Identifying Breast Cancer Patients at High Risk for Bone Metastases

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Purpose: **To identify patient populations at high risk for bone metastases at any time after diagnosis of operable breast cancer, because these patients are potential beneficiaries of treatment with bisphosphonates.**

Patients and Methods: **We evaluated data from 6,792 patients who were randomized in International Breast Cancer Study Group clinical trials between 1978 and 1993. Median follow-up was 10.7 years. A total of 1,275 patients (18.7%) presented with node-negative disease, whereas 3,354 patients (49.4%) had one to three and 2,163 patients (31.9%) had four or more involved axillary lymph nodes. We also assessed the incidence of subsequent bone metastases in the cohort of 1,220 patients who had a first event in local or regional sites or soft tissue alone. Median follow-up for this cohort was 7.7 years from first recurrence.**

Results: **For the entire population with operable disease, the cumulative incidence of bone metastases at any time was 8.2% at 2 years from randomization and 27.3% at 10 years. The highest cumulative incidences of bone metastases at any time were among patients who had four or more involved axillary nodes at the time of diagnosis (14.9% at 2 years and 40.8% at 10 years) and among patients who had as their first event a local or regional recurrence or a recurrence in soft tissue, without any other overt metastases (21.1% at 2 years from first recurrence and 36.7% at 10 years).**

Conclusion: **Treatments to prevent bone metastases may have a major impact on the course of breast cancer and may be most efficiently studied in populations with several involved axillary nodes at the time of presentation and in populations with local or regional recurrence or recurrence in soft tissue.**

J Clin Oncol 18:3925-3935.

MANY BREAST CANCER patients who are free of overt metastases after initial local and regional treatment eventually die from recurrence of distant disease. Current thinking is that occult micrometastases, present at the time of diagnosis and surgery, are responsible for relapse.[1,2] Overt metastatic breast cancer may affect virtually every organ, and the specific metastatic sites usually determine the type and degree of symptoms. In patients with node-positive breast cancer, bone (either alone or with other foci of relapse) is one of the most frequent sites of overt metastatic involvement.[3,4] Other frequent metastatic sites are the liver, lungs, and pleura, as well as soft tissues including mastectomy scars. Locoregional recurrence of breast cancer occurs in up to one third of patients after primary treatment.[5-8] Breast cancer patients with locoregional recurrence have been found to have 5-year disease-free survival rates of 13% to 37% and overall survival rates of 21% to 50%.[9-15] A 10-year estimated overall survival rate of up to 26% has been reported, indicating that long-term complications of disease are real and should be taken into account.[3,4,10] Adjuvant systemic therapy was found to reduce the risk of recurrence effectively in soft tissue. On

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Submitted November 4, 1999; accepted June 21, 2000.

Initial support was provided by the Ludwig Institute for Cancer Research, the Cancer League of Ticino, and the Swiss Cancer League. Continuing support for central coordination, data management, and statistics is being provided by the Swedish Cancer League, Australian Cancer Society, Australian New Zealand Breast Cancer Trials Group (National Health and Medical Research Council grants no. 880513 and 910420), Frontier Science and Technology Research Foundation, Swiss Group for Clinical Cancer Research, American-Italian Cancer Foundation (AICF 101-98 and 101-99), and National Cancer Institute (grant no. CA-75362).

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0732-183X/00/1823-3925

Table 1. Characteristics of IBCSG Trials I Through VII

Trial	Population	Years of Accrual	No. of Eligible Patients	Treatment Groups	Median Follow-Up (years)
I	Premenopausal women with 1-3 Pos nodes	1978-1981	491	CMF × 12 *v* CMFp × 12	15
II	Premenopausal women with ≥ 4 Pos nodes	1978-1981	327	CMFp × 12 *v* Ox + CMFp × 12	15
III	Postmenopausal women < 65 years old	1978-1981	463	Observation *v* p + T × 12 *v* CMFp + T × 12	15
IV	Postmenopausal women 66-80 years old	1978-1981	320	Observation *v* p + T × 12	16
V	Pre- or postmenopausal women with Neg nodes	1981-1985	1,275	Observation *v* PeCMF	12
V	Pre- or postmenopausal women with Pos nodes	1981-1985	1,229	PeCMF *v* CMFpT × 6 *v* PeCMF + CMFpT × 6	12
VI	Premenopausal women with Pos nodes	1986-1993	1,475	CMF × 6 *v* CMF × 6 + reint *v* CMF × 3 *v* CMF × 3 + reint	7
VII	Postmenopausal women with Pos nodes	1986-1993	1,212	T *v* T + delayed CMF *v* T + CMF × 3 *v* T + CMF × 3 + delayed CMF	7

Abbreviations: Pos, positive; Neg, negative; C, cyclophosphamide 100 mg/m^2 orally (PO) days 1-14 of each cycle; M, methotrexate 40 mg/m^2 intravenously (IV) days 1 and 8 of each cycle; F, fluorouracil 600 mg/m^2 IV days 1 and 8 of each cycle; p, prednisone 7.5 mg/d PO; Ox, oophorectomy; T, tamoxifen 20 mg PO once daily; PeCMF, perioperative CMF; reint, reintroduction of 3 cycles of CMF; delayed CMF, 3 cycles of CMF 9, 12, and 15 months after randomization.

the other hand, the incidence of recurrence in bone and viscera was less influenced by adjuvant systemic therapy.[10]

A better description of relapse patterns may improve patient outcome by permitting a better understanding of site-specific risk, which could lead to targeted therapeutic approaches. A strategy for prevention of bone metastases might be implemented using a specific treatment aimed at reducing clinical progression of disease in this site. Recent studies have suggested that using bisphosphonates in addition to systemic antineoplastic therapy might reduce the incidence and number of bone metastases. A total of 302 patients with primary breast cancer and tumor cells in the bone marrow were randomized to receive either clodronate therapy or standard follow-up.[16] A statistically significant reduction of new bone (and also visceral) metastases was observed with the clodronate treatment.[16] A study involving 1,079 patients with metastatic disease demonstrated a clinically relevant reduction in the risk of progression of bony lesions with the use of oral clodronate compared with placebo (relative risk, 0.51; 95% confidence interval, 0.30 to 0.88; $P = .012$).[17] However, a third study, involving 299 patients, found that administration of oral clodronate did not improve overall outcome and did not have a beneficial effect on the incidence of bone metastases.[18] It is therefore essential to identify a patient population in which there is a high incidence of bone metastases and in which events of interest occur in a short space of time, to allow rapid assessment of the potential benefit of the use of bisphosphonates.

