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Factors Influencing the Risk of Local Recurrence in the Breast

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This paper reviews what is currently known regarding possible factors influencing the risk of local failure in the breast after conservative surgery and radiation therapy for clinical stage I and II breast cancer. The best established features correlating with increased risk are young age at time of primary therapy, and the presence of an extensive intraductal component within the primary tumour. The interactions of tumour- and treatment-related factors is complex, but adequacy of surgical excision, quality of radiation therapy technique, and use of systemic therapy all appear to contribute to risk reduction.
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INTRODUCTION

TUMOUR GROWTH in the conservatively operated and radically irradiated breast represents a relatively new oncological event, whose clinical and pathological characteristics only began to be investigated and defined during the past decade. In contrast with local recurrence in the skin flaps after total mastectomy, failure in the conserved breast arises from progression of residual cancer adjacent to the excised primary or from the appearance of separate cancer foci elsewhere in the breast. Intramammary recurrences are generally considered to have a more protracted time course and a more favourable prognosis [1–3]. There is thus little reason to expect that the factors influencing the incidence of relapse in the breast are necessarily the same as those which correlate with the risk of local failure following primary radical surgery.

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Many factors have been proposed in the literature as playing a significant role in determining local recurrence risk. Assessment of the relative merits of individual factors is made difficult by the marked inhomogeneities within the published series: variations in patient selection, surgical and radiotherapeutic techniques, use of systemic treatments, and type of pathological evaluation. For clarity and simplicity of discussion, the present paper will consider separately those factors which are patient-related, those which relate to characteristics of the primary tumour, and those which are to a great extent treatment-related.

DEFINITION OF LOCAL RECURRENCE

Considered here is the clinical appearance of progressive cancer within the parenchyma or skin of the breast, occurring at some time after macroscopically complete primary tumour excision and standard megavoltage whole-breast radiotherapy. The results of excision alone without radiotherapy will not be discussed, as the risk factors for local failure in this setting have not yet been defined. As the available data is restricted to clinical

stage I and II tumours up to a maximum diameter of 5 cm, the treatment of more advanced lesions will not be considered, nor will data be included which was based on the use of radiotherapy alone, without primary tumour excision.

Most local failures occur at or near the site of primary tumour excision, and are sometimes termed "true" or, in less clear cases, "marginal" recurrences [1]. Less frequently, and more often as a late event [2], tumour formation is observed at a clear distance from the primary tumour bed, and is considered a "new" cancer. Presumably the former category represents residual elements of the primary tumour and its local extensions, whereas recurrences elsewhere in the breast reflect independent multicentric foci. Obviously, such distinctions are to some extent arbitrary, and any calculation of local recurrence rates should include both types.

In three large series, the risk of recurrent cancer elsewhere in the breast has been estimated at 1% at 5 years and 3–4% at 10 years [1, 4, 5]. This risk is independent of the type of surgical treatment of the primary lesion, and can be influenced most clearly by radiotherapy, and theoretically by systemic treatment as well. However, the dose of whole-breast radiotherapy is limited by normal tissue tolerance. The relative value of whole-breast irradiation, compared with radiotherapy restricted to the primary tumour area, is currently under investigation in a prospective, randomised trial [6]. No clinical or pathological features have yet been defined which appear to influence the likelihood of "new tumour" formation. Although most studies include both types of local recurrence in analyses of risk, the risk factors outlined in the subsequent discussion can be thought of as relating principally to recurrences within the immediate vicinity of the primary tumour area.

Localised recurrences involving the skin of the breast, and diffuse, inoperable recurrences extensively involving the skin and parenchyma of the entire breast represent about 10% of local failures [7]. Although difficult to classify according to the simple guidelines mentioned above, such recurrences are usually considered extensions of the original primary tumour, as they almost always occur within 2–5 years after initial treatment. Risk factors for such recurrences are not well defined, but probably are similar to factors related to local recurrence risk following total mastectomy [7].

