Local Recurrence After Mastectomy or Breast-Conserving Surgery and Radiation

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Approximately 10% to 15% of patients with stage I/II invasive breast cancer will develop a clinically isolated local recurrence. The standard management of an ipsilateral breast tumor recurrence following breast-conserving surgery and radiation is salvage mastectomy, while local excision and radiation are optimal treatment of a chest wall recurrence following initial mastectomy. Although there are few data regarding the efficacy of systemic therapy after isolated local relapse, chemotherapy and/or hormonal therapy should be considered for most patients because of the high risk of subsequent distant relapse. However, local relapse does not always herald distant metastases. A prolonged interval between initial treatment and local recurrence is the most important prognostic factor for subsequent outcome, and when combined with other favorable characteristics, can predict 5-year survival rates of 70% or higher. [ONCOLOGY 14(11):1561-1581, 2000]

Introduction

The isolated local recurrence in a patient previously treated for early-stage invasive breast cancer presents a unique challenge to the oncologist. The management of each patient requires a multidisciplinary approach that depends not only on factors specific to the recurrence itself but also on factors related to the original treatment. There is a paucity of clinical information, almost none prospective or randomized, to guide the clinician in choosing the optimal combination and sequence of surgery, radiation, and/or systemic therapy.

The clinical significance of an isolated local recurrence as a first event after treatment of early-stage invasive breast cancer, and its impact on survival, remains controversial. There is a strong association between local recurrence and the appearance of simultaneous or subsequent distant metastases. In many cases, local recurrence may be a manifestation of a more aggressive tumor biology that heralds the presence of distant metastases. Regardless of this association, durable local salvage is important in preventing the consequences of uncontrolled locoregional disease. However, if distant metastases are a common but not universal outcome after clinically isolated local recurrence, there may be a subgroup of patients for whom successful local salvage could result in long-term disease-free and overall survival.

The purpose of this review is to analyze the incidence and risk factors for local recurrence after initial treatment of invasive breast cancer. The risk factors for local recurrence will be compared for stage I/II breast cancer patients treated with breast-conserving surgery and radiation and stage I–IIIA breast cancer patients treated with mastectomy. Multidisciplinary management of an isolated chest wall recurrence after mastectomy and an ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery and radiation will be discussed separately. Regional recurrences and their management will not be addressed. Outcome and independent prognostic factors after salvage of a local recurrence will be reviewed, with particular attention given to the association between the clinically isolated local recurrence and subsequent distant metastases.

Incidence of Local Recurrence

Approximately 10% to 20% of patients with stage I/II invasive breast cancer will develop an IBTR within 10 years of breast-conserving surgery and radiation.[1-14] However, a similar percentage of all patients (10%–20%) with stage I–IIIA invasive breast cancer will experience chest wall failure, with
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or without simultaneous regional failure, within 10 years of undergoing mastectomy.[1,3,8,15-19]

TABLE 1

Table 1 shows data from six prospective randomized trials comparing breast-conserving surgery and radiation with mastectomy in stage I/II invasive breast cancer. Four of these trials report similar risks of local failure associated with these two methods of treatment for early-stage invasive breast cancer. The National Cancer Institute (NCI) and the European Organization for Research and Treatment of Cancer (EORTC) trials reported significantly higher rates of local failure for patients treated with breast-conserving surgery and radiation, compared to those treated with mastectomy. Inadequate surgery for the primary may have contributed to the higher rate of IBTR in these trials, since only gross removal of the tumor was required. For example, in the breast-conserving surgery arm of the EORTC trial, 81% had T2 tumors, and 48% of all patients had microscopically positive margins.

Factors Associated With Increased Risk of Local Failure

Clinical Risk Factors for Chest Wall Failure

• Young Age—Age groups of 35 years or less and 40 years or less have been associated with an increased risk of locoregional recurrence after mastectomy.[20-22] Lewis and Reinhoff[20] reported a crude local recurrence rate of 67% for patients aged 20 to 29 years and 41% for patients aged 30 to 39 years in an early radical mastectomy series, whereas in women aged ≥ 40 years, local failure rates were 21% to 25%. In another radical mastectomy series, Donegan et al[21] observed a similar crude failure rate of 67% for ages 20 to 29 years and 46% for ages 20 to 39 years, compared with < 25% for those ≥ 40 years of age. Mathews et al[22] reported that the crude rate of locoregional failure after mastectomy doubled with younger age; ie, from 6% to 7% for ages > 35 years to 12% for ≤ 35 years. However, in a more recent report from the same institution, the locoregional failure rate at 5 years was only 7.4% after modified radical mastectomy in 140 patients aged ≤ 35 years.[23] Studies using multivariate analysis to account for other known prognostic factors have shown that age may not be an independent predictor of locoregional recurrence.[16, 24-26] Recht et al[26] demonstrated on multivariate analysis that the number of positive axillary nodes and total number of nodes examined—but not age—were significant independent factors for locoregional recurrence. Pisansky et al[16] also used multivariate analysis to show that tumor size, nodal status, and estrogen-receptor (ER) status, not age, were significant independent factors for locoregional recurrence.

• Tumor Size—Patients with tumors ≥ 5 cm have a 25% or higher risk of isolated locoregional recurrence after mastectomy with or without adjuvant systemic therapy.[16,18,21,25-30] Tumors < 5 cm are not associated with an increased risk of chest wall recurrence, and there is no significant distinction between T1 or T2 tumors in most studies.[1,18,25,26]

• Gross Multifocal/Multicentric Disease—Multifocal or multicentric disease does not increase the risk of local failure after treatment by mastectomy. In a series of 57 patients with gross multicentric disease treated by mastectomy, Fowble et al [31] reported a low (< 10%) risk of chest wall recurrence in the absence of ≥ 4 positive nodes or T3 tumor size.

• Genetic Factors—Whether the presence of a BRCA1 or BRCA2 mutation increases the risk of chest wall failure following mastectomy is presently unknown.

