bloodstream occurs early in tumorigenesis and precedes lymph node infiltration [32]

stage of tumor development via the leaky vessels of the neovasculature and lymphaticovenous communications. Initially, circulating cells may be destroyed by the immune system and will fail to establish viable foci of micrometastases (Fig. 3). A corollary of Fisher's conclusions is that current forms of treatment have modest effects on reduction of mortality from breast cancer. Though a primary tumor can be excised surgically or may regress completely with chemotherapy and/or radiotherapy, it is the presence of micrometastases at the time of presentation that will determine a patient's clinical fate. Local recurrence is viewed as an indicator of poor prognosis and reflects a host–tumor relationship that favors development of distant disease or activation of processes leading to a "kick start" of micrometastasis [16]. The biological potential of residual tumor cells within the breast is resonant with this more aggressive phenotype. Distant disease and mortality are governed by innate pathobiological features of the disease, and not the extent of loco-regional treatment.

An intermediate or spectrum paradigm is less restrictive than either the Halstedian or the Fisherian paradigm in pure form, and acknowledges that some breast cancers behave in a more Halstedian manner and that others are more likely to disseminate early on in accordance with the theory of biological predeterminism espoused by Fisher. The latter conclusion is based on results of clinical trials demonstrating equivalence of survival between mastectomy (radical/modified radical) and breast conservation surgery. However, it is the significance attributed to local recurrence that is perhaps of greater interest and has until now been underestimated. An update of the largest breast conservation trial, conducted by the National Surgical Adjuvant Breast and Bowel Project of the National Cancer Institute, U.S. National Institutes of Health (NSABP B-06) with 20-year follow-up confirms that postoperative irradiation improves local recurrence-free survival and, in particular, lowers the rates of early local recurrence [17]. Of note, distant disease-free and overall survival are similar in the three arms of the trial; namely, wide local excision, wide local excision with radiotherapy, and modified radical mastectomy. In the NSAPB B-06 trial, 39.2% of patients undergoing wide local excision only (negative surgical margins) had developed local recurrence at 20 years follow-up, compared with only 14.3% for patients receiving radiotherapy post-lumpectomy. Despite great variation in the incidence of IBTR, this does not translate into survival differences, and it was concluded that no causal relationship existed between IBTR and distant disease (Fig. 4). Differences in distant disease-free survival (DDFS) were examined between patients with and without IBTR using a

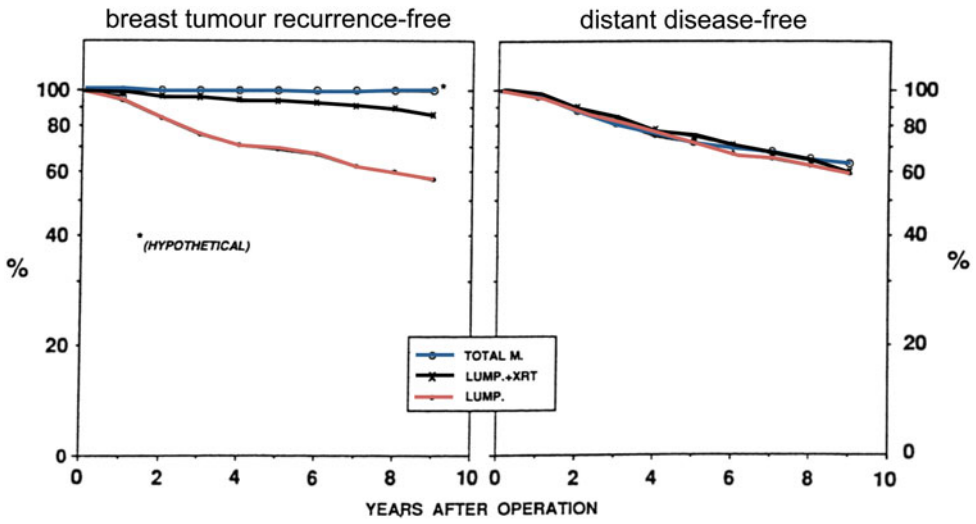

Fig. 4 Relationship of ipsilateral breast tumor recurrence (IBTR) to distant disease-free survival (DDFS) within the NSABP B-06 trial. Variations in local recurrence within the conserved breast due to local treatment differences do not translate into differences in DDFS [17]

Cox regression model based on the fixed co-variates of age, nodal status, tumor size and grade, together with the time varying co-variate of IBTR. In this analysis, IBTR was found to be the strongest predictor of distant disease and was considered to be a marker for increased risk but not a cause of distant metastases (3.41-fold increased risk; 95% CI 2.70–4.30) [1]. Early local recurrence was associated with a shorter distant disease-free interval, and IBTR was better correlated with distant disease than tumor size, which has been reported to be highly predictive for development of distant metastases. Thus IBTR is an independent predictor of distant disease and a marker of risk, but not an instigator of distant metastases. Though loco-regional treatment in the form of surgery or radiotherapy may prevent or reduce the chance of expression of the marker, such therapy does not alter the intrinsic risk of developing distant disease. The prognostic significance of IBTR has also been addressed by other workers. Haffty and colleagues examined the prognostic significance of IBTR among a group of almost 1,000 patients with invasive breast cancer treated with breast conservation surgery (BCS) and radiotherapy [18]. Overall rates of distant metastasis were higher in patients with IBTR (50%) than in those without local breast relapse (17%) [$p < 0.01$]. In particular, early IBTR was a significant predictor for distant metastases. However, the authors were unable to conclude whether IBTR was a marker of risk or a determinant of distant disease. Similar conclusions were reached more recently by a Japanese group, who evaluated outcomes in 1,901 patients who underwent BCS (with or without irradiation) for invasive tumors measuring $\leq$3 cm [19]. They used a Cox proportional hazards model to estimate the risk of distant metastases after IBTR. Though IBTR strongly correlated with subsequent development of distant metastases (hazard rate 3.93; $p < 0.0001$), it was unclear whether IBTR was an indicator or a cause of distant disease relapse. Survival data have been presented from the Nottingham group on 970 patients with and without local recurrence treated between 1990 and 1999 with breast conservation therapy (BCT) [20]. The relative risk of recurrence from avoidance of IBTR was 0.69—i.e., IBTR per se contributed to approximately one third of the overall recurrence risk (Fig. 5). A Cox analysis involving the co-variates of tumor size, grade, lymph node status, and lymphovascular invasion revealed that IBTR was the single most important risk factor and an independent prognostic factor for survival ($\beta = 1.41$; SE 0.15; $p < 0.001$). However, this analysis did not indicate whether IBTR was causal or just associated with survival. Whether IBTR is causal or merely associated with survival, treatments that reduce local recurrence definitely have an impact on survival, and therefore efforts to minimize recurrent disease in the conserved breast are justified.

