Prognostic factors for survival in breast cancer patients who developed distant metastasis subsequent to definitive surgery

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ABSTRACT

Introduction: The present study was undertaken to define the prognostic factors for overall survival subsequent to definitive surgery, and for survival after the development of distant metastasis in breast cancer patients who developed distant metastasis subsequent to definitive surgery.

Methods: The records of 470 breast cancer patients with T1–3 tumours and distant metastasis following surgery were reviewed. Prognostic factors were compared to the first metastatic sites as solitary skeletal, multiple skeletal, and visceral metastases, and were analysed for overall survival following surgery and survival after metastasis. Survival curves were generated by the Kaplan-Meier method, and multivariate analysis was performed by the Cox proportional hazard model.

Results: 79 patients (17 percent) had a solitary skeletal metastasis, 105 (22 percent) had multiple skeletal metastases, and 286 (61 percent) had a visceral metastasis. The five-year overall survival was significantly better for patients with a solitary bone metastasis (73 percent) compared to patients who had multiple bone metastases (46 percent), or a visceral metastasis (22 percent) (p-value is less than 0.0001). Pathological lymph node status 3, stage IIIC, grade 3, oestrogen receptor negativity, and visceral metastases were found to have independent detrimental influence on overall survival following surgery and survival after metastasis. A long-term metastasis-free interval affected post-metastatic outcome favourably. Radiotherapy improved overall survival.

Conclusion: Pathological lymph node status, stage, grade, and oestrogen receptor status predicted survival after surgery as well as after the development of metastasis. Solitary bone metastasis has a more favourable prognosis than multiple bone metastases, and compared to visceral metastasis, skeletal metastasis has a more favourable prognosis.

Keywords: apex axillary invasion, breast cancer, oestrogen receptor, skeletal metastasis, stage IIIC breast cancer

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INTRODUCTION

Patients with breast cancer who suffer systemic spread of their disease often present with bone metastasis.[1,2] Those who suffer bone metastasis as their first site of recurrence are known to have a longer survival than those who present first with visceral metastasis,[2-5] and survival for those with solitary bone metastasis is known to be better than those who present with multiple bone metastases.[3] New compounds of bisphosphonates are constantly being developed and used to treat osseous metastases.[6] As suggested by preclinical data, bisphosphonates have anti-tumour effects,[7] and may also be of use in an adjuvant setting.[8] Patients who are likely to develop visceral metastasis may also be candidates for participation in trials to receive novel and aggressive adjuvant therapy. Therefore, identification of prognostic factors for survival and for the prediction of the development and outcome of solitary skeletal, multiple skeletal and visceral metastases among breast carcinoma patients who developed distant metastasis after surgery, is of great importance. A previous study also demonstrated that solitary bone metastasis was an independent predictor of a better survival after metastasis.[9] However, the independent prognostic significance of solitary skeletal and multiple skeletal metastases for overall survival (OS) after definitive surgery and for survival subsequent to the development of metastasis have not been previously evaluated among

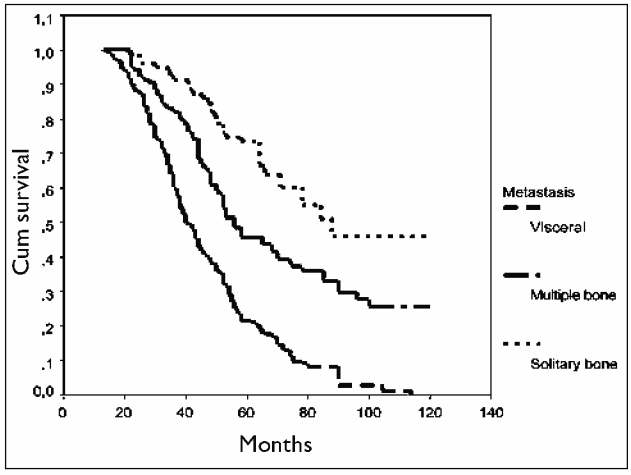

Fig. 1 Graph shows the five-year overall survival for solitary bone, multiple bone and visceral metastases from the time of initial diagnosis of breast cancer are 73.4%, 45.6%, and 21.5%, respectively (p = 0.002 for solitary compared to multiple metastases, and p = 0.0001 for solitary and multiple bone metastases compared to visceral metastasis).