Histopathologic Risk Factors for Chest Wall Failure

• Nodal Status—Patients with 4 or more positive axillary lymph nodes have a 25% or higher risk of
developing isolated locoregional recurrence after mastectomy with or without adjuvant systemic therapy.[16,18,21,25-29] There is controversy regarding the risk of chest wall recurrence in the subgroup of patients with 1 to 3 positive nodes, with three randomized trials from the Danish Breast Cancer Cooperative Group (DBCG) and the British Columbia Cancer Agency recently reporting rates of 30% or more.[28,29,32] This rate is significantly higher than the ≤ 15% risk predicted from historical mastectomy series for patients with 1 to 3 positive nodes.[33] The low number of axillary nodes—medians of 7[28, 29] and 11[32]—in the dissection specimens in these trials may be an important factor in the high risk of locoregional recurrence. According to a statistical model reported by Iyer et al[34], inaccuracy of the staging of a patient with ≥ 4 positive nodes vs 1 to 3 positive nodes increases as fewer total nodes are removed. For example, the model predicts that in order to have a 90% probability of accurately ruling out 4 or more positive nodes, a patient with 1, 2, or 3 positive nodes and a T1 tumor size would need 8, 15, or 20 nodes examined, respectively. Viewed in another way, the odds that a patient with a T1 tumor and 1, 2, or 3 positive nodes but with only 7 nodes examined actually has 4 or more positive nodes are 13%, 55%, or 93%, respectively. The model suggests that these randomized trials found higher rates of locoregional recurrence in patients with 1 to 3 positive nodes because a significant number were understaged by the small median number of nodes removed. There is also clinical support for this theory in the literature. Benson and Thorogood[35] reported a prospective nonrandomized trial of total mastectomy with either an axillary dissection or axillary sampling. The locoregional recurrence rate at 5 years was 11.7% after axillary dissection, compared with 19.4% in those with only axillary sampling (P = .0019). Recht et al[26] found that a greater number of nodes examined—from 2 to 5, 6 to 10, or ≥ 11—was associated with a decreased risk of locoregional failure that was independent of the number of positive nodes on multivariate analysis. In another series of 404 mastectomy patients with T1-2 tumors and 1 to 3 positive nodes, Katz et al[36] reported a locoregional recurrence risk of 24% with less than 10 nodes removed vs 11% for 10 or more nodes removed (P = .02). These factors may account for the 30% or higher rates of locoregional recurrence in the Danish and British Columbia series that would be more usual for patients with 4 or more positive nodes. The largest reported series of patients with 1 to 3 positive nodes treated with mastectomy and adjuvant systemic chemotherapy has recently been updated by Recht et al.[26] Among 983 patients with T1-2 tumors and 1 to 3 positive nodes, the 10-year cumulative incidence of local failure was only 8%. • Extracapsular Extension—The presence of extracapsular nodal extension has been associated with an increased risk of locoregional recurrence following mastectomy.[27,36,37] However, the presence of extracapsular nodal extension is a risk factor for chest wall recurrence and is not associated with an increase in the risk of axillary failure.[37,38] Kuske et al[37] reported that in the subgroup of patients with 1 to 3 positive nodes, extracapsular extension was associated with a 17% risk of chest wall failure, compared with a 7% risk among those without extracapsular extension (P = .08). However, nodal recurrence was rare with or without the presence of extracapsular extension. For patients with 4 or more positive nodes, extracapsular extension was not associated with a further increase beyond the already high rate of chest wall failure (22% vs 26%, P = .47). In other studies, extracapsular extension has been significantly related to the number of positive nodes, but was not an independent factor for chest wall or axillary recurrence following mastectomy.[39,40] • Margin Status—There is a paucity of data regarding the importance of margins after mastectomy for determining the risk of subsequent local relapse. Deep invasion of the pectoral fascia has been associated with an increased risk of local recurrence after mastectomy with or without chemotherapy.[21,41] Freedman et al[42] found a 28% risk of chest wall failure at 8 years after mastectomy with a margin ≤ 5 mm in women aged 50 years or less, who otherwise were considered at low risk for locoregional recurrence because of a tumor size < 5 cm and 0 to 3 positive nodes. In a series of node-positive postmenopausal women treated by mastectomy and tamoxifen (Nolvadex), Fisher et al[43] found that a positive margin was a significant predictor of locoregional recurrence on multivariate analysis. However, a close or positive margin after mastectomy has not been associated with a high risk of chest wall failures in all series.[27,44,45] For example, in a series of T1-2 node-negative women treated by mastectomy, Ahlborn et al[45] observed a crude rate of local recurrence of 6% with margins ≤ 4 mm compared with 3% with margins > 4 mm, but the difference was neither clinically nor statistically significant. Mentzer et al[44] reported outcomes from a series of patients with stage II disease (two-thirds with positive nodes) who were treated by modified radical mastectomy, with or without systemic therapy. Two-thirds of these patients were assessed using gross margins, which is less accurate than
microscopic assessment,[42] and one-quarter also received postmastectomy radiation, which minimizes the rate of chest wall failure with a close or positive margin.[46] The crude local recurrence rate was nearly four times higher in patients with a margin of 5 mm or less compared to patients with margins greater than 5 mm (11% vs 3%), but this finding was not statistically significant.

In another series of 608 patients treated with mastectomy, with or without systemic therapy, and postmastectomy chest wall irradiation in 8%, Jager et al.[27] found no statistical difference in locoregional recurrence between 57 patients with close (< 5 mm) or positive margins and 551 patients with negative margins.

• **Extensive Intraductal Component**—Extensive intraductal component has been defined as intraductal carcinoma occupying more than 25% of the area encompassed by the invasive tumor and extending beyond the infiltrating edge of the tumor into surrounding breast tissue, or present in random sections of grossly unremarkable breast tissue.[47] While an important prognostic factor for patients treated with breast-conserving surgery, the presence of an extensive intraductal component has not been associated with an increase in chest wall failure following mastectomy.[48]

• **High Grade**—Few studies have addressed the significance of high histologic grade, but this factor has been associated with an increased risk of locoregional recurrence after mastectomy in some series.[49,50] O’Rourke et al.[50] reported on a series of 966 patients treated with mastectomy, without radiation or systemic therapy, for breast cancer tumors smaller than 5 cm in diameter. More than half of the patients were node positive. The risk of a chest wall recurrence was 16%, 21%, or 27% for grade I, II, or III tumors, respectively. These differences remained significant on multivariate analysis, as did lymph node status and lymphovascular invasion.

• **Lymphovascular Invasion**—There is a paucity of data regarding lymphovascular invasion and the subsequent risk of chest wall recurrence after mastectomy. In the aforementioned series of mastectomies for T1-2 tumors investigated by O’Rourke et al.[50] there was a 36% risk of chest wall recurrence with lymphovascular invasion, compared to a 19% risk without lymphovascular invasion. This difference remained significant on multivariate analysis, as did lymph node status and tumor grade.

• **Oncogenes and Tumor-Suppressor Genes**—Most of the literature on HER2/neu and p53 expression discusses the impact of these genes on overall recurrence or survival, with less information available about their impact on local control. Pierce et al.[51] reported on a series of 107 patients with known HER2/neu overexpression who were treated with either breast-conserving surgery and radiation or mastectomy. In those treated with mastectomy, there was no difference in the subsequent chest wall failure rate, with or without overexpression. In contrast, Zellars et al.[52] found that p53-positive patients had a higher risk of local failure after mastectomy—with or without radiation—that remained significant on multivariate analysis.