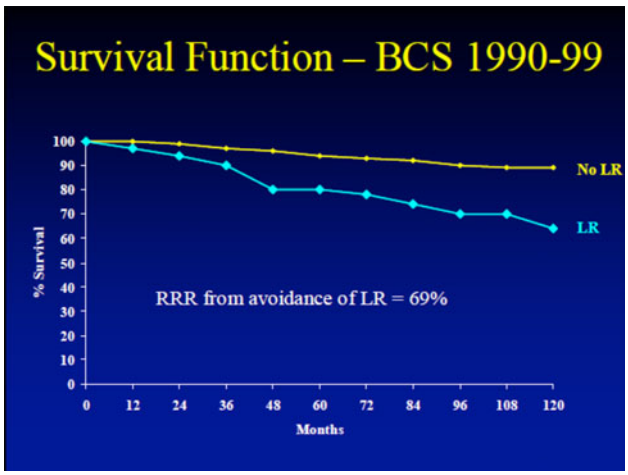

Fig. 5 Ipsilateral breast cancer recurrence contributes approximately one third to the overall recurrence risk within the Nottingham data set [20]

Longer term follow-up (25 years) of the NSABP B-04 trial reveals equivalent overall survival for clinically node-negative patients undergoing radical mastectomy compared with total mastectomy and radiotherapy or total mastectomy and delayed axillary lymph node dissection in the event of nodal recurrence (none of whom received adjuvant systemic therapies) [21]. Delayed axillary treatment did not have a negative impact on survival, which provides evidence that positive axillary lymph nodes do not serve as a nidus for distant spread but represent one manifestation of an innate propensity for disseminated disease.

Results of these trials individually support the contention that local treatments for breast cancer have minimal impact on overall survival outcomes, and that local recurrence is a marker of risk for development of distant disease, which reflects intrinsic biology of the tumor. Residual cancer cells are a determinant of local failure but not of clinically relevant distant disease [20].

Can local treatment influence mortality?

There is limited but increasingly cogent evidence that not all cases of breast cancer are systemic at the outset and that a subgroup of patients with early breast cancer exists for whom micrometastatic spread has not occurred before clinical (or mammographic) detection. Two randomized studies of post-mastectomy radiotherapy have shown a survival benefit (approximately 10%) in a subgroup of premenopausal node positive patients receiving chemotherapy, suggesting that persistence of local or regional disease can lead to distant metastases and impaired survival [22, 23]. In the smaller Canadian study, 318 node positive women were randomized to mastectomy and

chemotherapy, with or without irradiation. At 15-year follow-up, the overall survival rates were 54 and 46% for these two groups, respectively. In the larger Danish trial, 1,708 node positive or stage III breast cancer patients were similarly randomized, and overall survival rates at 10 years were 54% for the irradiated group compared with 48% for the non-irradiated group ($p < 0.001$). The results of these trials have generated some controversy because of the low number of nodes harvested at axillary dissection, and because of potential under-staging of patients due to sub-optimal management of the axilla. Some researchers have cautiously interpreted results of the Danish and British Columbia trials because nodal retrieval rates were poor and they have concerns that some patients received inadequate axillary surgery and in consequence had residual loco-regional disease or "oligometastases" [20].

Vinh-Hung and Verschraegen performed a pooled meta-analysis of 14 randomized trials comparing radiotherapy versus no radiotherapy after breast-conserving surgery (BCS) among almost 10,000 patients [24]. The outcome measures were IBTR and death from any cause; this study attempted to resolve some of the published discrepancies on the risks associated with omission of radiotherapy [25–27]. A pooled random-effects model was employed with formal assessment of heterogeneity using the Cochran Q-test. Wide local excision alone, without radiotherapy, was found to increase the relative risk (RR) of IBTR by a factor of 3.00 [95% CI 2.65–3.40], which translated into a marginal increase in breast cancer-related deaths (RR 1.086; 95% CI 1.003–1.175). This corresponded to a small excess of mortality (8.6%) when radiotherapy was withheld following wide local excision. A more definitive meta-analysis by the Early Breast Cancer Trialists' Collaborative Group suggests an overall survival benefit at 15 years from local radiation treatment to either the breast following BCT or the chest wall after mastectomy [5]. Data were available on 9,000 women in 14 randomized comparisons of breast conservation with or without radiotherapy. There was no significant heterogeneity between trials, and some patients received systemic therapy. Adjuvant radiotherapy reduced the rate of isolated local recurrence by two thirds, with a recurrence rate ratio of 0.32. Rates of local recurrence were reduced at 15 years from 28.3 to 10.4% in node negative patients and from 39.9 to 10.9% in node positive patients, for whom there was a greater absolute difference in local recurrence. Much of the effect of radiotherapy on local recurrence was evident in the first 5 years. The corresponding absolute breast cancer mortality reductions were 3 and 7.8% at 15 years for node negative and node positive patients, respectively. The overall proportional reduction in breast cancer mortality was 17%, with a breast cancer death rate ratio of 0.83 (SE 0.04; 95% CI 0.75–0.91; $2p = 0.002$). There is as yet no statistically significant difference in deaths from all causes. Of note, patient age and tumor grade (but not size) were significant predictors of 5-year local recurrence risk. Younger women benefited more from radiotherapy in terms of local relapse, with local recurrence gains at 5 years of 5.5% and 18% for women $\geq$50 years and <50 years age, respectively. The overall gain in mortality at 15 years follow-up was 5%, but node negative older women (50–59 years, 60–69 years, $\geq$70 years) with well-differentiated tumors did not derive any survival benefit from radiotherapy after BCT.