PATIENT-RELATED FACTORS

Age and menopausal status

The association of young age with increased risk of failure in the breast was first identified by the Institut Curie [8], and has since been confirmed by almost all investigators who have analysed this factor [5, 9–15]. Representative data, presented in Table 1 from two large series, suggest that there is a continuously increasing risk of local failure with decreasing age. Although age subdivisions are arbitrary, it is clear that patients in the oldest age groups have a very low risk of local failure with standard therapy, and that the youngest patients are exposed to a risk which is several times greater.

This gradation of risk is not well understood. It may reflect a tendency for younger patients to have a greater residual tumour burden after local excision, or alternatively may stand in relation to the effects of circulating oestrogens on residual cancer foci or premalignant changes in the treated breast. It is not known whether the risk of local recurrence in premenopausal patients can be reduced by oophorectomy or other hormonal manipulation. It is possible that this age effect is related to the age dependence of certain histologic features associated with local recurrence risk (see below).

Table 1. Crude rates of local recurrence in the breast as a function of patient age

Age range (years)	Local failure (%) Harvard	Marseille
<35	15/62 (24.2)	20/109 (18.4)
35–50	45/335 (13.4)	89/702 (12.7)
51–65	27/256 (10.5)	57/618 (9.2)
>65	4/130 (3.1)	19/254 (7.5)

Data are based on the treatment of T1 and T2 tumours treated at the Harvard Joint Center for Radiation Therapy (9, median follow-up 8.5 years) and at the Cancer Institute and associated clinics in Marseille (10, median follow-up 11 years).

Breast size

Recent data suggest that recurrence risk may be influenced by the size of the patient's breast [13]. In a series of 324 breast cancers 2 cm or smaller treated in a standard fashion, local failure was observed in 2% of patients with large breasts, 8% of patients with medium-sized breasts, and 14% of patients with small breasts. Although this is probably related to the facility of obtaining wide resection margins in voluminous breasts, a hormonal effect related to obesity cannot be excluded [13].

Family history and other patient-related factors

There are additional factors that might be of potential interest with regard to local recurrence risk, but few data are available. There is no evidence that patients with a family history of breast cancer are at increased risk of local failure. For 905 stage I and II patients in the Marseille series for whom information about family history was available, recurrence in the breast was observed in 31 of 205 (15%) patients with a positive versus 82 of 700 (12%) with a negative family history ($P > 0.1$). In addition, there was no association between local recurrence and age at first menarche, number of lactations, number of pregnancies, or number of births [16].

TUMOUR-RELATED FACTORS

Tumour location

There are no striking relationships between the location of the primary tumour and the risk of local failure, at least when tumours are subclassified as medial, lateral or central [12, 17]. Nonetheless, data from the large Marseille series suggest that tumours located at "12 o'clock" or in the upper inner quadrant have a somewhat higher incidence of recurrence, and those at the equator or in the lower half of the breast a somewhat lower incidence, compared with tumours in the upper outer quadrant or in the central portion of the breast (Fig. 1). This may reflect the relatively small amount of parenchyma in the upper inner portion of the breast, rendering a wide but cosmetically acceptable excision more difficult. Conservative excisions of central tumours are frequently considered unwise, reflecting a reluctance to resect the nipple–areolar complex. Most series presumably contain few patients with central tumours, but there is no evidence that such lesions are at higher risk of local recurrence [16, 17].

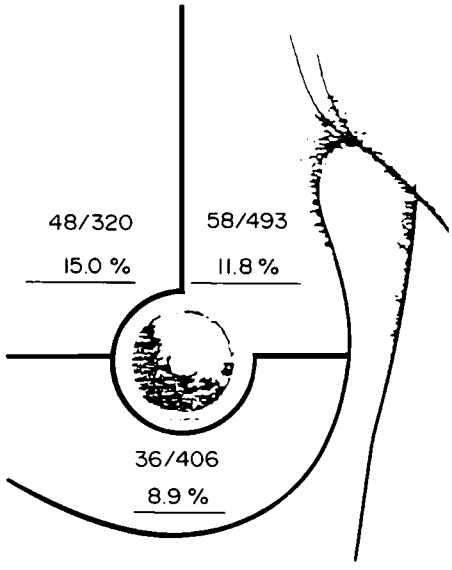

Fig. 1. Data from the Marseille series showing the crude rate of local recurrence in the breast according to primary tumour location [16]. The difference between the highest and lowest rates was statistically significant ($P < 0.01$, χ^2 test).