PATIENTS AND METHODS

We analyzed data from 6,792 eligible patients with breast cancer who were entered onto International Breast Cancer Study Group (IBCSG; formerly the Ludwig Breast Cancer Study Group) trials I through VII[19-23] between 1978 and 1993 (Table 1).

Trials I through IV investigated the use of chemoendocrine therapy in women with node-positive disease. Between 1978 and 1981, 1,601 eligible patients were accrued.[19] Trial V investigated the timing and duration of chemotherapy in women with node-positive disease[20] and the use of a single perioperative course of chemotherapy in patients with node-negative disease.[21] Between 1981 and 1985, 2,504 eligible patients were enrolled onto this study (1,229 with node-positive disease and 1,275 with node-negative disease). Trial VI investigated the duration and late reintroduction of chemotherapy in node-positive premenopausal patients,[22] and trial VII evaluated early and/or delayed chemotherapy added to tamoxifen, compared with tamoxifen alone, in node-positive postmenopausal patients.[23] Between 1986 and 1993, 1,475 eligible patients were accrued to trial VI and 1,212 eligible patients to trial VII.

Clinical, hematologic, and biochemical assessments of each patient were required every 3 months for 2 years, every 6 months until the end

of the fifth year, and yearly thereafter until death. All sites of disease recurrence, whether first or subsequent, were recorded in the study databases. In trials I through V, chest x-rays and bone scans were required every 6 months for 2 years and once yearly up to 5 years and were recommended beyond the fifth year only if clinically indicated. In trials VI and VII, chest x-rays and bone scans were required, but further x-rays and scans were obtained only if clinically indicated.

All patient data, including all data regarding disease- and survival-related events, were reviewed and classified by the medical study coordinators (A.G. and M.C.-G.)

Statistical Methods

Cumulative incidence functions for competing causes of recurrence were estimated.[24] These functions estimate the actual percentage of patients who will experience the various competing events within the study cohorts as opposed to the overestimated percentages obtained with the Kaplan-Meier method based on the cause-specific hazards.[25,26] Differences between the cumulative incidence functions according to patient subgroups were tested for statistical significance using the procedure of Gray.[27] Analyses were conducted to determine whether the risk of recurrence in bone increased according to baseline characteristics and after a first local or regional recurrence or a first distant recurrence in soft tissue. A cumulative incidence function regression model of Fine and Gray[28] was used for multiple regression analyses. Covariates included in the model were nodal status, pathologic tumor size, estrogen receptor (ER) status, menopausal status, and age. Likelihood ratio tests were used to obtain the statistical significance of each factor, including all other factors in the model. To determine whether a first local or regional event or a first event in soft tissue increased the risk of subsequent recurrence, we used Cox proportional hazards regression models, including a time-varying covariate for the occurrence of such a first event.[29] All *P* values were two-sided.

Categories of Sites of Recurrence

All first recurring breast cancer events were classified according to their sites, as follows: local recurrences, confined to the ipsilateral chest wall and including mastectomy scars; regional recurrences, including ipsilateral axillary, supraclavicular, and internal mammary lymph node metastases; distant recurrences in soft tissue; bone metastases; and visceral metastases, including all other organ involvement and diffuse intra-abdominal metastases. Other first events, including contralateral breast cancer, non–breast cancer second malignancies, and deaths without malignancies, were also recorded. Any event was considered to be a component of a first event if diagnosed within a 2-month time frame. Time to first event was defined as time from randomization to the occurrence of a first event of any type.

Because special emphasis was being placed on the incidence of recurrence in bone, occurrence of bone metastases with or without recurrence at any other site was classified as the event of interest. All other sites of first recurrence (not bone) and any other event, such as contralateral breast cancer, non–breast cancer second primary tumors, and deaths without recurrence, were considered competing events. The sum of the cumulative incidence of bone metastases plus the cumulative incidence of the other competing events equals the cumulative incidence of recurrence due to any cause.

In addition to evaluations according to site of first recurrence, we calculated cumulative incidence of events in bone at any time (either as first events or as subsequent recurrences). Time to recurrence in bone at any time was defined as the time from randomization to the first or subsequent event in bone, whichever occurred first. Death before recurrence in bone was considered the only competing event in this analysis. Otherwise, patients' data were censored at the time they were last known to be alive without recurrence in bone.

We analyzed data from two populations. The first population included all eligible patients who were enrolled onto the trials (6,792 patients). We evaluated data relating to bone as the first site of recurrence, as well as incidence of bone recurrence at any time. The second population included 1,220 patients whose first recurrence was local or regional or in soft tissue (including lymph nodes). Previous analysis of data from the IBCSG database indicated that these sites of recurrence share a similar pattern of subsequent recurrence.[3] The cumulative incidence of subsequent recurrence in bone and subsequent competing events was calculated. The time to subsequent recurrence was measured from the time of the first local or regional event or first event in soft tissue. We also analyzed the cumulative incidence of subsequent recurrence in bone at any time after a local or regional event or an event in soft tissue; death without subsequent recurrence in bone was the only competing event.