• **Estrogen-Receptor Status**—Negative ER status, alone or in combination with negative progesterone receptors, has been associated with an increased risk of chest wall recurrence after mastectomy.[16,25,26,43]

• **Adjuvant Systemic Therapy**—Adjuvant systemic chemotherapy has been associated with a modest decrease in the risk of chest wall recurrence after mastectomy.[26,33,35,53,54] Bonadonna et al.[53] updated a randomized trial of CMF (cyclophosphamide, Cytoxan, Neosar), methotrexate, fluorouracil) vs observation in 386 node-positive women treated with radical mastectomy. Patients in the trial received no adjuvant radiation or endocrine therapy. At 20 years, there was no significant difference (15% vs 13%) in the rate of locoregional recurrence as a first event, with or without chemotherapy. Tamoxifen alone or when added to chemotherapy also produces a modest reduction in the risk of chest wall recurrence.[26,33] Fisher et al.[55] reported the 10-year results from a trial by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 in which node-negative patients with ER-positive tumors were randomized to tamoxifen or observation. Of the 2,818 women entered into the trial, 62% were treated with mastectomy. The rate of local failures in the chest wall and scar as a first event decreased from 5% to 2% (P < .0001).

Goldhirsch et al.[56] reported a meta-analysis of five trials of adjuvant systemic therapy in node-positive patients treated by mastectomy without radiation. Approximately 2,108 patients received adjuvant systemic chemotherapy with (815) or without (1,293) tamoxifen or with oophorectomy (166), and 722 patients received no systemic therapy or only one cycle of chemotherapy. The 10-year cumulative incidence of local relapse as a first event was 8% vs 16%.

**Clinical Risk Factors for IBTR**
• **Young Age**—Patient ages of 35 years or less and 40 years or less have been associated with an increased risk of IBTR following breast-conserving surgery and radiation in most series.[4,5,7,12-14,23,57-64] This finding may be due partly to the association of young age with other factors predictive of IBTR, including an extensive intraductal component and close or positive resection margins.[58] Cowen et al[65] reported a 55% rate of IBTR in women 40 years old or younger with positive margins, although this finding was not significant on multivariate analysis. Freedman et al [unpublished data] conducted a recursive partitioning analysis to identify subgroups of patients at different levels of risk for IBTR. They found a significant dependence upon margin status in women aged 35 years or less with extensive intraductal component–negative tumors; the risk of developing IBTR at 10 years was only 3% with negative margins, compared with 34% for those with close or positive margins. Women ≤ 35 years old with extensive intraductal component–positive tumors had a 75% risk of IBTR, regardless of margin status. However, there is no evidence to suggest that women ≤ 35 years old have improved local control or disease-specific survival after mastectomy, as compared to breast-conserving surgery and radiation.[23]

• **Tumor Size**—For clinical tumors ≤ 5 cm that are eligible for breast-conserving surgery and radiation, there is no significant difference in the risk of IBTR between T1 and T2 tumors.[4,8,12,13,61,63,65,66] Little information is available on the risk of IBTR for operable T3 breast cancers treated with immediate breast-conserving surgery and radiation. In one series of 470 patients with operable stage III breast cancer, Toonkel et al[67] reported IBTRs in 2 (6%) of 34 patients treated with breast-conserving surgery and radiation after a mean follow-up of 8 years. Khanna et al[68] also reported that only 3 (8%) of 36 selected patients with T3 tumors developed an IBTR after a median follow-up of 46 months. Fortin et al[5] reported a 16% IBTR rate for T3 tumors, compared to 10% for T1 or T2 tumors, with a median follow-up of 5.2 years. More data are available on the use of neoadjuvant chemotherapy for T3 tumors with breast-conserving surgery and radiation offered to responding patients. In NSABP B-18, 13% of 1,523 patients had a T3 tumor size and were randomized to preoperative or postoperative chemotherapy.[69] Following chemotherapy, 33% of the T3 tumors were treated with breast-conserving surgery and radiation, compared to only 9% of those randomized to postoperative chemotherapy. The study showed a statistically significant increase in the rate of IBTR (14% vs 7%) for tumors that were downstaged by chemotherapy to become eligible for breast-conserving surgery and radiation, compared with those initially felt to be candidates for breast conservation prior to chemotherapy.[70] Although the results for T3 tumors were not reported separately, it is likely that a significant portion of the group that was downstaged and rendered eligible for breast conservation were those with tumors that were initially staged as T3.

In contrast, Danforth et al[71] reported no IBTRs in 18 patients treated with radiation after a clinical and pathologic complete response to induction chemotherapy from an initial group of 57 patients with stage IIIA disease. From a group of 84 women with tumors > 5 cm, Bonadonna et al[72] treated 52 chemotherapy responders with quadrantectomy and radiation; at 8 years, the IBTR rate was 4%. After a median follow-up of 41 months, Ellis et al[73] reported that there was a 7% risk of IBTR in responding patients treated with breast-conserving surgery and radiation after induction chemotherapy. However, Buzdar et al[74] selected 15 patients who responded to induction chemotherapy for breast-conserving surgery and radiation (from an original group of 60 women with T3 tumors) and found a 20% rate of IBTR after a median follow-up of only 43 months. In summary, the majority of T3 tumors remain ineligible for breast conservation, even after induction chemotherapy. Mastectomy should remain standard treatment for initial T3 tumors until the optimal selection factors, guidelines for treatment, and long-term rates of IBTR can be further defined.

• **Gross Multifocal/Multicentric Disease**—Clinically detected multifocal or multicentric disease, whether presenting as more than one palpable mass or as a mammographic abnormality, has been associated with nearly a 40% risk of IBTR.[75-77] A closer distance between separate clinically detected tumors has not been shown to be a predictor for a lower risk of recurrence.[75] The risk of IBTR may not be increased by the presence of multifocal disease first detected by the surgeon intraoperatively.[77] When detected by the pathologist on gross pathologic inspection, multifocal disease has generally been associated with a 20% to 36% risk of IBTR.[4,13,65,75,77] However, the risk of IBTR may be minimized after radiation with gross pathologic multifocal disease by selection of extensive intraductal component–negative tumors resected with negative margins.[78]

• **Genetic Factors**—In contrast to findings in the mastectomy setting, data show that a genetic mutation does not increase the risk of IBTR at 5 years following breast-conserving surgery and...
radiation. Chabner et al[79] reported on a series of 201 women aged 36 years or less treated by breast-conserving surgery and radiation, 29 of whom had a family history suggestive of inherited breast cancer but no documented BRCA1 or BRCA2 mutations. The crude 5-year local failure rate was lower in the subgroup with a strong family history (14% vs 3%), although this difference did not reach statistical significance.

Pierce et al[80] reported a study of 73 women with known BRCA1 or BRCA2 mutations treated with breast-conserving surgery and radiation. There was no significant difference in the local failure-free survival at 5 years between these 71 patients and a matched similarly treated cohort of 219 patients with presumed sporadic breast cancer (99% vs 96%).