Skin dimpling, nipple retraction

While deep tumour fixation and gross skin infiltration are considered contraindications for classical breast-conserving techniques, neither nipple retraction nor skin dimpling appear to be associated with a higher risk of local failure. Among 385 stage I and II patients noted preoperatively to have skin dimpling or nipple retraction, 41 (11%) local recurrences were observed, identical to the rate observed in patients without these changes (101/930, 10.9%) [16].

Tumour size

Within the range of tumour sizes generally considered for breast-conserving surgery, the clinical diameter of the primary tumour has no apparent influence on local recurrence risk, provided that a macroscopically complete resection had been performed and standard radiotherapy administered (Table 2). Holland *et al.* [18] in a study of serial subgross sectioning of mastectomy specimens, clearly demonstrated that the percentage of breasts having residual cancer foci outside of a 2 cm distance from the edge of the primary tumour was the same both for tumours smaller than 2 cm in diameter and for larger tumours between 2 cm and 5 cm in diameter. Although an adequate local excision may be more difficult to perform in larger tumours, depending on the volume of the breast, data from virtually all large series confirm that local failure is not more frequent in larger than in smaller tumours [9, 11, 14–17, 19, 20]. Data from Fisher *et al.* suggest that tumour size may influence local recurrence risk in patients not receiving radiotherapy [21, 22]. Larger tumours, however, may be responsible for the majority of the most aggressive local recurrences [3, 7, 14].

Table 2. Crude rate of local recurrence in the breast for 1350 stage I and II patients as a function of clinical tumour size

Clinical tumour size (cm)	Local recurrence (%)
<1	29/255 (11.4)
1.1–2.0	45/438 (10.3)
2.1–3.0	40/392 (10.2)
3.1–4.0	21/179 (11.7)
4.1–5.0	12/86 (13.9)

Patients were treated at the Cancer Institute and associated clinics in Marseille between 1962–1981 (16, median follow-up 10 years). None of the differences are statistically significant.

Axillary lymph node status

Although the extent of axillary nodal involvement is clearly a risk factor for both local and regional recurrence after primary radical surgery [23], its influence on the incidence of intramammary failure is far from clear. In fact, there are virtually no series in which the independent influence of nodal status can be adquately evaluated, as in most older series axillary dissections were not routinely performed, and in most contemporary series adjuvant systemic therapy was given preferentially to node-positive patients.

Although there is some suggestion from small series that node-positive patients have a greater inherent tendency to recur in the breast [24], most series tend to show fewer local failures in these patients than in those without nodal involvement [9, 15, 20, 25]. This is attributed to the use of adjuvant systemic treatment in node-positive patients (see below). Although node positivity cannot be considered a significant risk factor for local failure using current treatment strategies, it is likely that most inoperable local recurrences after breast-conserving therapy occur in patients with extensive nodal involvement [7].

Macroscopic multiplicity

The presence of gross multicentric disease is considered a contraindication to breast conservation, although almost no clinical data are available to substantiate this notion. Certainly patients with diffuse mammographic malignant calcifications or multiple gross tumour masses are seldom treated with conservative surgery and radiotherapy. A small number of patients with clinically or mammographically multifocal tumours, or tumours which consisted of more than one separate nodule on gross pathological examination, were treated with conservative surgery and irradiation at the Cancer Institute in Marseille. The local recurrence rates in these patients were approximately twice as high as in patients with unifocal tumours [26]. This study confirms the greater risk associated with macroscopically multiple tumours, although it remains open to debate under which circumstances such tumours can be safely treated with breast conservation.