Post-mastectomy radiotherapy (PMRT) prevents two thirds of local recurrences on the chest wall, with much of the effect occurring within the first 5 years. There is an absolute mortality reduction of 6.2% at 20 years (63.6 vs 57.4%; $2p = 0.0007$). For node negative patients (one third of whom had systemic treatment) the absolute gains for local recurrence at 5 years was relatively small (3.4%), with a negligibly increased survival at 20 years (2.1%; $2p > 0.1$). Indeed, there was evidence for increased mortality in a subgroup of older women receiving PMRT for node negative disease. There was a mortality loss of 2.2% with 1 woman in 50 being "killed" by radiotherapy due to adverse cardiac effects of radiation (correlation between cardiac mortality and mean cardiac dose).

These results therefore confirm an overall survival benefit at 15 years from local radiation treatment to either the breast following BCS or the chest wall after mastectomy. For those treatment comparisons where the difference in local recurrence rates at 5 years was less than 10%, survival was unaffected (Fig. 6). Among the 25,000 women where differences in local relapse were substantial (>10%), there were moderate reductions in breast cancer specific and overall mortality (Fig. 7). The absolute reduction in local recurrence at 5 years was 19%, and the absolute reduction in breast cancer mortality at 15 years was 5%. This represents one life saved for every four loco-regional recurrences prevented by radiotherapy at 5 years. It is unclear precisely what the proportional contribution of local versus regional reductions was, as nodal recurrence rates were very low. Though clinical trials should provide conclusive evidence on whether surgery affects local or distant relapse, there are now relatively fewer relapse events. If rates of local recurrence can be minimized in the first 5 years, this will eventually have an impact on overall survival (*Halstedian paradigm*). The exact relationship between local recurrence and mortality rather constitutes a "moving target" [20]. Nonetheless, the 4:1 ratio derived from the EBCTCG meta-analysis is a useful rule of thumb and emphasizes that prevention of local recurrence can save lives.

Interestingly, a recent re-analysis of the Danish Breast Cancer Group 82b and 82c trials involving 1,000 high risk patients has found that the magnitude of survival benefit from reduction of local recurrence varies between patient

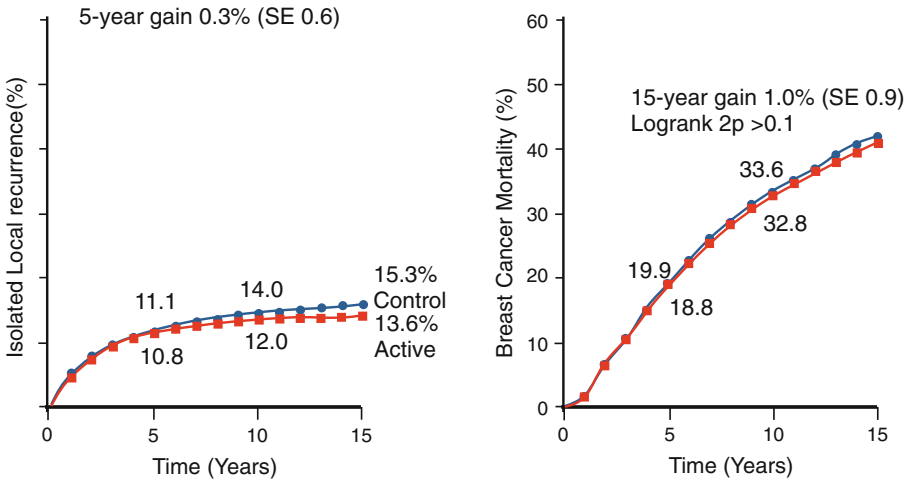

Fig. 6 Local recurrence and breast cancer mortality for treatment comparisons yielding a less than 10% absolute reduction in 5-year local recurrence risk [5]

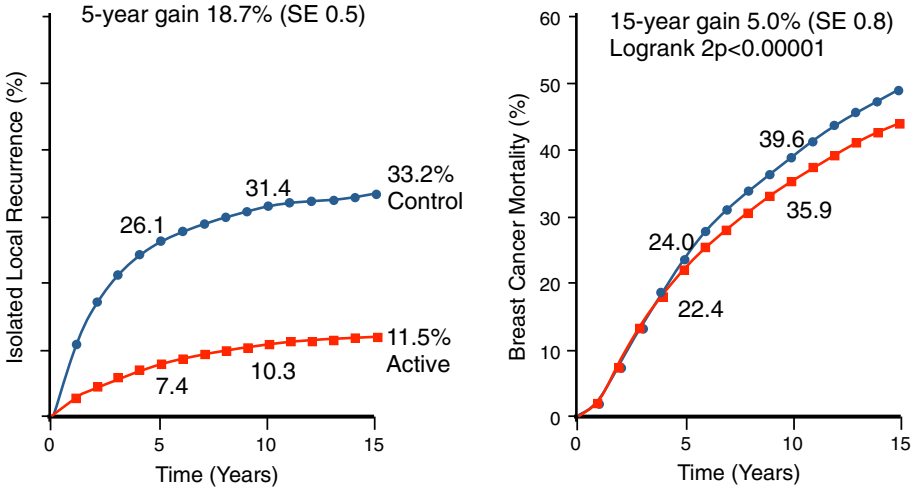

Fig. 7 Local recurrence and breast cancer mortality for treatment comparisons yielding more than 10% absolute reduction in 5-year local recurrence risk [5]