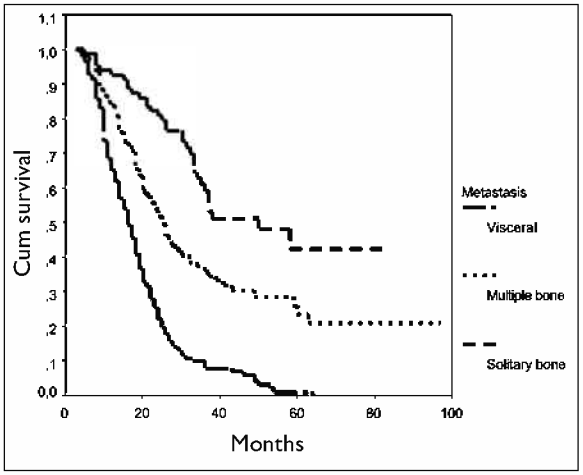

Fig. 2 Graph shows the survival after metastasis by sites. The five-year survival for solitary, multiple bone, and visceral metastases are 42.25%, 23.4%, and 0%, respectively. p=0.0003 for solitary vs. multiple metastases, and p<0.0001 for solitary and multiple metastases compared to visceral metastasis.

the same series of patients. According to the literature, prognostic significance of the axillary lymph node status is also controversial for survival after the development of distant metastasis among breast cancer patients presenting with metastasis following surgery.[1,3-5,10,11]

To the best of our knowledge, there are no studies that compare the prognostic significance of the axillary lymph node status at the time of definitive surgery to survival rates of those patients who later develop metachronous metastasis. Moreover, we have found no previous study that analysed prognostic and predictive factors for OS relevant to the current 2002 AJCC staging system after definitive surgery, or survival after the development of metastasis in the same series of breast cancer patients. The aims of this study were to analyse the prognostic and predictive factors relevant to the current 2002 AJCC staging system for OS subsequent to definitive surgery and for survival after the development of distant metastasis in T1–3 breast cancer patients with metachronous presentation of metastasis.

METHODS

Among 1,510 consecutive patients with T1–3 breast cancers and who underwent modified radical mastectomy (MRM) in our hospital between January 1995 and 2001, 478 subsequently developed metastasis. Eight patients with insufficient histological information were excluded, and five patients who had second primary malignancy subsequent to the metastasis were included in the study. Thus, 470 patients with histologically-proven invasive breast carcinoma and subsequent development of distant skeletal or visceral metastasis following surgery were the subject of the present study. We analysed the prognostic and predictive factors for OS after MRM and for survival subsequent to metastasis. The institutional review board of our hospital approved the study design. All patients had levels I, II, and III axillary dissection. The technique of axillary dissection has been described in our previous article.[12] The same surgical team performed all operations, and all patients received identical axillary treatment. Following axillary dissection, the three Berg levels were marked with silk sutures to be identified for pathological examination. All surviving patients were followed-up for at least 60 months with a median follow-up of 77 (range 60–120) months. No patients were lost to follow-up for the first six years, but by eighth year, eight patients had been lost to follow-up and were excluded. In addition, eight deaths due to cardiac and respiratory failures, not breast carcinoma, were also treated as censored observations.