In another series of 28 Ashkenazi women with known BRCA1 and/or BRCA2 mutations, Robson et al[81] reported IBTR rates of 15% at 5 years and 22% at 10 years, compared with rates in controls without the mutations of 5% and 7%, respectively. The difference in IBTR at 10 years did not reach statistical significance ($P = .25$). Women with mutations were more likely to be under the age of 50 years, which itself was the only significant variable associated with the risk of IBTR.

Seynaeve et al[82] reported on the risk of IBTR following breast-conserving surgery and radiation in a series of 79 patients with hereditary breast cancer based on BRCA1 or BRCA2 mutations (18 patients) or a strong family history of three or more first-degree relatives with breast/ovarian cancer (61 patients). The risk of IBTR at 5 years was 14%, compared to a rate of 5% observed in 79 matched controls of presumed sporadic breast cancers. However, the magnitude of this difference continued to increase to 27% with longer follow-up at 10 years and to 48% at 13 years in hereditary cases, compared with only 18% in controls ($P = .09$).

Turner et al[83] found that 8 (15%) of 52 patients with IBTR following breast-conserving surgery and radiation retrospectively tested positive for BRCA1 or BRCA2 mutations. The mean time to IBTR in these women was 8.7 years, compared with an interval of 4.3 years for the overall population. In addition, differences between relapse histology and location in the breast compared to the original tumors suggested that the majority of these IBTRs were actually new primaries in the treated breast. Therefore, 5-year rates of IBTR should be viewed with caution, and additional studies with 10-year follow-up will be needed to define the risk of IBTR—whether a true recurrence or a new breast primary—in patients with genetic mutations.

**Histopathologic Risk Factors for IBTR**

- **Nodal Status**—Compared with node-negative patients, patients with node-positive disease do not have an increased risk of IBTR following breast-conserving surgery and radiation and are generally at lower risk because of the combined use of adjuvant systemic therapy.[2,4,8,12,54,59,61]

- **Extracapsular Extension**—In patients undergoing breast-conserving surgery, axillary dissection, and radiation, extracapsular nodal extension is not associated with an increased risk of IBTR.[84,85]

However, just as in the mastectomy setting, extracapsular extension is more prevalent in patients with a higher number of positive nodes but not an independent factor for axillary recurrence following breast-conserving surgery and radiation.[84,85]

- **Margin Status**—In most series, the presence of positive resection margins is associated with a two to three times increased risk of developing IBTR (compared to negative margins) following breast-conserving surgery and radiation.[5,7,54,62,65,86-90] There is controversy regarding the impact of a close margin on the risk of IBTR, with close margin defined variously as cancer cells within a distance of 1 mm[62,89,91] or 2 mm[86-88,90,92,93] but not involving the resection edge. Obedian et al[90] found the relapse-free survival rate was the same 98% at 10 years with close ($\leq$ 2 mm) or negative margins.

In a retrospective series from the Joint Center for Radiation Therapy, Park et al[89] reported the same crude rate of IBTR (7%) at 8 years with close ($\leq$ 1 mm) or negative margins. However, in a prospective trial reported by Recht et al from the same institution, a close ($\leq$ 1 mm) margin was a significant predictor of IBTR in a randomized trial of sequencing chemotherapy before or after radiation following breast-conserving surgery.[91] The overall crude 5-year risk of IBTR with close margins ($\leq$ 1 mm) was 11%, compared to 3% with negative margins, with a greater risk of IBTR observed in patients receiving chemotherapy before radiation (23% for $\leq$ 1 mm vs 0% for negative margins).

Peterson et al[93] reported an 8-year actuarial IBTR risk of 17% with close ($\leq$ 2 mm) margins, compared to 8% with negative margins, although this did not reach statistical significance. Freedman et al[86] reported no significant difference in the 5-year cumulative incidence of IBTR at 5 years with a close or negative margin, although by 10 years, a significant difference became apparent (14% vs 7%, respectively, $P = .04$). A long delay of 10 years or more until the rates of IBTR
with close margins diverge from those of negative margins has also been shown in other series.[87,88]

- **Extensive Intraductal Component**—The presence of an extensive intraductal component—positive tumor has been associated with an increased risk of IBTR following breast-conserving surgery and radiation, although this effect is minimized by more extensive breast-conserving surgery and wide negative margins.[4,54,59,63,86,88,89]
- **High Grade**—High histologic grade has been variably associated with the risk of IBTR following breast-conserving surgery and radiation, with an increased risk reported by some series[65,94] but not others.[4,13,95]
- **Lymphovascular Invasion**—Lymphovascular invasion has been associated with an increased risk of IBTR in many[13,14,59,62,94] but not all[4,12,65] series.
- **Oncogenes and Tumor-Suppressor Genes**—Similar to the mastectomy setting, there is a paucity of data addressing the impact of HER2/neu or p53 expression on the risk of local failure. Haffty et al[96] reported a case-control study in which 56% of patients with IBTR had overexpression of HER2/neu in the original tumor, compared with only 18% of matched control patients without IBTR. However, Pierce et al[51] reported a series of 107 patients with known c-erbB-2 expression treated with either breast-conserving surgery and radiation or mastectomy. The risk of IBTR was 8% with overexpression, compared to 24% with no overexpression. Silvestrini et al[97] found p53 overexpression was associated with a higher risk of IBTR following breast-conserving surgery alone but not following breast-conserving surgery with radiation.
- **Estrogen-Receptor Status**—Estrogen-receptor–negative tumors have not had a higher risk of IBTR following breast-conserving surgery and radiation in most series.[7,13,57,66]
- **Adjuvant Systemic Therapy**—The risk of IBTR has been reported to decrease with the use of adjuvant chemotherapy in subgroups of patients with node-positive disease[2,8,54,59] or focally positive margins[89] following breast-conserving surgery and radiation. Adjuvant tamoxifen has also been associated with a significant decrease in the rate of IBTR following conservative surgery and radiation.[5,12,55,98-101] Cowen et al[13,65] reported that adjuvant hormone use increased local recurrence-free survival with positive margins but not with negative margins up to 10 years following breast-conserving surgery and radiation without chemotherapy. Freedman et al[86], using a cumulative incidence methodology, also showed no significant decrease in IBTR at 5 or 10 years with adjuvant systemic therapy in patients with negative margins. However, in patients with positive margins, adjuvant systemic therapy was associated with a lower rate of IBTR at 5 years (compared with no adjuvant systemic therapy) but no significant decrease in the ultimate 10-year cumulative incidence of IBTR.