subgroups based on relative risk of loco-regional relapse and competing risks for uncontrolled distant metastatic disease [28]. Kaplan–Meier plots were used to define three prognostic categories for local recurrence risk (1) "good," (2) "intermediate," and (3) "poor." The good group had at least four favorable pathological criteria: ≤3 positive nodes, tumor size <2 cm, grade I, estrogen receptor (ER) or progesterone receptor (PR) positive or human epidermal growth factor receptor 2 (HER2) negative. By contrast, the poor group had at least two of the following: >3 nodes positive, tumor size >5 cm or grade III, whereas the intermediate group was in between. The smallest absolute reduction in local recurrence risk after PMRT occurred in the good prognostic group (11%; [33 vs 22%]). By contrast, the greatest absolute reduction in local recurrence risk was seen in the poor prognostic group (36%; [50 vs 14%]). These reductions are consistent with the EBCTCG overview [5]. However, spectrum analysis revealed that there was variability in how these reductions of local recurrence translated into any survival benefit. Continuously improved breast cancer specific and overall survival following PMRT was observed in the good and intermediate prognostic subgroups, but no survival gains were evident in the poor prognostic group. Thus the corresponding reductions in 15-year mortality for the good and poor prognostic groups were 11% [61 vs 50%] and 0% [81 vs 81%], respectively (Fig. 8) [28]. The authors surmise that patients in the poor prognostic group are more likely to have established distant micrometastases at initial presentation that are unresponsive to systemic therapy and fail to be eradicated. Micrometastatic foci eventually develop into overt metastatic disease from which the patient succumbs—they are the driver of mortality and represent a competing risk for distant metastatic disease over and above that which is derived from loco-regional recurrence. Postmastectomy radiotherapy can only affect overall survival when it prevents local recurrence from acting as a source for distant micrometastases. However, these findings conflict with the recent results from the EBCTCG overview, in which the largest mortality reduction was reported for patients at highest risk of local recurrence. Though high-risk groups were defined from probability of recurrence risk in both these studies, subgroups in the Danish Breast Cancer 82b and 82c

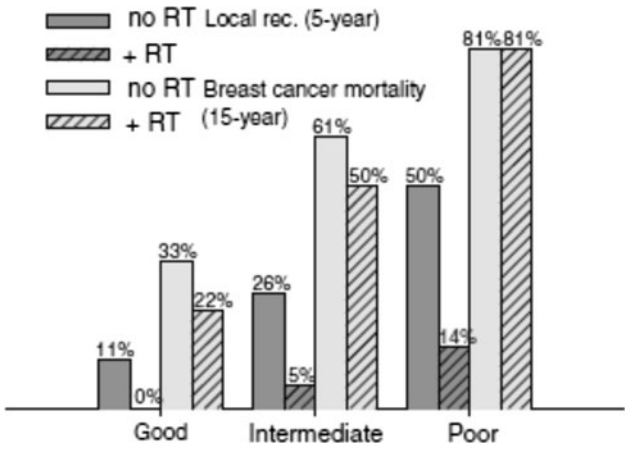

Fig. 8 Histogram of 5-year local recurrence probability and 15-year breast cancer mortality within the "good," "intermediate," and "poor" prognostic subgroups in high-risk breast cancer patients randomly assigned to receive or not receive postmastectomy radiotherapy (RT) in the re-analysis of the DBCG 82b and 82c trials [28]

studies were constructed from prognostic markers as apposed to outcome parameters. The high-risk category in the Danish analysis was likely to contain a greater proportion of intrinsically more aggressive tumors with increased tendency to form distant micrometastases leading to earlier death. Further improvements in systemic therapies (taxanes, herceptin, and other biological agents) may reduce the proportion of patients with unresponsive distant micrometastases and permit emergence of a survival benefit from PMRT in the higher risk subgroups. The SUPREMO trial will help clarify the role of PMRT in patients with 1–3 positive nodes who may have a smaller proportion with unresponsive distant micrometastases and hence less chance of competing uncontrolled distant metastatic disease [29].

Therefore the 4:1 ratio is an overall average based on all prognostic categories. The estimated ratios for the good, intermediate, and poor groups are 1:1, 2:1, and 0, respectively. The proportional benefit from each local recurrence avoided is greater in the good prognostic group, who have a lower likelihood of co-existent distant micrometastases that represent a competing cause of mortality. Within this prognostic category, an absolute reduction of 11% in local recurrence translates into a mortality gain of 11% at 15 years. This reflects a more favorable ratio, approaching one death prevented for each local recurrence avoided [28].

There is some evidence that local recurrence might be a cause of distant metastases from analysis of hazard rates for distant metastases in patients who have undergone breast conservation surgery with and without local control [30]. Those patients with local control demonstrate a peak in the hazard rate at about 2 years, after which there is a continual decline in the rate of distant metastases. By contrast, for those patients with local failure, a second hazard peak was seen at or