RESULTS

Included in the analysis were 6,792 eligible patients from IBCSG Trials I through VII. A total of 6,074 patients (89.4%) had total mastectomy and axillary clearance as the primary treatment; 10.6% had lumpectomy and axillary clearance with irradiation of the breast. A total of 1,275 patients (18.7%) had node-negative disease at the time of presentation, 3,354 (49.4%) had one to three positive axillary lymph nodes, and 2,163 (31.9%) had four or more positive lymph nodes. Of the patients with known pathologic tumor size, 55.6% had tumors that were larger than 2 cm. For all trials, ER-positive status was defined as ER levels $\geq$ 10 fmol/mg cytosol protein based on biochemical assay (3,724 patients were considered ER-positive), low ER levels were defined as levels of 1 to 9 fmol/mg (967 patients

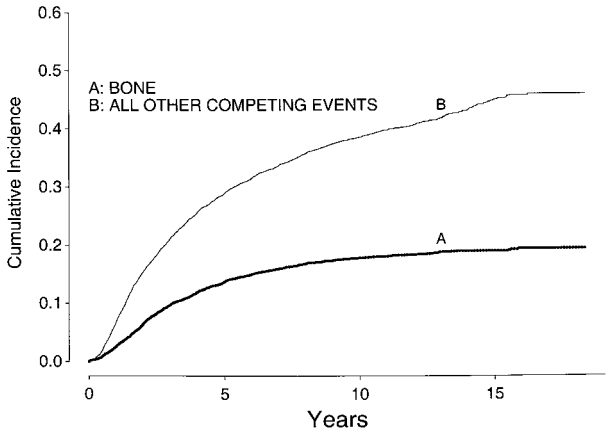

Fig 1. Cumulative incidence of bone metastases and other competing events as first recurrences among 6,792 patients. Time was measured from the date of randomization.

Table 2. Site-Specific Cumulative Incidence: First Site of Recurrence (measured from date of randomization)

	No. of Events	% of Patients*	Incidence (%)				P
			2-Year	5-Year	10-Year	15-Year	
Site of 1st recurrence: bone							
Total	1,158	17.0	6.6	13.7	17.8	19.0	
Nodal status							
Node-negative	114	8.9	3.2	6.3	8.5	9.6	< .01
1-3 positive nodes	488	14.5	4.2	11.4	16.1	17.1	
≥ 4 positive nodes	556	25.7	12.2	21.8	26.8	28.5	
Pathologic tumor size							
≤ 2 cm	398	13.7	4.0	10.2	14.2	15.8	< .01
> 2 cm	720	19.8	8.7	16.6	20.7	21.4	
ER status							
ER-negative	118	13.3	7.6	11.4	13.2	14.3	< .01
Low ER levels	153	15.8	7.2	14.2	16.9	16.9	
ER-positive	656	17.6	6.2	14.1	19.0	20.5	
Menopausal status							
Premenopausal	641	17.3	6.3	13.7	18.2	19.3	.63
Postmenopausal	517	16.7	6.8	13.7	17.2	18.5	
Age							
< 35 years	65	20.8	10.2	18.3	21.5	21.5	.26
35-49 years	451	16.8	6.1	13.4	17.6	19.0	
50-59 years	338	16.4	6.2	13.1	17.2	18.5	
≥ 60 years	304	17.5	7.1	14.2	18.1	19.0	
Competing risks†							
Total	2,556	37.6	15.6	29.0	38.5	44.9	
Nodal status							
Node-negative	415	32.5	10.5	21.6	30.9	34.9	< .01
1-3 positive nodes	1,123	33.5	11.9	24.9	34.9	43.1	
≥ 4 positive nodes	1,018	47.1	24.3	39.7	49.2	53.1	
Pathologic tumor size							
≤ 2 cm	965	33.2	10.7	23.1	33.6	42.3	< .01
> 2 cm	1,516	41.6	19.8	34.1	42.7	47.3	
ER status							
ER-negative	387	43.5	23.9	37.5	43.2	46.2	< .01
Low ER levels	369	38.2	19.8	32.5	39.2	42.6	
ER-positive	1,300	34.9	12.2	26.0	38.0	46.0	
Menopausal status							
Premenopausal	1,308	35.4	14.3	27.6	36.0	41.1	< .01
Postmenopausal	1,248	40.4	17.0	30.7	41.4	49.9	
Age							
< 35 years	129	41.2	20.7	36.4	42.0	43.1	< .01
35-49 years	935	34.9	13.8	27.3	35.8	41.2	
50-59 years	764	37.2	16.5	29.0	38.1	42.6	
≥ 60 years	728	41.8	16.1	30.2	42.5	52.6	

Abbreviation: ER, estrogen receptor.

*The numbers of patients in the subpopulations were as follows: 6,792 overall; 1,275 node-negative; 3,354 with 1-3 positive nodes, 2,163 with ≥ 4 positive nodes; 2,909 with pathologic tumors ≤ 2 cm, 3,644 with pathologic tumors > 2 cm (not shown: 239 with pathologic tumors of unknown size); 889 ER-negative, 967 with low ER levels, 3,724 ER-positive (not shown: 1,212 ER status unknown); 3,700 premenopausal, 3,092 postmenopausal; and 313 < 35 years old, 2,682 35-49 years old, 2,055 50-59 years old, 1,742 ≥ 60 years old.

†Visceral, local, regional, soft tissue, contralateral breast, second primary, death without recurrence, unknown.

were considered to have low ER levels), and ER-negative status was defined as ER levels equal to zero (889 patients were considered ER-negative). ER status was unknown in 1,212 patients. A total of 3,700 patients (54.5%) were premenopausal, whereas 3,092 were postmenopausal at the time of study entry. A total of 313 patients (4.6%) were younger than 35 years, 39.0% were 35 to 49, 30.0% were 50 to 59, and 25.6% were ≥ 60 years of age.