**Summary**

TABLE 2

Factors Related to Risk of Chest Wall Recurrence After Mastectomy for Stage I-IIIA or Ipsilateral Breast Tumor Recurrence After Breast-Conserving Surgery and Radiation for Stage I/II Breast Cancer

Differences between the clinical and histopathologic risk factors associated with local recurrence following breast-conserving surgery and radiation or mastectomy are shown in Table 2. Significant factors contributing to an increased risk of local recurrence following either treatment are tumor size ≥ 5 cm, close or positive margins, young age ≤ 35 to 40 years, and lymphovascular invasion. Factors that increase the risk of chest wall recurrence but not IBTR include 4 or more positive axillary nodes, ER negativity, and p53 positivity. The few studies addressing high histologic grade suggest
that there is an increased risk of chest wall recurrence but a variable association with IBTR. Extracapsular extension, particularly in those with 1 to 3 positive nodes, may also have an impact on chest wall recurrence but not on IBTR. In contrast, gross multicentric disease or extensive intraductal component positivity increases the risk of IBTR but not chest wall recurrence. Patients with hereditary breast cancer are not at increased risk of developing IBTR within 5 years, but there are no data regarding its prognostic value for chest wall failure. Tumor size < 5 cm, adjuvant systemic chemotherapy, and HER2/neu overexpression are associated with a low risk of local recurrence after either treatment.

Local Recurrence After Mastectomy

Characteristics

Approximately 10% to 20% of patients with stage I–IIIA breast cancer will have a chest wall recurrence alone or as a component of failure within 10 years of undergoing mastectomy.[1,3,8,15-19] The median time to local recurrence after mastectomy is 2 to 3 years,[1,17,18,21,102-106] although a delay in recurrence has been observed in ER-positive patients and with the use of adjuvant tamoxifen.[16,107] The location of a chest wall recurrence is not specified in most series, but involvement of the mastectomy scar has been reported to vary from a low of 23% of cases to a high of 70% of cases.[21,102,105] More than half of patients with chest-wall-only recurrences present with solitary nodules, and the remainder have more than one nodule or diffuse chest wall disease.[50,102,105,108] The majority of these locoregional recurrences involve the chest wall alone or occur simultaneously with regional nodal failure.[3,17,18,27,102-105,108-110] There is wide variability—from 10% to 60%—in the reported incidence of simultaneous locoregional and distant recurrence.[1,8,16,17,19,26,29]

Treatment

A multidisciplinary approach is required for the management of a chest wall recurrence after mastectomy. Overall, local control is achieved after salvage of chest wall failures in 43% to 86% of patients.[15,102,104,108,109] There is a high risk (> 50%) of subsequent distant metastases following a clinically isolated chest wall recurrence after initial mastectomy.[1,17,18,21,103,105,109-111]

- **Surgery**—Wide local excision of all gross disease is recommended whenever possible for solitary or multiple nodules amenable to resection.[21,103,104,106,112] Wide excision alone has been associated with a second local recurrence in over 60% to 70% of patients, despite its use in a more favorable group of patients with smaller tumor sizes and solitary nodules, compared to patients typically managed with surgery and radiation or radiation alone.[15,21,106] The excision of gross disease serves the purpose of both maximizing subsequent local control and moderating the required dose of chest wall irradiation. A negative resection margin is preferable, although there are no data on the risk of subsequent second chest wall relapse with a close or positive margin, as compared with a negative margin.

- **Radiation**—Chest wall irradiation is recommended for patients after wide local excision if there is no history of previous postmastectomy radiation as part of their initial breast cancer treatment.[21,103,104,106,107,109,112] Halverson et al[109] reported that all of their chest wall recurrences < 3 cm that were excised prior to irradiation were controlled locally with doses of 45 to 59 Gy. Schwaibold et al[102] reported that 48% of patients had locoregional control after wide excision and radiation. In that series, no dose-response effect was observed above 50 Gy when irradiating after a gross total excision. Even for small isolated recurrences that are completely excised, the whole chest wall and area of recurrence should be treated rather than just small limited-sized fields.[105] Some have reported boosting the dose to the mastectomy scar or site of local recurrence,[103,104] but it is unclear if this contributes to an improvement in local control.

For isolated chest wall recurrences, the supraclavicular nodes should be electively treated concurrently with the entire chest wall because of the increased risk of subsequent relapse without radiation.[109] Elective irradiation of a clinically uninvolved axillary or internal mammary node region is not necessary.[109] The response rate to salvage chest wall irradiation after less than an excisional biopsy is high (73% to 96%), but approximately 60% to 70% will subsequently experience...
Schwaibold et al[102] reported a dose-response effect with doses of 60 Gy or higher for local control of tumors ≤ 4 cm, but only 30% of larger or diffuse unresectable disease was controlled even with doses as high as 70 Gy. There is no benefit to hyperfractionated chest wall radiation, with or without complete excision of gross disease.[104]

- **Systemic Therapy**—Systemic therapy should be considered for most patients following treatment of a clinically isolated chest wall recurrence.[103,104,106,112] As previously noted, the majority of patients are at risk for a subsequent second local recurrence and/or distant metastasis. Schwaibold et al[102] reported improved locoregional control after excision and radiation of isolated locoregional recurrence with the addition of systemic chemotherapy (78% vs 38%, \( P = .15 \)). These investigators also found a nonsignificant trend to improvement in relapse-free and overall survival with the use of chemotherapy, but only in the subgroup of patients treated with wide excision and radiation.

In another retrospective series, Halverson et al[113] found that the addition of hormonal therapy after local recurrence significantly improved disease-free and overall survival. Nevertheless, chemotherapy but not hormonal therapy was associated with a trend toward improved locoregional control.

Haylock et al[103] reported a nonsignificant trend towards improvement in overall survival (62% vs 51% at 10 years, \( P = .24 \)) in one cohort treated with immediate chemotherapy, compared to another control cohort treated without initial chemotherapy. Based on this trial, chemotherapy should be sequenced following radiation, with or without wide excision, in order to permit full delivery of the chest wall irradiation.[103]

Hsi et al[107] studied a series of 18 patients selected for favorable prognostic factors following initial mastectomy and isolated locoregional recurrence. The rates of subsequent disease-free survival were 83% with tamoxifen, compared to 33% without. The only randomized trial in this setting has been reported by Borner et al.[114,115] Patients with ER-positive isolated locoregional recurrence, or with a disease-free interval > 1 year and less than four tumor nodules (none greater than ≤ 3 cm), were randomized to tamoxifen or placebo after complete local excision and radiation. The incidence of second local failure at 5 years was significantly reduced—from approximately 30% to 10%—in patients randomized to receive tamoxifen (\( P < .001 \)). There was no significant overall survival benefit demonstrated with the use of tamoxifen.[114]

However, a later subset analysis of the trial showed an improvement in the 5-year disease-free survival (29% vs 60%) and overall survival (71% vs 78%) of postmenopausal women treated with tamoxifen. In this subgroup, there was a reduction in subsequent local failure (27% vs 9%, \( P < .001 \)) and distant metastases (30% vs 24%, \( P = .16 \)) as first events.[115] However, in premenopausal women, there was no improvement in disease-free survival (55% vs 57%), and there was an unexpected decrease in 5-year survival (90% vs 60%) for tamoxifen vs observation.[115]