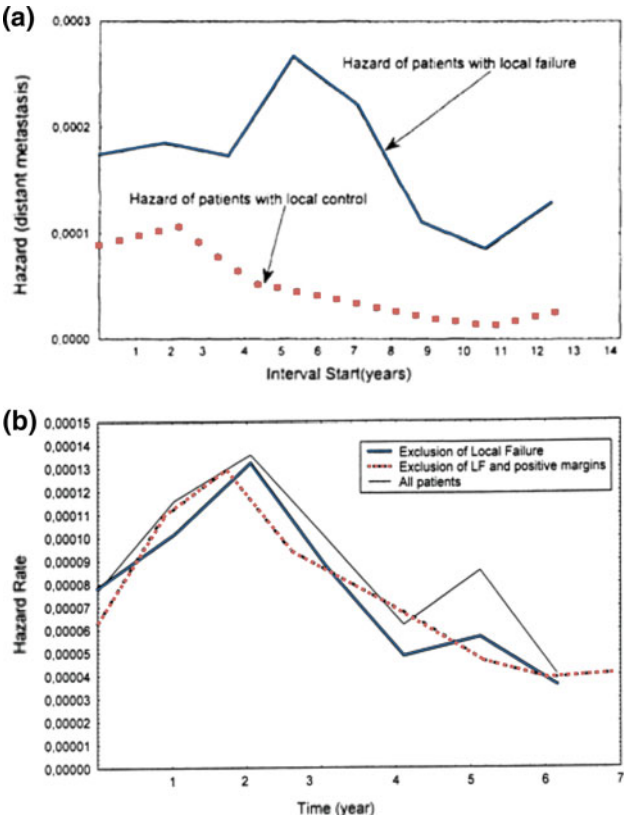

Fig. 9 **a** Hazard rate for distant metastases for patients with and without local control [31]. **b** Effect on late mortality peak from exclusion of patients with local failure or local failure together with positive margins [31]

beyond 5 years, which was absent in those patients without local recurrence (Fig. 9a). It should be noted that the hazard rate for metastases is always higher in patients with local failure compared to those with local control. The first peak, which is seen in patients with or without local control, represents micrometastases present at the time of diagnosis. When patients with local failure are excluded from the analysis, the late mortality peak is reduced in amplitude and actually disappears when patients with local failure and positive margins are excluded (Fig. 9b) [31]. It therefore appears that local failure has a causal relationship to this late mortality peak, and this second peak is evidence that local failure can be a source of new distant metastases and subsequent mortality; when this occurs, patients are more likely to have suffered early loco-regional or contralateral recurrence.

Local recurrence as determinant or indicator of distant metastases

Loco-regional treatments such as surgery or radiotherapy are potentially curative in the absence of micrometastases when disease is confined to the breast and lymph nodes.

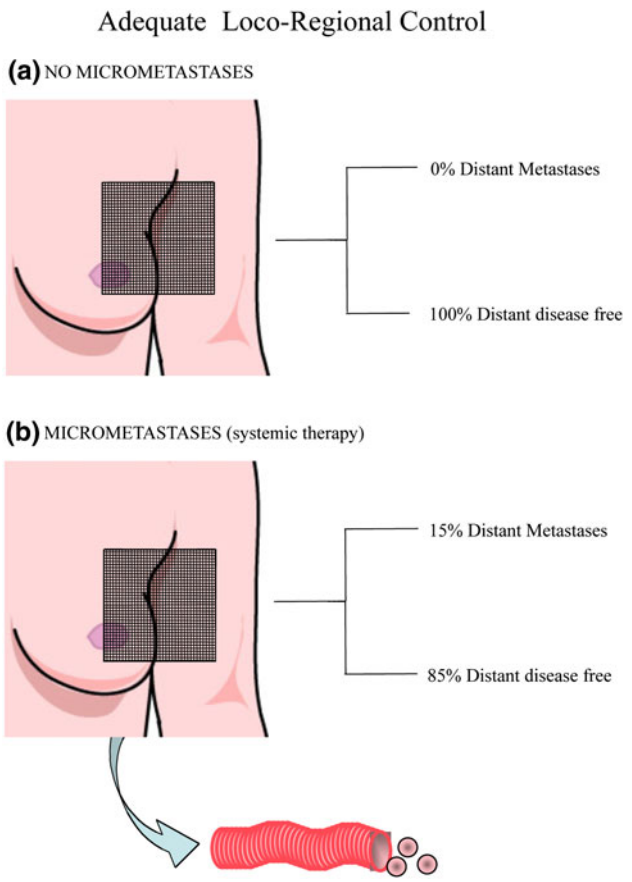

Fig. 10 **a** Adequate loco-regional treatment is potentially curative in the absence of micrometastases [32]. **b** In the presence of micrometastases, about 15% of patients will experience relapse at distant sites, despite therapies, with local recurrence being an indicator of poor prognosis [32]

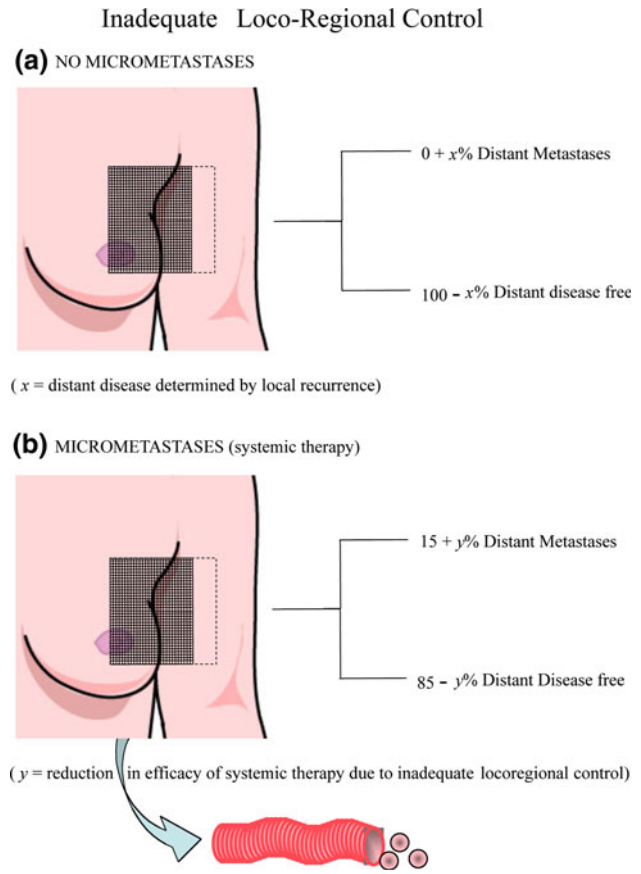

Fig. 11 **a** When loco-regional control is inadequate, residual tumor cells will cause local recurrence, and possibly distant disease, in a proportion (x axis) of patients. Despite the absence of micrometastases, survival is reduced because of poor loco-regional management [32]. **b** Even with micrometastases, inadequate loco-regional treatment will reduce the efficacy of systemic therapy, leading to a reduction (y axis) in the number of patients remaining free of distant disease [32]