Biological markers

Despite the fact the oestrogen and progesterone receptors have been routinely available for more than a decade, there are few data published on their possible influence on the risk of recurrence in the breast. Evaluation of receptor data with regard to local failure is difficult, since the frequency of observed recurrences can be confounded by interrelated factors such as menopausal status and hormonal manipulations. In a report from a large prospective study, hormone receptors had no relation to the risk of local failure [22]. In the Marseille study, oestrogen receptor negative patients failed more frequently in the breast than did patients with positive or unknown receptors, but this effect was not significant in multivariate analysis. There

was no effect of progesterone receptor status [27]. In the experience of the Joint Center for Radiation Therapy, breast failure at 5 years was 14% for oestrogen receptor negative tumours, compared with 9% for those with positive or unknown receptors, a non-significant difference [17]. Thus, at present, there is no evidence that hormone receptor status is useful as a risk factor for local recurrence.

A host of other biological features are under investigation as prognostic factors in breast cancer, including markers of cell proliferation, measures of tumour cell DNA content, growth factors, and oncogene amplification. To date there are no published studies on the possible influence of such factors on local failure risk.

Morphological features

Although 80–90% of breast cancers are classified as invasive ductal carcinomas, the limited data available suggest that standard breast-conserving therapy achieves local control rates with the less common histological types which are similar to those observed after treatment of infiltrating duct cancers [28]. Single institutional series of *in situ* carcinomas are generally small, and reliable information on long-term results has only recently been gained from the pooling of data from multiple centres. In a combined series of 261 non-invasive intraductal carcinomas selected for breast-conserving therapy, 5- and 10-year local control rates were comparable with those commonly reported for invasive breast cancers [29].

Because of their predilection for multicentricity, invasive lobular carcinomas may be preferentially excluded from breast conservation therapy. However, local control in patients selected for such treatment appears to be adequate, at least with 5-year follow-up. In a clinical-pathological study of 861 clinical stage I and II breast cancers, local failure at 5 years was 13.5% for invasive lobular and 9% for invasive ductal carcinomas respectively, an insignificant difference [28]. Similarly, in a report from Boston, 5-year local failure rates of 12% for invasive lobular and 11% for invasive ductal carcinomas were observed [30]. These satisfactory results reflect the effectiveness of breast irradiation. In the short-term results from a randomised trial, patients with lobular cancers whose radiotherapy was restricted to the primary tumour area had a breast failure rate of 21%, compared with 5% in patients receiving irradiation to the entire breast [6]. In the two previously cited series, however, lobular carcinomas appeared to have a greater tendency to late recurrence, and local recurrences tended to be more extensive than in invasive ductal cancers [28, 30]. A more reliable assessment of the risks associated with the conservation treatment of invasive lobular cancers thus awaits the accumulation of more extensive experience with longer follow-up.

Medullary carcinomas appear to have a particularly favourable response to radiotherapy, and are probably well-suited for conservative management [31]. In a small series of 27 typical medullary carcinomas, the 5-year local recurrence rate was 4% [28]. No local recurrences were observed after 79 months median follow-up of 10 patients with invasive colloid carcinoma [28].

Morphological risk factors for invasive ductal cancers have been most extensively studied, particularly the extent of intraductal carcinoma and its influence on local failure. Extensive intraductal component (EIC) was defined by investigators at Harvard University Medical School as being present when at least 25% of an invasive tumour mass was composed of intraductal cancer, provided that intraductal cancer could also be identified outside the limits of the main mass. The definition also includes tumours which are predominantly intraductal with foci of invasion [9]. Although varying definitions have been employed by different investigators, the original observation that tumours having a prominant *in situ* component are at high risk of failure in the breast has been since confirmed by several groups (Table 3).