**Prognostic Factors**

The prognosis for distant metastases and survival depends most upon interval to recurrence.[1,15,17,19,102,105,106, 108,110,111,114] The critical interval to recurrence that is associated with the highest risk of subsequent distant metastases and death is within 2 years from the time of initial mastectomy. In a recent update of the EORTC 10801 trial, van Dongen et al[1] observed that 73% of patients with clinically isolated locoregional recurrence < 2 years after mastectomy had subsequent distant metastases, compared to 35% for an interval ≥ 2 years. Other favorable prognostic factors for survival are an isolated chest wall relapse (as opposed to one with an associated regional failure).[15,105,109,110] a smaller initial tumor size, and/or less extensive initial nodal disease.[15,17,19,105, 108,109,111] Estrogen-receptor positivity has been associated with improved distant disease-free survival[15,103] or overall survival[19,105] in some series. The ability to achieve local control after salvage of an isolated chest wall recurrence has also been prognostic for survival in some series.[102,105]

Many studies have looked at combinations of factors that together may be more predictive of subsequent outcome compared to individual factors. Schmoeor et al[19] reported that 114 patients (24% of all locoregional recurrences) with both initial node-negative disease and disease-free interval greater than 2 years had a 5-year survival rate of 66%, compared to 27% for those with initial node-positive disease and a disease-free interval less than 2 years. Schwaibold et al[102] found three factors independently prognostic for survival on multivariate analysis: a disease-free interval of 24 months or more, use of excisional biopsy, and locoregional control. In their most
favorable patient subgroup with all three factors (18% of all patients with isolated locoregional recurrence), the 5-year relapse-free and overall survival rates after recurrence were 59% and 61%, respectively.

Hsi et al[107] reported on a favorable subgroup of 18 patients (25% of isolated locoregional recurrences) with a disease-free interval of more than 2 years, isolated chest wall disease, and tumor size < 3 cm or complete resection prior to radiation. In this subgroup, overall survival with salvage treatment was 81% at 5 years and 72% at 10 years. Willner et al[105] reported a 5-year survival of 90% and a 10-year survival of 67% for a subgroup of 30 patients (26% of isolated locoregional recurrences) with a disease-free interval of at least 1 year, solitary recurrence, initial T1-2 disease, and absence of necrosis. Magno et al[111] found that 43 patients (26% of their series) with three of five favorable prognostic factors—ie, T1 tumor, node negative, interval to recurrence more than 2 years, solitary recurrence, or recurrence ≤ 1 cm—had a 5-year survival of 75% vs 15% for those with no more than two of these factors.

In summary, these favorable subgroups of patients represent only 20% to 25% of all isolated locoregional recurrences after mastectomy, and a smaller percentage of all locoregional recurrences, but may be associated with a survival of 60% to 90% at 5 years and up to 70% at 10 years.[19,102,105,107,111]

Local Recurrence After Breast-Conserving Surgery and Radiation

Characteristics

Approximately 10% to 20% of patients with stage I/II invasive breast cancer will develop an IBTR at 10 years after breast-conserving surgery and radiation.[1-14] The median interval to IBTR is 3 to 4 years,[1,4,5,9,10,13,14,61,63,65,86,116-120] but this may be significantly prolonged to 5 to 7 years after chemotherapy and/or tamoxifen therapy.[86]

At least two-thirds of breast recurrences are clinically detectable by physical examination with or without mammographic findings, and approximately one-third are detectable by mammography alone.[10,116-122] Philpotts et al[123] observed that, on mammogram, 81% of breast recurrences had a similar appearance to their initial tumors (eg, tumors initially presenting as masses without calcifications usually recurred as masses, and tumors initially presenting with calcifications usually recurred as masses).

More than 80% to 90% of breast recurrences are invasive,[60,116-119,122] and 60% to 85% of recurrences are of the same histologic subtype as the original primary.[4,59,60,120,123]

Three-quarters of recurrences are clinically solitary[63,65,120] with an average size ranging from 1 to 2 cm.[4,59,60,123,124] Approximately 75% of patients present with an isolated recurrence in the breast only, 5% to 15% present with a clinically positive simultaneous regional nodal recurrence, and 5% to 15% present with simultaneous breast and distant metastases.[4,10,11,14,61,63,116,117,120,122,125]

The recurrence occurs in the same quadrant as the original primary tumor in approximately 50% to 90% of cases.[4,6,10,11,14,59-61,63,65,86,108,116-123] The distinction between an IBTR as a recurrence of the original tumor vs a new primary tumor arising in the breast is generally made on clinical grounds. Veronesi et al[59] considered 79% of cases as true local recurrences (ie, in the region of the original tumor) and 21% as new ipsilateral breast tumors (ie, in a separate quadrant from the original tumor).

Kurtz et al[11] also considered recurrences ≥ 5 cm from the initial tumor site as new primary tumors. They reported that 32% of late failures more than 5 years after treatment were away from the primary tumor site (compared to 14% of earlier recurrences \( P < .005 \)) and considered 64% of recurrences after 10 years and all recurrences after 15 years to be new primaries.

Recurrences elsewhere in the breast have been reported to occur at a later interval than in the original location in several other series as well.[118-120,126] Philpotts et al[123] observed that 91% of tumors recurring in the same quadrant were similar in mammographic appearance to their initial tumor, compared with only 25% of tumors recurring elsewhere \( P < .02 \). Haffty et al[126] classified recurrences as new primaries if they occurred at a different site in the breast, had a different histology than the original tumor, or had discordant DNA flow cytometry.

The clinical significance of this distinction between a new primary vs IBTR is uncertain. Several series have found that survival decreased with local failures in the same location as the initial tumor (compared to elsewhere in the breast),[5,118,126] but others have not.[6,11,122] However, this may be related to the longer interval to failure for the recurrences elsewhere in the breast rather than the location itself.
Local Recurrence After Mastectomy or Breast-Conserving Surgery and Radiation

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Treatment

**Surgery**—Mastectomy is the standard treatment of a clinically isolated IBTR following breast-conserving surgery and radiation.[112] At least 85% of patients will have operable disease at the time of detection of the local recurrence.[8,11,59,116,119,122,125] At the time of mastectomy, an exploration of the axilla with consideration of additional axillary dissection is advisable, since 31% to 58% of patients undergoing a dissection will have pathologically positive axillary nodes.[11,14,116,127] Salvage mastectomy for IBTR has resulted in local control rates of approximately 85% to 95%. [8,10,116,117,119,120,122,125]

The role of additional attempts at breast conservation remains investigational. Fowble et al,[116] reported that only 42% of patients with an IBTR after breast-conserving surgery and radiation had no residual tumor at salvage mastectomy after a wide local excision, and half of those with residual disease had involvement of two or more quadrants. They could not identify characteristics that would permit prospective identification of an appropriate subgroup for wide local excision alone after IBTR.