At a median follow-up of 10.7 years, 54.7% of all patients (3,714 of 6,792) experienced a first event, namely disease

Table 3. Cumulative Incidence of Recurrence in Bone at Any Time (measured from date of randomization)

	No. of Events	% of Patients*	Incidence (%) 2-Year	5-Year	10-Year	15-Year	P
Recurrence in bone at any time							
Total	1,777	26.2	8.2	19.6	27.3	30.5	
Nodal status							
Node-negative	202	15.8	4.0	10.5	15.0	17.0	< .01
1-3 positive nodes	735	21.9	5.4	15.6	24.1	27.4	
≥ 4 positive nodes	840	38.8	14.9	31.1	40.8	44.6	
Pathologic tumor size							
≤ 2 cm	597	20.5	5.0	14.2	21.2	24.6	< .01
> 2 cm	1,120	30.7	10.8	24.1	32.0	35.2	
ER status							
ER-negative	197	22.2	10.5	18.4	22.3	24.6	.01
Low ER levels	238	21.7	9.4	21.3	26.5	27.2	
ER-positive	983	26.4	7.2	19.4	28.7	33.2	
Menopausal status							
Premenopausal	991	26.8	7.9	19.9	27.8	31.8	.27
Postmenopausal	786	25.4	8.5	19.1	26.7	29.0	
Age							
< 35 years	110	35.1	13.7	29.7	36.3	37.4	< .01
35-49 years	699	26.1	7.7	19.6	27.0	31.3	
50-59 years	513	25.0	7.8	18.7	26.0	29.5	
≥ 60 years	455	26.1	8.4	18.8	27.6	29.6	
Competing risk: death before recurrence in bone							
Total	1,284	18.9	4.3	12.0	19.2	25.3	
Nodal status							
Node-negative	168	12.8	1.9	6.8	11.6	15.2	< .01
1-3 positive nodes	543	16.2	3.2	9.4	17.0	24.1	
≥ 4 positive nodes	573	26.5	7.3	19.0	27.9	32.7	
Pathologic tumor size							
≤ 2 cm	469	16.1	2.9	9.1	15.8	24.2	< .01
> 2 cm	788	21.6	5.5	14.6	22.3	26.8	
ER status							
ER-negative	233	26.2	8.2	20.8	25.6	30.4	< .01
Low ER levels	210	21.7	6.6	16.8	23.3	27.2	
ER-positive	554	14.9	2.6	8.2	16.7	23.6	
Menopausal status							
Premenopausal	580	15.7	3.7	10.6	16.2	19.8	< .01
Postmenopausal	704	22.8	5.0	13.6	22.7	31.9	
Age							
< 35 years	58	18.5	3.8	13.7	18.5	22.8	< .01
35-49 years	404	15.1	3.5	10.1	15.7	19.4	
50-59 years	394	19.2	4.9	12.4	19.9	24.2	
≥ 60 years	428	24.6	4.9	13.9	23.7	34.9	

*See the corresponding footnote in Table 2.

recurrence at known sites (n = 3,162), contralateral breast cancer (n = 206), recurrence at an unknown site (n = 8), a non–breast cancer second primary tumor (n = 173), or death without recurrence (n = 165). Overall, bone was a component of first recurrence in 17.1% of patients; viscera, and not along with bone, were components of first recurrence in 11.5%; local or regional sites or soft tissue was a component in 18.0%, and other events were components in 8.1%. Forty-five percent of patients were alive without recurrence.

The site-specific cumulative incidences of bone metastases and other competing events as first recurrences are shown in Fig 1. At 10 years from study entry, the cumulative incidence of bone metastases as components of first recurrences was 17.8%, and the cumulative incidence of competing first events was 38.5%. At 10 years, the total cumulative incidence of recurrence due to any cause as a first event was 56.3% (17.8% + 38.5%).

Listed in Table 2 are the cumulative incidences of bone metastases and competing events at 2, 5, 10, and 15 years

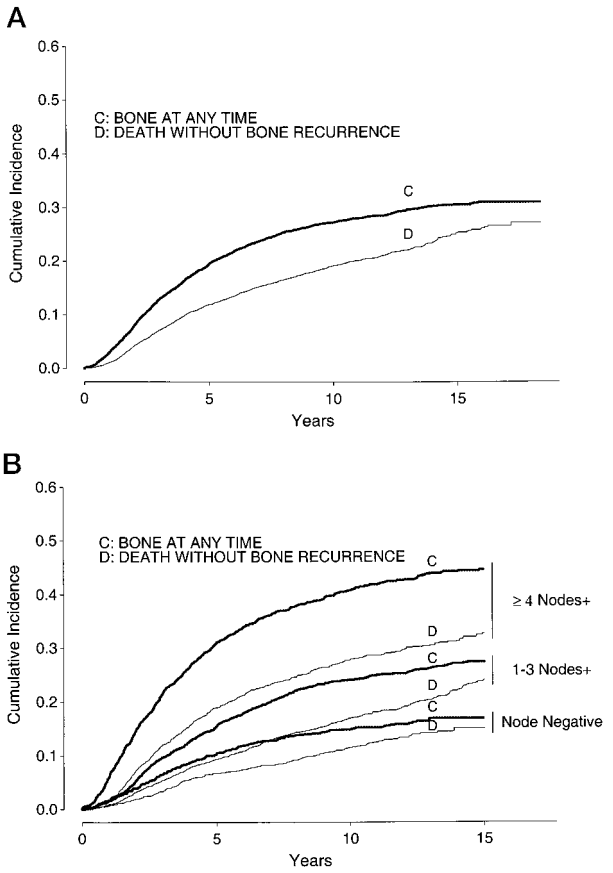

Fig 2. Cumulative incidence of bone recurrence at any time, from the time of randomization, among 6,792 patients. (A) Overall results and (B) results according to nodal status (node-negative, n = 1,275; one to three positive nodes, n = 3,354; ≥ four positive nodes, n = 2,163) are shown.

from randomization, for the overall population and for subpopulations defined according to lymph node involvement, pathologic tumor size, ER status, menopausal status, and age. Significant differences across categories of lymph node status, pathologic tumor size, and ER status were observed in univariate analyses among patients with recurrence in bone. The highest cumulative incidence of bone metastases was observed among patients who presented with four or more involved axillary nodes at the time of diagnosis. Among those presenting with four or more involved nodes, the cumulative incidence of bone metastases as first events was 12.2% at 2 years and 26.8% at 10 years. Bone disease was significantly higher among patients with ER-positive primary tumors, with a 10-year cumulative incidence of 19.0% noted, compared with an incidence of 13.2% among patients with ER-negative primary tumors ($P < .01$). However, the difference was evident only after prolonged observation. Also, larger tumor size was predictive of a significantly higher incidence of bone involvement at 10 years (20.7% *v* 14.2%; $P < .01$). All three factors retained statistical significance in the multiple regression analyses (results not shown).