Table 3. Crude rate of local recurrence in the breast as a function of the extent of intraductal carcinoma (DCIS) within the primary tumour in patients treated by local tumour excision and radiation therapy

Institution (reference)	Local recurrence (%) <25% DCIS	>25% DCIS
Harvard JCRT (34)	16/279 (5.7)	37/166 (22.3)
Marseille C.I. (35)	39/382 (10.2)	22/114 (19.3)
Institut Curie (32)	33/361 (9.1)	12/63 (19.0)
Westminster Hosp. (33)	21/213 (9.9)	13/59 (22.0)

Differences were statistically significant in each case.

Subsequent investigations suggest that EIC is an important marker of residual tumour burden following local excision of an apparently localised breast cancer. Patients undergoing re-excision of the primary tumour area following excisional biopsy showed a high likelihood of positive re-excision specimens for EIC+ tumours, particularly with regard to the presence of extensive residual intraductal cancer [36, 37]. In a study of serial subgross sections of mastectomy specimens, Holland *et al.* [38] showed that breasts with EIC+ tumours had a much higher likelihood than those with EIC− tumours to have residual carcinoma, predominantly intraductal, at any given distance from the edge of the primary tumour mass. In addition, the amount of residual intraductal cancer tended to be much more extensive in breasts with EIC+ tumours. It thus appears that EIC can be considered a marker for both the presence of residual tumour as well as for the quantity of residual cancer present, at least after a narrow local excision. The value of EIC as a risk factor may be less important in patients treated with very wide excisions such as quadrantectomy.

None of the other morphological features studied have proven to be as consistently reliable as EIC, nor are the gradations of risk associated with other factors generally as striking as those between EIC+ and EIC− tumours. In a large cooperative study comparing lumpectomy with or without irradiation, lymphatic vascular invasion was an important risk factor for local failure in unirradiated patients, but this effect became insignificant when radiotherapy was added [21]. In most studies to date patients with lymphatic vessel invasion were at higher risk of local failure [17, 24, 27, 32, 33], and in some instances this effect was marked [24]. As lymphatic invasion potentially represents a significant mechanism of local tumour extension, this remains a plausible risk factor for further study.

The evaluation of tumour grade as a risk factor is made difficult by the variety of grading systems used. With one exception [32], groups employing histological grading based on the Bloom-Richardson system show a clear correlation between increasing grade and local failure in the breast [24, 27, 33, 39]. Necrosis within the invasive cancer was found to correlate significantly with local recurrence risk in the Marseille study, but lost significance in multivariate analysis [27]. The interaction between EIC and the degree of intraductal necrosis was studied at the Westminster Hospital [33]. Tumours with both EIC and

extensive intraductal necrosis had the highest risk of local failure. This suggests that the presumed relative radioresistance of large necrotic intraductal foci may play a role in the high recurrence rate associated with EIC [40]. The presence of a moderate-to-marked lymphocytic stromal reaction was highly correlated with local recurrence in both the Marseille and Westminster series [27, 33], but this apparently has not been investigated by other groups. It is unclear whether the above features represent independent determinants of local recurrence risk, or whether their influence might be confounded by their coexistence with other, more important, and perhaps as yet unidentified factors.

It is important to note that an age-dependence in the prevalence of certain morphological risk factors has been shown by some authors. It is clear that the proportion of ductal cancers demonstrating EIC is greater in premenopausal patients [9, 27]. In the Marseille study, a particularly marked form of EIC was more frequently observed in patients younger than 40 years, who also had a higher incidence of high grade tumours and marked lymphocytic stromal reactions [10]. This age-dependence of risk factors may reflect the well-established correlation between age and local recurrence, and may allow identification of young patients at particularly high risk.