The majority of patients (451) received adjuvant systemic treatment with tamoxifen and/or six cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil), FAC (5-fluorouracil, doxorubicin, cyclophosphamide), or FEC (5-fluorouracil, epirubicin, cyclophosphamide) chemotherapy. Prior to adjuvant radiotherapy, two or three cycles of systemic chemotherapy were given, and the complementary cycles were given after radiotherapy. All patients with positive oestrogen receptor (ER) were given tamoxifen treatment, and patients with any positive axillary node, T2–3 tumour, or grade 3 tumour received adjuvant chemotherapy. According to the current 2002 AJCC staging system, 1–3 and 4–9 positive axillary nodes at level I and/or II were defined as pathological lymph node status 1 (pN1) and pN2, respectively. Any

Table I. Comparison of patient and tumour characteristics and treatment factors by sites of metastasis.

Variable	No.	Solitary bone	Multiple bone	Visceral	p-value
Median age (range) at diagnosis (years)		50 (28–72)	48 (31–67)	47 (25–75)	0.73
Level of invasion					
0 (node negative)	96	28 (35)	18 (17)	50 (18)	0.009
I ± II	169	24 (31)	39 (37)	106 (37)	
III (± II ± I)	205	27 (34)	48 (46)	130 (45)	
No. metastatic axillary lymph nodes					
0	96	28 (36)	18 (17)	50 (18)	0.18
1–3	125	17 (28)	21 (20)	87 (30)	
4–9	154	16 (20)	46 (44)	92 (32)	
≥ 10	95	18 (16)	20 (19)	57 (20)	
Pathological node status					
0	96	28 (35)	18 (17)	50 (18)	0.031
1	95	14 (18)	15 (14)	66 (23)	
2	67	8 (10)	24 (23)	35 (12)	
3	212	29 (37)	48 (46)	135 (47)	
Stage					
I	15	6 (7)	5 (5)	4 (1.5)	0.027
IIa	77	19 (24)	12 (11)	46 (16)	
IIb	73	14 (18)	6 (6)	53 (18.5)	
IIIa	93	11 (14)	34 (32)	48 (17)	
IIIc	212	29 (37)	48 (46)	135 (47)	
Tumour size (cm)					
≤ 2	37	6 (7)	8 (8)	23 (8)	0.60
2.1–5	297	48 (61)	71 (68)	178 (62)	
> 5	136	25 (32)	26 (25)	85 (30)	
Age (years)					
< 50	265	35 (44)	69 (66)	161 (56)	0.25
≥ 50	205	44 (56)	36 (34)	125 (44)	
Menopausal status					
Premenopausal	262	36 (57)	62 (59)	164 (57)	0.12
Postmenopausal	208	43 (43)	43 (41)	122 (43)	
Grade					
1	72	23 (29)	20 (19)	29 (10)	< 0.001
2	221	38 (48)	58 (55)	125 (44)	
3	177	18 (23)	27 (26)	132 (46)	
Median (95% CI) metastasis-free interval (months)		31 (26.6–35.3)	29 (23.1–34.8)	24 (22.6–25.3)	0.007 †
ER status					
Negative	158	19 (24)	37 (35)	102 (36)	0.011 ††
Positive	160	36 (46)	39 (37)	85 (30)	
Unknown	152	24 (30)	29 (28)	99 (35)	
Systemic treatment					
None	19	3 (4)	5 (5)	11 (4)	0.1
Tamoxifen alone	17	4 (5)	3 (3)	10 (4)	
Chemotherapy alone	232	24 (30)	58 (55)	150 (52)	
Tamoxifen + chemotherapy	202	48 (61)	39 (37)	115 (40)	
Radiotherapy					
No	142	35 (38)	22 (24)	85 (30)	0.29
Yes	328	58 (62)	69 (76)	201 (70)	

Unless otherwise stated, data is expressed as no. (%).

† p = 0.007 and 0.72 for solitary metastasis compared to visceral and multiple metastases, respectively. p = 0.0015 for multiple metastases compared to visceral metastasis.