The cumulative incidences of recurrence in bone at any time (whether first or subsequent recurrences) are listed in Table 3. With a median follow-up of 10.7 years, bone was a site of recurrence at any time in 26.2% of patients. Fifty-five percent of patients were still alive without bone metastases, and 18.9% had died without bone metastases. The 10-year incidence of bone recurrence at any time was 27.3% (Fig 2A). Among patients presenting with four or more involved nodes, the cumulative incidence of bone metastases at any time was 14.9% at 2 years from randomization and 40.8% at 10 years (Fig 2B). The cumulative incidence of bone metastases at any time was significantly higher among patients with ER-positive tumors than among patients with ER-negative tumors (28.7% *v* 22.3% at 10 years, $P = .01$). Younger patients (< 35 years) and those with larger tumors also had significantly higher incidences of metastases in the bone. Again, these factors remained statistically significant in the multiple regression analyses (results not shown).

Listed in Table 4 are incidences of first subsequent recurrence in bone among 1,220 patients whose first recurrence was local or regional or in soft tissue or nodes. Among these patients, the incidence of recurrence in bone as the first subsequent event was particularly high: 18.2% 2 years after the first recurrence and 25.2% at 5 years. Univariate as well as multiple regression analyses demonstrated that only patients with four or more involved lymph nodes had a significantly higher incidence of bone metastases. Figure 3 shows the cumulative incidence of first subsequent recurrence in bone among the 1,220 patients whose first recurrence was local or regional or in soft tissue or nodes.

The cumulative incidences of subsequent recurrence in bone at any time after a first recurrence in local or regional sites or soft tissue are listed in Table 5. The cumulative incidence was 21.1% 2 years after the first recurrence and 32.0% at 5 years. Figure 4 shows the cumulative incidence of bone at any time among the 1,220 patients whose first recurrence was local or regional or in soft tissue or nodes. Based on time-varying Cox model analysis, the risk of recurrence in bone at any time after a first recurrence in local or regional sites or in soft tissue was 3.89 times greater than the risk of recurrence in bone at any time before such a first recurrence (95% confidence interval, 3.46 to 4.37).

DISCUSSION

In this study, we evaluated patterns of recurrence among 6,792 patients included in IBCSG trials of adjuvant treat-

Table 4. Site-Specific Cumulative Incidence (measured from date of first recurrence): First Subsequent Site of Recurrence After First Local or Regional Recurrence or First Recurrence in Soft Tissue

	No. of Events	% of Patients*	Incidence (%)				P
			2-Year	5-Year	10-Year	15-Year	
Site of 1st recurrence: bone							
Total	300	24.6	18.2	25.2	28.0	28.6	
Nodal status							
Node-negative	27	19.3	13.4	18.2	22.0	—	.04
1-3 positive nodes	116	22.5	16.3	23.8	27.2	27.8	
≥ 4 positive nodes	157	27.8	21.1	28.1	30.4	—	
Pathologic tumor size							
≤ 2 cm	89	21.4	17.5	22.1	25.2	—	.14
> 2 cm	200	26.3	18.9	26.4	28.9	29.7	
ER status							
ER-negative	41	20.9	17.5	21.2	22.6	—	.56
Low ER levels	40	22.9	19.5	24.2	24.2	—	
ER-positive	154	24.6	17.8	25.5	28.8	30.3	
Menopausal status							
Premenopausal	169	25.1	18.3	25.8	29.2	—	.43
Postmenopausal	131	23.9	18.2	24.5	26.7	26.7	
Age							
< 35 years	24	30.4	25.8	29.8	32.6	—	.29
35-49 years	119	24.2	17.9	24.6	28.3	—	
50-59 years	89	26.6	19.2	27.9	29.6	—	
≥ 60 years	68	21.7	15.8	21.8	24.9	24.9	
Competing risks†							
Total	622	51.0	34.4	51.4	57.8	60.8	
Nodal status							
Node-negative	57	40.7	26.0	40.2	43.9	—	< .01
1-3 positive nodes	244	47.4	30.2	48.5	57.4	61.8	
≥ 4 positive nodes	321	56.8	40.2	56.9	61.9	—	
Pathologic tumor size							
≤ 2 cm	195	46.9	31.7	48.7	54.6	—	.10
> 2 cm	412	54.2	36.3	53.5	59.5	61.4	
ER status							
ER-negative	120	61.2	50.0	64.0	67.6	—	< .01
Low ER levels	102	58.3	47.2	58.8	65.4	—	
ER-positive	280	44.7	26.5	45.9	53.3	56.5	
Menopausal status							
Premenopausal	329	49.0	34.0	51.0	56.2	—	< .50
Postmenopausal	293	53.5	35.0	51.9	59.4	62.7	
Age							
< 35 years	45	57.0	34.8	60.0	61.7	—	.20
35-49 years	239	48.6	35.2	50.5	55.9	—	
50-59 years	160	47.8	32.1	48.3	53.6	—	
≥ 60 years	178	56.7	35.6	53.8	63.3	68.5	

*See the corresponding footnote in Table 2.

†Subsequent visceral, local, regional, soft tissue, contralateral breast, second primary, death without recurrence, unknown.

ment and the patterns of subsequent recurrence among the 1,220 patients who had a first recurrence in locoregional sites or soft tissue. Our focus was on the incidence of bone metastases with the possibility of investigating treatments including bisphosphonates that are targeted against this site of recurrence. Since 1978, the IBCSG (formerly the Ludwig Breast Cancer Study Group) has conducted a regular life-long follow-up of study patients and recorded all sites of disease recurrence, whether the recurrence was a first or subsequent event. The database for the IBCSG trials thus makes it possible to evaluate sites of first recurrence as well as sites of recurrence at any time after diagnosis. Evaluation of sites of recurrence at any time is a major strength of the current analysis.