Under these circumstances, when local management is incomplete, cancer cells persist within loco-regional tissues and can develop into distant metastases at a later date (Fig. 10a, b). Therefore where micrometastases are either absent at presentation or have been obliterated by systemic therapy, local recurrence is a determinant of distant disease and assumes a different significance from Fisher's postulate of local recurrence being a marker for distant disease. By contrast, where micrometastases exist and have not been ablated with systemic therapy, local recurrence would be an indicator of poor prognosis, with foci of residual tumor and distant occult disease maintained in a state of dynamic equilibrium until some event triggers recurrence (Fig. 11a) [32]. However, studies have revealed partial independence among prognostic factors in determining the potential for local and distant relapse. In their study of IBTR in more than 2,000 patients undergoing BCS with quadrantic resection, Veronesi and colleagues found that tumor size and nodal status are correlated with distant but not local disease recurrence while young age and peritumoral invasion predict for both local and, to a lesser extent, distant disease relapse [2]. Local recurrence conferred an overall increased risk of distant relapse of 4.62-fold (95% CI 3.34–6.39). There was actually evidence of an inverse relationship between nodal status and local recurrence, which may be due to confounding effects of concomitant chemotherapy. Furthermore, the presence of an extensive intraductal component (EIC) predicts for local recurrence only, which under these circumstances represents inadequate local treatment and is not a marker for inherently increased risk of distant metastases. Where there are both invasive and ductal carcinoma in situ (DCIS) components involved in local recurrence after BCT, it is the invasive element that confers the increased risk of distant failure. In situ disease does not contribute to distant metastases, and when local recurrence is exclusively DCIS, the systemic risk is determined by features of the original primary tumor [20].

Of interest, the benefits of chemotherapy may be compromised when loco-regional control is inadequate, because of the reduced efficacy of chemotherapy in the presence of a greater tumor cell burden in loco-regional tissues (Fig. 11b). Any persistent loco-regional disease could become a source of distant metastases (oligometastases) [33]. Within the trials of breast conservation, most of the cases of local recurrence occur against a background of micrometastatic disease and therefore represent a marker of distant relapse. Those patients without micrometastases at presentation and who undergo adequate loco-regional treatment have the same outcome irrespective of the type of surgery. However, where there is inadequate or incomplete loco-regional therapy survival differences may emerge because local recurrence is a determinant of distant disease and may render systemic therapy less effective. It is perhaps not surprising that no survival difference is detectable in BCT trials because the majority of patients have received adequate primary loco-regional treatment (with or without mastectomy at time of relapse) and local recurrence is not a cause of distant disease. Those cases where local recurrence is a determinant of distant failure are probably too few and follow-up too short to have any statistical impact. Molecular profiling may allow distinction between these two basic groups and avoid under- and overtreatment with both loco-regional and systemic therapies [34].

Though randomized clinical trials have previously failed to identify any group of patients for whom local recurrence produces a decrement in survival, these trials may not have possessed the power to detect any effect of attenuated loco-regional treatment on overall survival. The number of events is relatively small, and some cases of distant recurrence may not yet have occurred at the time of analysis. The overview by the EBCTCG previously referred to implies that survival and local recurrence are related, but not in a simple one-to-one manner (as discussed above). Interestingly, in the EBCTCG overview, those patients in whom the difference in local relapse rates was <10%, had presumably received adequate loco-regional treatment from surgery alone with little further reduction from more surgery or radiotherapy [4]. These latest clinical results accord with the intuitive assumption that viable cancer cells remaining in the peritumoral tissue of the breast following conservation surgery will ultimately proliferate and metastasize to distant sites.

Extent of local surgery

The overview by the EBCTCG confirmed that long-term mortality was also influenced by reduction in loco-regional disease attributable to more extensive surgery, as well as addition of radiotherapy. With improvements in surgical margins of clearance, the absolute benefits from radiotherapy in terms of local control will be less in the future. Breast-conserving surgery is now an established surgical modality and is the preferred standard of care for management of women with early stage breast cancer. Introduction of conservative forms of breast surgery has coincided with instigation of widespread mammographic screening over the past 25 years. With a smaller average tumor size at presentation, the majority of patients are eligible for BCS, though rates of mastectomy are variable at both institutional and geographical levels. Within the United Kingdom, rates of BCS vary from 5 to 70%, with an average of 58% [35]. These variations in patterns of surgical management are likely to reflect differences in philosophy and training among surgeons, together with an element of fear and concern about recurrence. Selection of patients for BCS is of crucial importance, with an inverse relationship between the oncologic demands for surgical radicalism on the one hand and cosmesis on the other. There is a balance between the risk of local recurrence and cosmetic results. Most patients deemed eligible for BCS will have a favorable tumor to breast size ratio and be suitable for conventional forms of wide local excision in which the tumor is excised with an approximate 2 cm margin of surrounding breast tissue without any formal breast re-modeling. It is no longer acceptable to merely attain gross macroscopic clearance of the tumor at operation; all radial margins should be clear of tumor at the microscopic level. The NSABP and others have reported higher rates of local recurrence with microscopically positive margins, with rates increasing significantly with duration of follow-up compared with negative margin tumors (regression coefficients of 0.75 [$p = 0.008$] and –0.31 [$p = 0.35$], respectively) [36–40]. However, some studies have found no correlation between local recurrence and positive resection margins [41, 42], although relapse rates may have been influenced by modification of radiotherapy regimens with a proportionate increased booster dose to "compensate" for positive margins.