Kurtz et al,[127] reported a series of 50 patients with stage I or II breast cancer treated with breast-conserving surgery and radiation who subsequently underwent wide local excision for a clinically isolated IBTR, with or without axillary recurrence. Of the recurrences, 80% were less than 2 cm in size, 62% were in the vicinity of the original tumor, and all were without skin involvement. The second local failure rate in the salvaged breast was 38% at 5 years, with a 5- and 10-year survival of 67% and 42%, respectively. The only significant factors for local control on multivariate analysis were a disease-free interval greater than 5 years (92% vs 49%) and negative resection margins (73% vs 36%).

Salvadori et al,[125] reported a second local failure rate of 19% at 5 years after reexcision, compared to 4% after mastectomy. However, the 5-year survival rate was 85% after reexcision, compared to 70% after mastectomy.

Abner et al,[122] reported a study of 17 patients who refused a salvage mastectomy after IBTR; 11 had noninvasive and 6 had invasive tumors. Two of the 10 noninvasive tumors treated with excisional biopsy experienced a second local failure, and two others developed distant metastases and died. One patient with a noninvasive tumor treated by incisional biopsy had a second local failure treated with mastectomy. Of the six patients with invasive tumors, three had a second local relapse, and one other developed isolated distant metastases and died. Overall, 5 of 16 patients (31%) had a second local recurrence after wide excision for IBTR.

Stotter et al,[10] reported local control in five of seven patients treated with local excision for breast only relapse. Voogd et al,[118] reported that two of four patients treated for noninvasive recurrences with wide excision had a second local failure, compared to none of 21 patients treated with mastectomy. In the same series for invasive tumors, the recurrence rates were 38% for wide excision and 25% for mastectomy ($P = .27$).

**Radiation Therapy**—There has been limited experience with salvage therapy of an IBTR following breast-conserving surgery and radiation by means of additional radiation. In the previously mentioned series of wide local excision for IBTR by Kurtz et al,[127] 11 of 50 patients who had recurrences away from the original tumor bed were given additional radiation. Seven patients received a boost by electron beam to doses of 20 to 30 Gy, and four underwent an interstitial implant to a dose of 50 Gy. Second local failures occurred in 36% of patients given the supplemental irradiation, compared with 31% of those not given additional radiation.

Deutsch,[128] reported on a series of 26 women treated for IBTR by repeat wide local excision and an electron boost of an additional 50 Gy. Of the 26, 16 also received tamoxifen after treatment for their IBTR. The subsequent breast recurrence rate was 19% at a follow-up of 7 to 139 months, without reported serious sequelae from the additional radiation.

Maulard et al,[129] studied 15 patients treated for IBTR by second tumorectomy and brachytherapy (30-Gy single implant) and 23 patients treated for IBTR by brachytherapy alone (60 to 70 Gy in two implants). After an average of 40 months follow-up, the rate of second local failures was 21% and 5-year survival was 55%. The cosmetic result was good or acceptable in 16 patients, but there were serious complications from treatment in three patients, who required salvage mastectomy.

Jolicoeur et al,[130] reported a series of 32 patients with isolated IBTR treated by repeat wide local excision and perioperative interstitial brachytherapy to a mean dose of 33 Gy (range: 29 to 50 Gy). The 5-year rates of second local relapse and overall survival were 27% and 80%, respectively. A good or acceptable cosmetic result was achieved in 75%, with only one case of skin necrosis requiring salvage mastectomy.
In summary, the risk of second local failure in these retrospective series using wide excision and radiation for salvage of an IBTR does not appear to be significantly different than it is in series using wide excision alone. Moreover, the combined doses of irradiation that result in high-dose regions receiving 90 Gy or higher may be a risk factor for radiation-related sarcoma, which has been previously reported to occur in the region of high-dose irradiation created by overlap at the junction of incorrectly matched fields.[131,132] The high 5-year survivals in these retrospective series of reirradiation, which are attributable to selection of patients with favorable prognostic favors for survival after IBTR (ie, isolated breast relapse, location away from the original tumor, long interval to failure, or no skin involvement), make the avoidance of serious local complications from salvage therapy clinically relevant.

**Systemic Therapy**—Given the absence of data in the setting of an IBTR, systemic therapy may be appropriately considered following salvage mastectomy based upon its efficacy in the adjuvant setting.[112] Fortin et al[5] found that antiestrogen therapy rather than chemotherapy improved 10-year survival following IBTR (72% vs 47%, P = .04).

Estrogen-receptor negative recurrences have been shown to have a worse prognosis than ER-positive recurrences.[121] Other retrospective series have been unable to show an improvement in survival with systemic therapy at the time of IBTR.[116, 122] The interval to IBTR, and therefore, the perceived magnitude of the risk of subsequent distant metastatic disease, may be useful in selecting patients for immediate systemic therapy rather than local therapy alone.

**Prognostic Factors**

Similar to the setting of chest wall failure, the interval to IBTR is an important prognostic factor following IBTR. Veronesi et al[59] reported that the risk of distant metastases within 1 year after an IBTR was 6.6 times the risk of patients developing an IBTR more than 3 years after surgery (P = .004). Touboul et al[4] found that the only prognostic factor significant for survival after an isolated IBTR on multivariate analysis was an interval of 2 years or less vs more than 2 years (5-year survival: 38% vs 90%, P = .026). Other studies have also found that an interval of 2 years or less is an important predictor of survival,[5,6,133] but many series suggest that the interval to IBTR critical for determining prognosis may be longer.

Fourquet et al[14] reported a 5-year survival of 44% after breast recurrence with an interval to failure of 3 years or less, compared to 87% with an interval of more than 3 years (P < .01). Van Dongen et al[1] observed a 92% rate of distant metastases following isolated locoregional recurrence when the interval from primary treatment was less than 2 years, 53% when the interval was 2 to 5 years, and 22% when the interval was more than 5 years.

Haffty et al[9] reported a 50% rate of distant metastases with an interval to IBTR ≤ 4 years vs 17% for more than 4 years. Survival at 5 years after salvage of an IBTR was 50% for those with an interval to IBTR ≤ 4 years, compared to 78% for an interval greater than 4 years (P < .05). Furthermore, although the 10-year rate of distant metastases in their series was 36% vs 22% (P < .05) with and without IBTR, the rate was not significantly different between patients with an interval to IBTR greater than 4 years and those who did not develop an IBTR.

Kurtz et al[11] found the same 15-year survival between patients with a late interval to IBTR of 5 to 10 years and those who never had an IBTR. Approximately 30% to 40% of patients with an IBTR will have a favorable interval to recurrence of greater than 4 to 5 years.[1,5,6,9,11,116] Initial tumor size also has prognostic importance following IBTR. Fowble et al[116] observed a 5-year survival of 62% for initial T2 tumors, compared with 95% for T1 tumors following salvage mastectomy for isolated IBTR (P = .03). Fortin et al[5] reported an improved 10-year post-IBTR survival of 59% for initial T1 tumors, compared with 16% for T2 tumors (P = .0009). Although the size of the recurrence was prognostic in one series,[118] the presence of invasion[118,120,122] or skin involvement[5,6,117,118] is of greater importance.