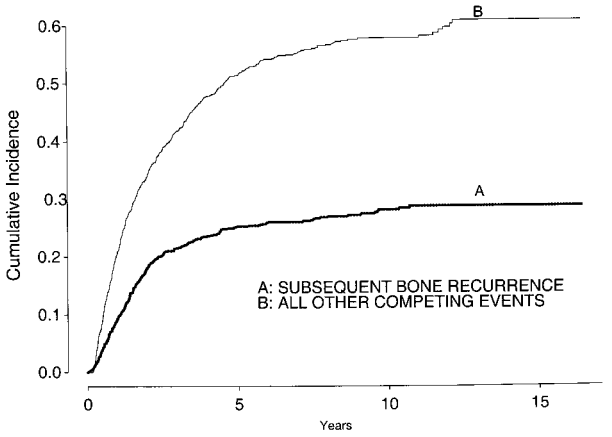

Fig 3. Cumulative incidence of recurrence in bone as the first subsequent recurrence among the 1,220 patients whose first recurrence was local or regional or in soft tissue or nodes. Time was measured from the date of the first recurrence.

We used cumulative incidence estimates for bone metastases, considering recurrences at other sites, second primary tumors (breast and nonbreast), or death without recurrence as competing events.[25,26] Unlike percentages calculated using the Kaplan-Meier method, such approaches do not lead to overestimation of the percentage of patients developing bone metastases. The cumulative incidence of competing events provides the background against which bone metastases might be observed; for example, a high risk of competing events reduces the chance of observing bone metastases. Thus, presentation of both cumulative incidence of bone metastases and cumulative incidence of competing events is required for a comprehensive evaluation.

Considering patients in the adjuvant treatment setting, we found the incidence of bone metastases to be highest among those presenting with four or more positive nodes. Other authors recently presented a higher incidence of first recurrence in bone among patients with node-positive disease.[30-32] The National Surgical Adjuvant Breast and Bowel Project concluded, on the basis of an analysis of 14,614 patients, that node-positive patients have a higher 5-year incidence of bone metastases than do patients with node-negative disease.[32] Results of this study have been reported only in abstract form, and a detailed analysis by number of axillary nodes involved was not presented, nor was the cumulative incidence within specific time frames. Furthermore, only the incidence of bone metastases as first metastases could be assessed. In our study, among patients with four or more axillary lymph nodes involved, the cumulative incidence of bone metastases as first metastases was 12.2% 2 years after randomization and 26.8% at 10 years. With regard to bone metastases at any time as a possible end point for future evaluations of bisphosphonates, the cumulative incidence was 14.9% at 2 years and 40.8% at 10 years. Bone metastases also occur during follow-up in patients with high-risk node-negative disease, but the relatively limited number of skeletal metastases in this population (202 of 1,275 patients had recurrence in bone) did not allow further definition of predisposing features for such event.

Patients with larger primary tumors had a higher risk of both bone metastases and competing events. The initial site of recurrence differed according to ER content in the primary tumors. In fact, although patients with ER-negative tumors or tumors with low ER levels had a higher early incidence of bone metastases than did patients with ER-positive tumors, ER-positive primary tumors were ultimately predictive of a higher long-term incidence of recurrence in bone. This might be due primarily to a better control of disease with endocrine treatments among patients with ER-positive tumors (as indicated by a lower risk of competing events), leaving them at higher risk for later recurrence in the form of slow-growing tumors.

Although the incidence of bone metastases did not differ according to menopausal status, there was a suggestion that younger patients ($<$ 35 years of age) were at higher risk. Multiple regression analyses showed that nodal status, tumor size, ER status, and young age predicted statistically significant differences in the incidence of bone metastases. Other histologic factors, such as tumors growing in a strand growth pattern or with fibrotic focus[33] or tumors without either squamous features or diffuse involucrin expression,[34] might also become useful for predicting a high risk of bone metastases. On the basis of routinely available features, however, it can be said that patients with four or more nodes are at high risk of developing a bone metastasis either as a first recurrence or at any time.

The most relevant observation concerning the patterns of distant metastases was the high incidence of subsequent bone involvement among patients with first recurrence in local sites or in soft tissue or nodes. In these patients, we found a high incidence of subsequent recurrence in bone within 2 years of the first recurrence (21.1%) and a 10-year cumulative incidence of 36.7% with regard to skeletal involvement at any time (Table 5). There was no significant difference between premenopausal and postmenopausal patients in terms of rates of bone metastases, nor was there any significant difference between any other baseline features that would indicate a different pattern of recurrence.

Table 5. Cumulative Incidence of Subsequent Recurrence in Bone at Any Time After a First Local or Regional Recurrence or Recurrence in Soft Tissue (measured from date of first recurrence)