†† negative vs. positive.

positive lymph node at the apex axilla (level III) and/or ≥ 10 positive axillary nodes were classified as pN3.[13] T1 N0 M0 was categorised as stage I, T1 N1 M0 and T2 N0 M0 as stage IIA, T2 N1 M0 and T3 N0 M0 as stage IIB, T3 N1 M0 and T1–3 N2 M0 as stage IIIA, and any T N3 M0 as new stage IIIC. In all, 328 patients (70%) received adjuvant radiotherapy to the chest wall, to three axillary levels, and to the supraclavicular region within three months of surgery. Radiotherapy was indicated for one of the following criteria; ≥ 4 positive axillary nodes, extra nodal extension, or T3 tumour.

Patients were investigated to rule out distant metastasis before surgery by physical examination, abdominal and pelvic ultrasonography (US), chest radiograph, and bone scintigraphy. Computed tomography (CT) and correlation radiographies were performed as necessary. Patients were followed-up for examination every three months after surgery for the first two years, every four months during the third year, every six months during the fourth year, and annually thereafter. Blood chemistry analysis and full blood count were required for every examination. Chest radiograph, and abdominal

Table II. Univariate survival analysis of prognostic and treatment factors from the initial diagnosis and median survivals after surgery and first distant metastasis.

Variable	Five-year survival rate (%)	Median (95% CI) survival after surgery (months)	p-value log-rank	Median (95% CI) survival after first distant metastasis (months)	p-value log-rank
Level of invasion					
0 (node negative)	49	58 (49.5–66.4)	< 0.0001	27 (22.3–31.6)	< 0.0001
I ± II	48	57 (46.9–67.0)		23 (19.5–26.4)	
III (± II ± I)	19	43 (39.9–46.0)		18 (16.3–19.6)	
No. metastatic axillary lymph nodes					
0	49	58 (49.5–66.4)	0.0021	27 (22.3–31.6)	0.0014
1–3	37	48 (43.5–52.4)		20 (18.2–21.7)	
4–9	34	46 (40.2–50.8)		19 (16.6–21.3)	
≥ 10	22	45 (39.3–50.6)		17 (15.2–18.7)	
Pathological node status					
0	49	58 (49.5–66.4)	< 0.0001	27 (22.3–31.6)	< 0.0001
1	49	57 (37.2–66.7)		27 (17.0–37.0)	
2	44	54 (50.9–77.0)		21 (17.1–24.8)	
3	21	43 (39.9–46.1)		18 (16.5–19.4)	
Stage					
I	60	90 (43.7–136.2)	< 0.0001	24 (12.1–35.8)	< 0.0001
IIa	43	54 (58.8–49.1)		26 (22.2–29.4)	
IIb	48	56 (30.0–81.9)		23 (18.9–27.0)	
IIIa	50	64 (72.4–55.6)		23 (17.1–28.9)	
IIIc	20.5	43 (39.9–46.1)		18 (16.5–19.4)	
Tumour size (cm)					
≤ 2	38	50 (46.4–53.5)	0.99	18 (16.5–19.4)	0.79
2.1–5	36	47 (39.6–54.3)		20 (17.6–22.3)	
> 5	36	47 (43.6–56.3)		19 (16.6–21.3)	
Age (years)					
< 50	32	46 (42.7–49.2)	0.0035	19 (17.2–20.7)	0.02
≥ 50	41	54 (50.0–57.9)		22 (19.2–24.8)	
Menopausal status					
Premenpausal	32	47 (43.5–50.4)	0.018	19 (17.2–20.7)	0.037
Postmenpausal	40	52 (48.3–55.6)		22 (19.4–24.5)	
Grade					
1	55	68 (44.0–91.9)	< 0.0001	36 (24.4–47.5)	< 0.0001
2	38	53 (50.5–55.4)		21 (19.0–21.9)	
3	22.5	39 (35.7–42.2)		17 (15.2–18.7)	
ER status					
Negative	20	40 (35.3–44.6)	< 0.0001	17 (15.2–18.7)	< 0.0001
Positive	41	54 (50.5–57.4)		24 (21.2–26.8)	
Systemic treatment					
None	37	48 (33.5–62.5)	< 0.0001	19 (13.3–24.6)	< 0.0001
Tamoxifen alone	53	90 (52.7–79.3)		29 (20.2–37.7)	
Chemotherapy alone	25.4	43 (40.0–45.9)		18 (16.6–19.3)	
Tamoxifen + chemotherapy	46	56 (49.7–62.2)		24 (21.5–26.4)	
Radiotherapy					
No	34.5	45 (39.1–50.8)	0.82	20 (16.2–23.7)	0.28
Yes	36	51 (48.2–53.8)		20 (18.3–21.6)	
Metastasis-free interval (months)					
< 12	–			12 (9.88–14.1)	< 0.0001
12–60	–			20 (18.3–21.6)	
> 60	–			42 (33.8–51.2)	
Metastatic site					
Solitary bone	73	88 (78.4–95.3)	< 0.0001	50 (32.8–67.1)	< 0.0001
Multiple bone	46	56 (46.7–65.2)		25 (20.8–29.1)	
Visceral	22	40 (37.2–42.7)		16 (14.5–17.4)	