Ipsilateral breast tumor recurrence

Two factors emerge as principal determinants of true local recurrence within the ipsilateral breast: (1) margin status and (2) the presence or absence of an (EIC [36, 43]. Other factors have been implicated in determining risk of local relapse, but correlations are in general much weaker than for margin status and EIC. Among these, lymphatic invasion, young age (<35 years), and absence of chemohormonal therapy have been shown to be primary predictors for increased risk of local recurrence [44–46]. Consistent associations have been found for larger tumor size (>2 cm) and higher histological grade, but not for tumor subtype or

nodal status. These findings are consistent with the notion that local recurrence develops from regrowth of residual cancer cells in peritumoral tissue. Increased rates of local recurrence associated with positive margins and EIC suggest that incomplete removal of tumor may contribute to local recurrence. A web-based tool has been developed as a predictive nomogram for IBTR after BCS. This tool uses relative risk ratios for seven clinicopathological variables, and a modification of the original nomogram has been devised using two independent population-based data sets. The nomogram predicts an overall risk of IBTR of 4.0% at 10 years with an observed estimate of 2.8%. It is accurate for most patients at low (<3%) to moderate (3–5%) risk of recurrence, but it overestimates risk in a minority of higher risk patients [47]. The risk of local recurrence, both within the breast after BCS and in the chest wall following mastectomy, can be predicted from gene microarray data that has classified breast tumors into distinct biological subtypes (luminal A, luminal B, normal, basal, HER2). The basal subtype appears to be associated with a higher risk of local recurrence after BCS and mastectomy compared with luminal subtypes and may have stronger and more consistent associations than some of the conventional histopathological factors (grade, subtype, nodal status) [48, 49].

Surgical margins

There has been lack of uniformity in definition of a positive resection margin, and this in turn has compounded issues relating to microscopically negative margins and degrees of surgical clearance: How wide must a negative margin be to result in acceptable rates of local recurrence (<1–1.5% per annum) [43]? Some authors have defined a further category of "close margins" and found correlations between margin status and local recurrence based on strict and consistent criteria [42]. Several studies have examined the impact of close margins (≤2 mm) on rates of local recurrence. Although these are relatively small studies with some variability in other factors, such as age, EIC, and systemic therapies, they all reveal a statistically significant increase in rates of local recurrence for "close" compared with negative margins [50–53]. Freedman and colleagues reported 10-year actuarial local recurrence rates of 14% when surgical margins were ≤2 mm and 7% when margins exceeded 2 mm (median follow-up: 76 months) [53]. Similar figures were found by Park and colleagues at a median follow-up of 82 months (17 vs 9%, respectively) [46]. Many surgeons consider a margin clearance of 2–3 mm to be appropriate, though up to 45% of American radiation oncologists consider a margin as negative if there are no tumor cells at the inked edge [54]. A survey of 200 breast surgeons from the United Kingdom found wide variation in opinions on adequacy of margins, with 65% aiming for a margin of ≥2 mm and one quarter accepting a clearance of just over 1 mm [55]. Further surgery may be necessary to obtain the requisite radial margin clearance, be this 1, 2, or 5 mm [56]. Most studies confirm that tumor size, lobular phenotype, lymphovascular invasion, and nodal involvement are associated with close margins [46, 56–59]. About 30% of breast units in continental Europe and a mere 10% in the United States strive for a radial margin clearance of 5 mm. However, a wider margin mandate can lead to re-excision rates of almost 50% without necessarily resulting in lower recurrence rates compared with a less stringent margin policy [56]. The authors' group has reported a 5-year actuarial rate of 1.1% for IBTR following BCS for invasive breast cancer when a 5 mm margin was enforced [60]. This compares favorably with average contemporary rates of 3.5–10% at 10 years [61]. There is less chance of finding further tumor when re-excision is performed to achieve a wider margin rather than a negative margin per se. Thus Pittinger and colleagues found residual disease in 44% of cases with involved margins, 24% of cases with free margins of ≤3 mm, and no further tumour in wider excision/mastectomy specimens when the free margin exceeded 3 mm [62]. An analysis of data from the authors' unit has shown that residual disease is found in 60% of patients with involved margins, 40% of those with negative margins up to 2 mm, and only 6% for patients with a margin of 2–5 mm (OR: 2–5 mm margin versus involved margin = 0.05; $p = 0.004$) [63]. Other investigators have similarly reported a low probability of finding residual disease upon further resection when the margin of clearance is at least 2 mm (2.3%), compared with one third of cases where the clearance is between 0.1 and 0.9 mm [56]. Singletary has provided a useful analysis that shows median rates of IBTR of 3, 6, and, 2% when margins of clearance were 1 mm, 2 mm, or just clear, respectively [64]. Thus patients with no tumor cells within one microscopic field of the cut edge had the lowest rates of recurrence (range: 2–4%). When studies of local recurrence are grouped according to how a negative margin is defined, there is a consistent and statistically significant difference between positive and negative margins (Fig. 12). Thus, although rates of recurrence are determined by negative margin status, no direct relationship exists between margin width and rates of local recurrence. When the first re-excision fails to achieve surgical clearance, mastectomy is often indicated and becomes necessary if margins remain positive after a "reasonable" number of surgical attempts [65]. Larger tumor size and a lobular phenotype are more likely to be associated with close/positive margins, and patients should be warned that they are at higher risk for re-excision or mastectomy. It remains unclear whether a mandate of 2–3 mm pertains equally to DCIS and invasive malignancy. Some surgeons have

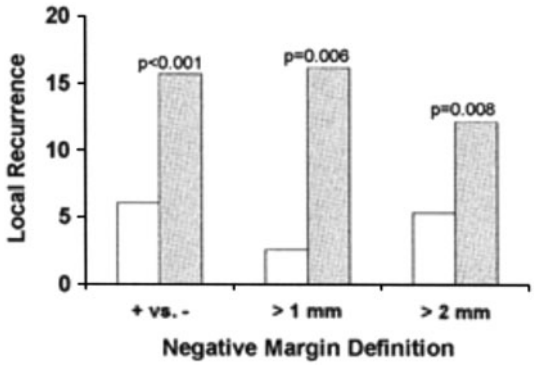

Fig. 12 Relationship of local recurrence to margin status (defined as "positive" and "negative") [63]

advocated the need for a wider margin of clearance for DCIS (up to 10 mm) [66]. Nonetheless, a recent meta-analysis suggests that a 2 mm margin of clearance is adequate when radiotherapy is administered to the whole breast postoperatively [67], and this accords with the UK's current NICE (National Institute of Clinical Excellence) guidance [68].