	No. of Events	% of Patients*	Incidence (%)				P
			2-Year	5-Year	10-Year	15-Year	
Recurrence in bone at any time							
Total	391	32.1	21.1	32.0	36.7	38.6	
Nodal status							
Node-negative	39	27.9	16.4	25.8	31.2	—	.08
1-3 positive nodes	153	29.7	18.8	30.4	35.8	38.8	
≥ 4 positive nodes	199	35.2	24.2	35.1	38.9	—	
Pathologic tumor size							
≤ 2 cm	119	28.6	20.5	29.0	34.6	—	.17
> 2 cm	259	34.1	21.8	33.3	37.4	40.0	
ER status							
ER-negative	51	26.0	20.6	25.4	28.1	—	.12
Low ER levels	51	29.1	23.2	30.5	30.5	—	
ER-positive	206	32.9	20.5	33.7	39.0	42.9	
Menopausal status							
Premenopausal	221	32.9	21.1	33.0	38.5	—	.26
Postmenopausal	170	31.0	21.1	31.1	34.8	35.4	
Age							
< 35 years	33	41.8	28.4	39.9	46.9	—	.06
35-49 years	156	31.7	21.1	32.2	37.2	—	
50-59 years	114	34.0	22.7	34.6	38.2	—	
≥ 60 years	88	28.0	17.5	27.2	31.9	33.1	
Competing risk: death before recurrence in bone							
Total	485	39.8	21.2	38.3	46.6	50.6	
Nodal status							
Node-negative	41	29.3	8.9	26.1	33.0	—	< .01
1-3 positive nodes	183	35.5	17.5	35.2	44.9	49.7	
≥ 4 positive nodes	261	46.2	27.6	44.2	52.0	—	
Pathologic tumor size							
≤ 2 cm	150	36.1	18.4	35.5	45.5	—	.15
> 2 cm	322	42.4	22.7	40.1	47.6	50.8	
ER status							
ER-negative	109	55.6	38.0	55.5	60.4	—	< .01
Low ER levels	85	48.6	33.9	49.1	56.9	—	
ER-positive	193	30.8	13.1	30.2	39.9	42.5	
Menopausal status							
Premenopausal	244	36.3	20.5	36.7	43.8	—	.07
Postmenopausal	241	44.0	22.1	40.3	49.7	54.7	
Age							
< 35 years	30	38.0	15.5	36.3	45.2	—	.04
35-49 years	177	36.0	21.6	36.8	43.4	—	
50-59 years	128	38.2	20.2	36.1	43.7	—	
≥ 60 years	150	47.8	23.3	43.6	54.3	60.4	

*See the corresponding footnote in Table 2.

Bisphosphonates might reduce the release of growth factors from microfoci of bone destruction, thereby reducing bone absorption and decreasing stimuli of micrometastatic breast cancer.[35,36] This therapeutic pathway, which should be distinguished from the effect on osteolytic lesions, is likely to influence tumor growth and progression more efficiently with early rather than delayed use of these compounds.[37,38] The effect of bisphosphonates is thus hypothesized to be additive to the effect of other antineoplastic drugs used in the adjuvant treatment setting. The combination of bisphosphonates and other systemic treatments might be used to redefine an adjuvant strategy.[39] In addition, a specific site-related effect might be achieved with bisphosphonates, because adherence of tumor cells to the bone is reduced if bisphosphonates are absorbed by the bone matrix.[40-42]

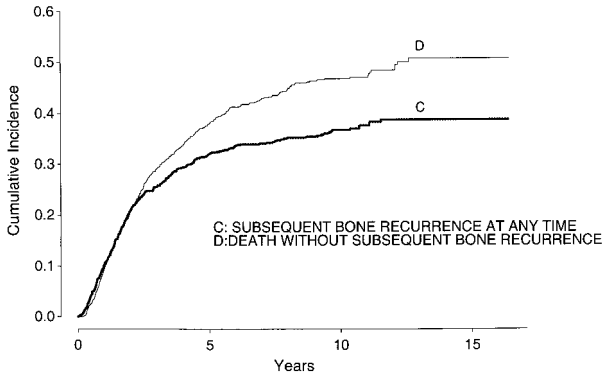

Fig 4. Cumulative incidence of bone events at any time, from the date of first recurrence, among the 1,220 patients whose first recurrence was local or regional or in soft tissue or nodes.

Thus, in this study, two patient populations were found to have a high incidence of bone metastases at any time: patients with four or more involved axillary lymph nodes and patients who had a first recurrence in local, regional, or distant soft tissue sites. The second patient population had a steep cumulative incidence curve within the first 2 years, making this population particularly suitable for rapid evaluation of the effectiveness of treatment with bisphosphonates. It might be important, therefore, to study the effects of bisphosphonates within both subpopulations, to take advantage of the different patterns of subsequent events and because few clinical research trials are conducted in women like those in the latter group.

ACKNOWLEDGMENT

We thank the patients, physicians, nurses, and data managers who participate in the International Breast Cancer Study Group trials. We acknowledge Mary Isley for her special contributions as chief data manager for the group and Robert J. Gray, PhD, for his help with statistical analysis of the cumulative incidence estimates.

REFERENCES

1. Goldhirsch A, Gelber R for the Ludwig Breast Cancer Study Group: Adjuvant treatment for early breast cancer: The Ludwig Breast Cancer studies. NCI Monogr 1:55-70, 1986

2. Gelber RD for the Ludwig Breast Cancer Study Group: Adjuvant therapy for postmenopausal women with operable breast cancer: Part II. Randomized trials comparing endocrine therapy with surgery alone, in Jones SE, Salmon SE (eds): Adjuvant Therapy of Cancer IV. Orlando, FL, Grune & Stratton, 1984, pp 393-404

3. Goldhirsch A, Gelber RD, Castiglione M for the Ludwig Breast Cancer Study Group: Relapse of breast cancer after adjuvant treatment in premenopausal and perimenopausal women: Patterns and prognoses. J Clin Oncol 6:89-97, 1988

4. Kamby K, Senegelov L: Pattern of dissemination and survival following isolated locoregional recurrence of breast cancer: A prospective study with more than 10 years of followup. Breast Cancer Res Treat 45:181-192, 1997

5. Henderson IC, Canellos GP: Cancer of the breast: A past decade. N Engl J Med 302:17-30, 78-90, 1980

6. Veronesi U, Cascinelli N, Greco M, et al: Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. Ann Surg 202:702-707, 1985

7. Fisher B, Redmond C, Poisson R, et al: Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 320:822-828, 1989

8. Donegan WL: Patterns and prognosis of advanced breast carcinoma. Mo Med 67:853-858, 1970

9. Valagussa P, Tess JD, Rossi A, et al: Adjuvant CMF effect on site of first recurrence, and appropriate follow-up intervals, in operable breast cancer with positive axillary nodes. Breast Cancer Res Treat 1:349-356, 1981

10. Goldhirsch A, Gelber RD, Price KN, et al: Effect of systemic adjuvant treatment on first site of breast cancer relapse. Lancet 343:377-381, 1994