TREATMENT-RELATED FACTORS

Adequacy of surgical excision

The quality of surgical resection can be influenced by the type of primary excision technique employed, by the histopathological evaluation of the margins of excision, and by the use of re-excision. The relative merits of different types of wide local resection in comparison with the results of gross macroscopical tumour excision are difficult to assess outside of randomised trials, in that the endpoint to be studied is also influenced by a number of other patient, tumour and treatment characteristics. Nonetheless, a clear reduction in the rate of recurrences within or immediately around the tumour bed can be attributed to the use of quadrantectomy rather than excisional biopsy or lumpectomy, at least if no control of microscopical resection margins is carried out and re-excision is not performed. The 10-year cumulative risk of "true" or "marginal" recurrence was 4% in the Milan quadrantectomy series (5), compared with 10% in two large series using more limited excision techniques [1, 4]. These long-term results could be confirmed by preliminary data from a randomised clinical trial [41].

However, the value of very wide excisions such as quadrantectomy presumably relates to greater reliability in achieving microscopically negative margins of resection; pathological studies suggest that this can also be obtained in most T1 and T2 tumours with less generous, and cosmetically more acceptable resections [18]. It is now generally accepted that margins should be routinely assessed, although agreement is lacking as to how this evaluation should be performed [9, 21, 42]. Criteria for what constitutes "inadequate" margins are often arbitrary; nonetheless, most studies indicate that positive or close resection margins are correlated with a higher risk of local failure [19, 27, 32, 41]. In one large study in which no correlation between local recurrence and margin status was found, the dose of radiotherapy had been individualised as a function of the closeness of resection margins [43].

The status of excision margins is best considered a marker of residual cancer in the breast, rather than a precise indicator of the radicality of resection. Given the adequate local control of breast-conserving treatment, even in older series, it is likely that microscopical margins represent an important element only for a minority of patients, depending on the presence of other tumour-related risk factors. In a study of local recurrence related to the volume of excised tissue, Vicini *et al.* found local control in excess of 90% for both T1 and T2 tumours, independent of the resected volume, provided that EIC was not present [44]. For EIC+ tumours, however, only excisions in excess of 48 cm^3 for T1 tumours and 75 cm^3 for T2 tumours resulted in a comparable level of local control.

Concern about resection margins has given rise to the increased use of local re-excision, which is positive for residual cancer in 32–62% of patients suspected of having inadequate margins at initial resection [43]. It is likely that the examination of re-excision specimens can be used to assess risk, as this procedure may provide additional information regarding the amount of residual disease remaining in the conserved breast. In a study of 324 patients from Basel, patients in whom a re-excision was histologically negative had the same local failure rate (6%) as patients who had not required a re-excision; if tumour was found in the re-excision specimen, however, the local failure rate was 21% [45].

Adequacy of radiotherapy

Factors potentially influencing the effectiveness of radiation therapy include the delay between surgery and the beginning of treatment, the technique of whole breast irradiation, and the use of supplemental irradiation to the tumour bed ("boost"). In one study, local-regional recurrence was found to be significantly more frequent in patients beginning radiotherapy 7 or more weeks after conservative surgery, compared with those who started treatment more promptly [39]. The interval between surgery and radiotherapy is of increasing concern, as radiation treatment is frequently deferred several months until completion of adjuvant chemotherapy. In a retrospective study of 295 node-positive patients who received combination chemotherapy as part of initial treatment, the 5-year breast failure rate was 5% for patients beginning radiotherapy within 16 weeks after breast surgery, compared with 35% for patients whose radiation treatment was delayed longer than 16 weeks [46]. The question of timing of radiotherapy and chemotherapy is currently being addressed in a prospective randomised trial [9].

The effectiveness of external-beam whole-breast irradiation has been precisely quantified by a large randomised study. A dose of 50 Gy in 2 Gy fractions applied homogeneously to the entire breast after microscopically complete tumour excision results is a relative risk of intramammary recurrence of 0.22 compared with patients not receiving radiotherapy [22]. An increase in the total dose of whole-breast irradiation much beyond 50 Gy will not be possible without incurring the risk of unacceptable cosmetic results in a significant percentage of patients. It is not known to what extent the total dose may be reduced, or other fractionation programs employed, without adversely influencing the effectiveness of treatment. There is evidence suggesting that undue protraction of treatment, with weekly doses less than 8 Gy, may be associated with poorer local control [47]. As treatment techniques in most Western countries are quite standardised with respect to therapy equipment, definition of treatment volumes, dose and fractionation [48], it is unlikely that differences in the technical aspects of whole breast irradiation will prove to have marked influence on the risk of local failure.