Oncoplastic surgery

The newer techniques of oncoplastic surgery are advancing the limits of surgical resection that may be associated with an increased chance of tumor-free margins, although not necessarily lower rates of IBTR. Furthermore, positive margins under these circumstances usually reflect extensive disease for which mastectomy (rather than re-excision) is indicated. It has been suggested that the chance of local relapse could be reduced by more aggressive approaches to BCS [69], but there are not yet any data on longer term follow-up of these oncoplastic procedures. Moreover, there is no information from clinical trials on the safety of BCS for invasive tumors in excess of 4 cm [70]. Though margin status and the presence or absence of an extensive in situ component are the principal determinants of local recurrence, consistent associations have been found for tumors >2 cm in size [71]. For node-positive patients, tumor size exceeding 5 cm was the only risk factor for local recurrence on multivariate analysis [72]. Therefore it is likely that the risk of relapse would remain high for larger tumors, despite adequate surgical clearance. Nonetheless, it may be possible to excise large areas of non-high-grade DCIS (>4 cm) with clear margins and to partially reconstruct the breast with autologous tissue replacement. Age less than 35 years and family history of breast cancer are additional factors that must be considered when selecting patients for either oncoplastic surgery with a high percentage breast volume excision or skin-sparing mastectomy with whole breast reconstruction (higher risk of local recurrence or *de novo* cancer risk). Though it may not be feasible in routine clinical practice to formally estimate the percentage excision from radiological measurements of tumor and breast size, consideration of magnetic resonance imaging (MRI) assessment of the breast is advisable. This can confirm unifocality or exclude multifocal disease involving different quadrants. Where imaging is equivocal and tumor parameters are borderline for BCS, it may be preferable to undertake a two-stage procedure; initial "wide" local excision of tumor permits full histopathological evaluation with assessment of margins. A definitive oncoplastic procedure can subsequently be carried out, either 2–3 weeks later or following radiotherapy to the breast. A one-stage procedure is optimal and avoids any technical difficulties relating to the sequelae of previous surgery and radiotherapy (scarring, fibrosis). There are less likely to be problems with skin viability when completion mastectomy is undertaken after simple excision of tumor compared with a more complex oncoplastic procedure with parenchymal undermining and transposition [73].

Local treatments at presentation versus relapse

Where local recurrence is a determinant of distant disease, treatment at relapse may prevent distant dissemination, and the timing of diagnosis and initiation of treatment would be critical. However, where local recurrence develops against a background of pre-existing micrometastatic disease and distant relapse risk, it represents a marker for distant disease, which would have developed whatever the extent of primary loco-regional treatment. For the former group, it is important to administer maximal loco-regional therapy at the time of initial diagnosis with curative intent. For the latter group, minimal early loco-regional treatment would suffice, as any local recurrence developing secondary to "inadequate" loco-regional treatment would not affect survival but would be an indicator of a relationship between tumor and host that favored distant relapse. It would be an indication for maximal treatment at the time of local recurrence, including systemic therapy.

There is evidence that systemic treatments administered at the outset influence not only distant disease-free and overall survival but also reduce risk of loco-regional recurrence as the first site of relapse (EBCTCG) [74]. The magnitude of proportional risk reduction is about 30%, and the principle applies to all forms of systemic therapy, including chemotherapy, hormonal therapy, and use of biological agents such as herceptin. These loco-regional effects of systemic treatments will tend to reduce the impact of surgery and radiotherapy on mortality; the chance of any persistent or recurrent disease in the breast and regional nodes acting as a source of distant disease will be minimized, and patients will be more likely to succumb

from competing risks of pre-existent distant metastases. Techniques of gene profiling can potentially characterize the biology of individual tumors and provide a molecular "portrait," which can guide treatment strategies. Recurrence scores predicting the risk of both local and distant relapse can be incorporated into clinical decision-making processes once rigorous clinicopathological correlation has been achieved [34, 49, 75].

Conclusions

There is now convincing evidence that prevention of local recurrence following either breast conservation surgery or mastectomy can save lives in the longer term and is a worthwhile aim. Management of breast cancer patients must now be guided by an "intermediate" or spectrum paradigm that encompasses elements of both Halsted and Fisher but has inherent flexibility and can accommodate contradiction. It is difficult for clinicians to ascertain precisely how a tumor will behave within this conceptual "coalition," but genetic profiling may offer insight into innate risks of relapse and allow more tailored treatments that avoid under- and over-treatment. Such techniques may ultimately select those patients for whom more aggressive loco-regional treatment at the outset may confer a survival advantage. This is likely to include younger patients for whom the risk of local recurrence in the conserved breast is almost twice as high as for older women. Obviously, avoidance of death from breast cancer gains more additional years of life expectancy for younger women. With the stage shift witnessed in recent years, fewer women will in theory have micrometastases at presentation and thus local recurrence assumes a greater significance and consequence as a source and determinant of distant metastases. It is important that this group of women receive adequate loco-regional treatment to both breast and axilla, especially if systemic therapy is minimal. Low volume residual disease within the breast, chest wall, and axillary tissues may not be manifest as distant disease and translate into any detriment to survival for many years, and clinicians should therefore be wary about "reductionist" approaches to loco-regional treatments based on trials with limited years of patient follow-up [76].

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