Distal carcinoma in situ or focally invasive recurrences have mastectomy salvage rates of over 90%.[118,120,122] Abner et al[122] reported no further relapses after salvage mastectomy for IBTR in 24 patients with noninvasive or minimally invasive IBTR, compared to 52% at 5 years in 99 patients with invasive IBTR (P = .001). Skin involvement has been reported in 3% to 22% of breast recurrences.[5,6,61,63,117,118,124] In a large series reported by Gage et al,[124] only 8% of all breast recurrences were skin recurrences without associated parenchymal disease. Uncontrolled local failure was more common with a skin recurrence, compared to other recurrences (50% vs 14%, P = .0007). In addition, there was an increased risk of simultaneous (44% vs 5%, P < .0001) and sequential (60% vs 39%, P = .07) distant...
metastases with skin recurrences, so that their overall survival at 5 years was worse than that of women with other breast recurrences (34% vs 77%, \(P = .001\)).

TABLE 3

Characteristics of Local Recurrence After Initial Mastectomy or Breast-Conserving Surgery and Radiation

Voogd et al[118] reported a series of 266 patients with IBTR after breast-conserving surgery and radiation. The prognostic factors for survival on multivariate analysis were skin involvement, initial tumor grade, and initial nodal status. Van Tienhoven et al[108] studied 67 patients with first isolated locoregional recurrences after breast-conserving surgery and radiation, from the randomized trials vs mastectomy conducted by the EORTC and DBCG. On multivariate analysis, only initial pathologic nodal status was significant for survival after salvage treatment. The interval to first locoregional recurrence, and whether the recurrence was solitary and \(\leq 3\) cm, were the only prognostic factors for subsequent local control.

Local Recurrence After Mastectomy vs Breast-Conserving Surgery and Radiation

TABLE 4

Survival After Salvage of a Local Recurrence Without Distant Metastases by Initial Treatment of Invasive Breast Cancer

A comparison of the characteristics of local failures following mastectomy or breast-conserving surgery and radiation is shown in Table 3. There is no clear association between the location of the recurrence on the chest wall and involvement of the mastectomy scar. However, the majority of IBTRs occur in the same quadrant as the original tumor, although the location is more likely to be
elsewhere in the breast when intervals to recurrence are longer. While the median interval to chest wall failure is 2 to 3 years, the median interval to IBTR is 3 to 4 years and may be prolonged significantly by the use of adjuvant systemic therapy.

Simultaneous regional failures are uncommon after either treatment, but there generally is a higher incidence of simultaneous distant metastases with chest wall failure than with IBTR. In a randomized trial by the NCI, 60% of locoregional recurrences following mastectomy were associated with distant metastases, compared with only 5% following breast-conserving surgery and radiation.[8] In contrast, 38% and 32%, respectively, had locoregional recurrence and simultaneous distant metastases in the EORTC randomized trial.[1] From a comparison of retrospective series, the reported frequency of isolated local recurrence without distant metastases is between 10% and 40% following mastectomy[16,17,19,26,29] and between 5% and 15% following breast-conserving surgery and radiation.[4,10,11,14,61,63,116,117,120-122,125]

A comparison of overall survival following salvage of an IBTR or chest wall recurrence, with or without systemic therapy, is shown in Table 4. Following chest wall failure, survival ranges from 35% to 80% at 5 years and 25% to 60% at 10 years. Following IBTR, survival ranges from 45% to 80% at 5 years and 40% to 65% at 10 years. Local control following salvage treatment for chest wall failure ranges from 50% to 70%, and is generally higher—from 85% to 95%—for salvage mastectomy following IBTR. A comparison of prognostic factors for survival following chest wall recurrence vs IBTR is shown in Table 5.

### TABLE 5

<table>
<thead>
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<th>Prognostic Factors for Survival After Local Recurrence Following Mastectomy or Breast-Conserving Surgery and Radiation</th>
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<td>The interval to recurrence, a larger initial tumor size, and initial node-positive disease are unfavorable prognostic factors after local recurrence following either treatment. Local recurrence only, noninvasive histology of the recurrence, small size of the recurrence, and the absence of inflammatory symptoms are also favorable prognostic factors for both. Estrogen-receptor positivity and a gross total wide excision have been shown to be favorable prognostic factors following chest wall recurrence, while the absence of skin involvement is associated with a better prognosis following IBTR. Between 30% and 40% of patients with IBTR will have a favorable combination of prognostic factors, compared with only 20% to 25% of patients with chest wall failure. The interval to local recurrence is the most important prognostic factor following either mastectomy or conservative surgery and radiation (Table 6). Most chest wall recurrences within 2 years are associated with distant metastases and a 5-year survival of 20% to 30%. The prognosis improves to 60% to 70% at 5 years for intervals longer than 2 years. While an IBTR within 2 years is also associated with a poor prognosis, the 5-year survival following salvage of an IBTR is 80% to 90% for intervals greater than 4 to 5 years.</td>
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### Conclusions

Approximately 10% to 15% of patients with invasive breast cancer treated by mastectomy or breast-conserving surgery and radiation will have a clinically isolated local recurrence. Factors predictive of a significant risk (20% or higher) of local failure after either treatment are patient age ≤ 35 to 40 years, tumor size ≤ 5 cm, lymphovascular invasion, and close or positive resection margins. Factors increasing the risk of chest wall failure (but not IBTR) include 4 or more positive axillary nodes, negative estrogen receptors, and p53 positivity, while extracapsular extension, 1 to 3 positive nodes, and high histologic grade are variably associated with increased risk. Factors increasing the risk for IBTR following breast-conserving surgery and radiation include extensive intraductal component positivity and gross multifocal or multicentric disease. TABLE 6
Importance of Interval to Failure on 5-Year Survival Following Salvage of a Local Recurrence

Management of a clinically isolated chest wall failure following initial mastectomy involves wide local excision of all gross disease whenever possible, followed by postoperative chest wall and supraclavicular radiation in those not previously given postmastectomy radiation. The standard salvage of a clinically isolated IBTR is mastectomy. Systemic therapy should be considered in most patients following local failure, depending upon the perceived risk of subsequent distant relapse. After either mastectomy or breast-conserving surgery and radiation, a long interval to the development of local failure, early stage of initial disease, and isolated local recurrence are important prognostic factors. A complete wide excision of disease and ER-positive recurrence are also favorable prognostic factors following chest wall failure, as is the absence of skin involvement following IBTR. In most cases, local failure within 2 years is a marker of more aggressive disease and simultaneous distant micrometastases. In contrast, the prognosis improves for the favorable subgroups of patients with late local failures, so that salvage treatment is associated with survival rates of 70% or higher at 5 years.

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