The application of supplemental irradiation limited to the primary tumour area provides an opportunity to reduce the risk

of true or marginal recurrences, without significantly jeopardising the cosmetic result. Clinical dose–response data suggest a risk reduction of approximately 50% by the application of an additional 15 Gy [49]. Retrospective analyses of patients treated by tumourectomy and radiotherapy concluded that significantly higher local control was achieved if a total dose equivalent to 60–65 Gy in standard fractionation had been applied to the tumour bed [12, 39], and a large Canadian series indicated a reduction of 5-year local failure from 13% to 7% associated with boost irradiation of 10–15 Gy [11].

The application technique of boost irradiation remains controversial. Either external beam irradiation (either electrons or photons) or interstitial iridium-192 implantation may be used with satisfactory results. At present no comparative data exist which convincingly demonstrated a clear advantage for either method over the other [50]. The absolute risk reduction resulting from boost irradiation is likely to be modest compared with the marked benefit associated with whole-breast treatment, particularly in patients having had microscopically complete excision in the absence of tumour-related risk factors. The precise effect of boost treatment is currently evaluated in a prospective randomised trial by the EORTC Radiotherapy Group.

Effect of systemic therapies

Assessment of the effect of chemotherapy or hormone therapy on the risk of local failure is made difficult by differences in tumour-related characteristics between patients traditionally offered adjuvant systemic treatment and those treated with local-regional modalities alone. The first convincing evidence of a significant local effect of combination chemotherapy in conjunction with breast irradiation was provided by data from a large cooperative American study [25]. Patients treated by lumpectomy and breast irradiation had a 8-year local failure rate of 12% when no adjuvant chemotherapy was administered (node-negative patients), compared with 6% in conjunction with chemotherapy (node-positive patients). This presumably additive effect of chemotherapy and breast irradiation was apparent despite the inherently high local failure risk of node-positive patients compared with node-negative patients when only chemotherapy but no radiotherapy was administered (43% vs. 37%). This observations are supported by retrospective data from older series [9, 15]. In addition, preliminary data from a randomised trial suggest that the administration of tamoxifen to oestrogen receptor-positive patients results in a lower rate of local failure in patients treated with standard breast-conserving therapy [51]. It is unknown whether an interaction between radiotherapy and systemic agents is operative in this setting, or whether the observed effects are simply additive, nor is it clear whether the sequencing of treatments is important.

CONCLUSIONS

Extensive investigation over the past decade has uncovered only a relatively small number of factors which appear to significantly influence the risk of local failure after macroscopically complete excision and radiotherapy for T1 and T2 breast cancers. It is clear that recurrence risk is a decreasing function of age, and that premenopausal patients comprise the group at greatest risk (Table 1). Efforts to define tumour-related factors that might allow identification of high-risk subgroups have met with a certain success. The only feature thus far identified which reproducibly predicts for a higher local failure risk is extensive intraductal component (Table 3). EIC has been shown to be a marker for the extent of residual cancer after limited local excision. However, in most series EIC accounts for less than half of local recurrences, and reliable risk factors for the definition of other high-risk subgroups have not been clearly identified.

If whole-breast radiotherapy is given according to current standards, treatment-related factors are likely to have modest effect on the overall risk of local failure. Quadrantectomy studies have shown that local control can be improved by very wide excision, but it is unclear which subgroups benefit from this procedure. It is likely that equivalent results can be obtained by lumpectomy in most patients, if particular attention is paid to microscopic resection margins. Wider re-excision can be selectively employed, especially in cases with tumour-related risk factors, particularly EIC. It is likely that supplemental irradiation to the tumour bed will also reduce risk, and modest reductions in local failure have been demonstrated with effective systemic therapies.

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