11. Borner M, Bacchi M, Goldhirsch A, et al: First isolated locoregional recurrence following mastectomy for breast cancer: Results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. J Clin Oncol 12:2071-2077, 1994

12. Schwaibold F, Fowble BL, Solin LJ, et al: The results of radiation therapy for isolated local recurrence after mastectomy. Int J Radiat Oncol Biol Phys 21:299-310, 1992

13. Willner J, Kiricuta JC, Kolb O: Locoregional recurrence of breast cancer following mastectomy: Always a fatal event? Results of univariate and multivariate analysis. Int J Radiat Oncol Biol Phys 37:853-863, 1997

14. Crowe JP, Gordon NH, Antunez AR, et al: Recurrence patterns in a prospective study of patients with stage II breast cancer treated with endocrine-chemotherapy. Surgery 102:622-627, 1987

15. Whelan T, Clark R, Roberts R, et al: Ipsilateral breast tumor recurrence postlumpectomy is predictive of subsequent mortality: Results from a randomized trial. Int J Radiat Oncol Biol Phys 30:11-16, 1994

16. Diel IJ, Solomayer EF, Costa SD, et al: Reduction in new metastases in breast cancer with adjuvant clodronate treatment. N Engl J Med 339:357-363, 1998

17. Powles TJ, McCloskey E, Paterson A, et al: Adjuvant clodronate will reduce the incidence of bone metastases in patients with primary operable breast cancer. Presented at the 21st Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 12-15, 1998 (abstr)

18. Saarto T, Blomqvist C, Virkkunen P, et al: No reduction of bone metastases with adjuvant clodronate treatment in node-positive breast cancer patients. Proc Am Soc Clin Oncol 18:128a, 1999 (abstr 489)

19. Castiglione-Gertsch M, Johnsen C, Goldhirsch A, et al: The International (Ludwig) Breast Cancer Study Group trials I-IV: 15 years follow-up. Ann Oncol 5:717-724, 1994

20. Ludwig Breast Cancer Study Group: Combination adjuvant chemotherapy for node-positive breast cancer: Inadequacy of a single perioperative cycle. N Engl J Med 319:677-683, 1988

21. Ludwig Breast Cancer Study Group: Prolonged disease-free survival after one course of perioperative adjuvant chemotherapy for node-negative breast cancer. N Engl J Med 320:491-496, 1989

22. International Breast Cancer Study Group: Duration and reintroduction of adjuvant chemotherapy for node-positive premenopausal breast cancer patients. J Clin Oncol 14:1885-1894, 1996

23. International Breast Cancer Study Group: Effectiveness of adjuvant chemotherapy in combination with tamoxifen for node-positive postmenopausal breast cancer patients. J Clin Oncol 15:1385-1394, 1997

24. Kalbfleisch JD, Prentice RL: The Statistical Analysis of Failure Time Data. New York, NY, Wiley, 1980

25. Gaynor JJ, Feuer EJ, Tan CC, et al: On the use of cause-specific failure and conditional failure probabilities: Examples from clinical oncology data. J Am Stat Assoc 88:400-409, 1993

26. Gooley TA, Leisenring W, Crowley J, et al: Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 18:695-706, 1999

27. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1154, 1988

28. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496-509, 1999

29. Cox DR: Regression models and life tables. J R Stat Soc B 34:187-220, 1972

30. Smith R, Jiping W, Bryant J, et al: Primary breast cancer (PBC) as a risk factor for bone recurrence (BR): NSABP experience. Proc Am Soc Clin Oncol 18:120a, 1999 (abstr 457)

31. Mundy GR: Mechanisms of osteolytic bone destruction. Bone 12:S1-S6, 1991 (suppl 1)

32. Mundy GR, Martin TJ: Pathophysiology of skeletal complications of cancer, in Mundy GR, Martin TJ (eds): Physiology and Pharmacology of Bone. Berlin, Germany, Springer-Verlag, 1993, pp 641-671

33. Koyama T, Hasebe T, Tsuda H, et al: Histological factors associated with initial bone metastasis of invasive ductal carcinoma of the breast. Jpn J Cancer Res 90:294-300, 1999

34. Tsuda H, Sakamaki C, Fukutomi T, et al: Squamoid features and expression of involucrin in primary breast carcinoma associated with high histological grade, tumour cell necrosis and recurrence sites. Br J Cancer 75:1519-1524, 1997

35. Kanis JA: Bone and cancer: Pathophysiology and treatment of metastases. Bone 17:S101-S105, 1995 (suppl 2)

36. Nemoto R, Uchida K, Tsutsumi M, et al: A model of localized osteolysis induced by the MBT-2 tumor in mice and its responsiveness to etidronate disodium. J Cancer Res Clin Oncol 113:539-543, 1987

37. Krempien B, Manegold C: Prophylactic treatment of skeletal metastases, tumor-induced osteolysis, and hypercalcemia in rats with the bisphosphonate CL2MBP. Cancer 72:91-98, 1993

38. Krempien B, Wingen F, Eichmann T, et al: Protective effects of a prophylactic treatment with the bisphosphonate 3-amino-1-hydroxypropane-1,1-bisphosphonic acid on the development of tumor osteopathies in the rat: Experimental studies with the Walker carcinosarcoma 256. Oncology 45:41-46, 1988

39. Stearns ME, Wang M: Effects of alendronate and Taxol on PC-3 ML cell bone metastases in SCID mice. Invasion Metastasis 16:116-131, 1996

40. van der Pluijm G, Vloedgraven H, van Beek E, et al: Bisphosphonates inhibit the adhesion of breast cancer cells to bone matrices in vitro. J Clin Invest 98:698-705, 1996

41. Boissier S, Magnetto S, Frappart L, et al: Bisphosphonates inhibit prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrices. Cancer Res 57:3890-3894, 1997

42. Yoneda T, Sasaki A, Dunstan C, et al: Inhibition of osteolytic bone metastasis of breast cancer by combined treatment with the bisphosphonate ibandronate and tissue inhibitor of the matrix metalloproteinase-2. J Clin Invest 99:2509-2517, 1997