and pelvic US were performed every six months, and bone scintigraphy and mammography were performed annually. Mammography was used every six months for two years and annually thereafter following breast-conserving surgery. When patients had complaints or signs of disease, and/or whenever the physician required blood analysis and imaging modalities, including bone radiograph, CT, magnetic resonance (MR) imaging and bone scintigraphy, were performed. Bone scintiscans that suggested metastasis or were equivocal for metastatic lesions were correlated with direct radiographs. If the radiograph was correlated with metastatic lesions, it was accepted as metastasis. If a radiograph revealed a benign lesion, such as degenerative arthritis, the lesion was labelled as benign. When a radiograph was normal, further imaging modalities, such as CT and MR imaging, were used to rule out metastasis, and when imaging modalities failed to define metastasis, a follow-up study or a biopsy was warranted for decision-making purposes. All bone scintiscans were evaluated in comparison to the previous

Table III. Independent prognostic factors for overall survival following surgery in multivariate analysis.

	Hazard ratio (95% CI)	p-value
Invasion by level		
0 (node negative)	1*	
Apex axillary	1.9 (1.39–2.58)	< 0.001
No. metastatic lymph nodes		
0	1*	
4–9	1.4 (1.03–1.95)	0.034
≥ 10	1.6 (1.13–2.20)	0.007
Pathological node status†		
pN0	1*	
pN3	1.8 (1.32–2.42)	< 0.001
Stage††		
I	1*	
IIIC §	2.5 (1.21–5.47)	0.014
Grade		
1	1*	
3	1.8 (1.27–2.67)	0.001
ER status		
Negative	1*	
Positive	0.5 (0.39–0.66)	< 0.001
Radiotherapy		
No	1*	
Yes	0.67 (0.51–0.87)	0.004
Metastatic site		
Solitary bone	0.6 (0.38–0.89)	0.012
Multiple bone	1*	
Visceral	2.2 (1.69–2.96)	< 0.001

* reference value

† When the pathological node status is included in the analysis, instead of the invasion level and metastatic nodes.

†† When the stage is included in the analysis, instead of invasion level and metastatic nodes.

§ Hazard ratios for stages I, IIA, IIB, IIIA are 0.38, 0.45, 0.52 and 0.57, respectively, if IIIC is taken as reference ($p < 0.001$).

one, if one existed.

Histological grade was assessed using the Elston-Ellis modification of the Bloom-Richardson grading method.[14] ER status was defined by immunohistochemistry, and staining of 10% of tumour cells was accepted as ER positive. ER status was known in 68% of the patients. Patients with unknown ER status were included in the study, because excluding them would have introduced selection bias. However, the results would not have changed when patients with unknown ER status were not included in the multivariate survival analysis. All pathological slides were evaluated by two experienced staff pathologists.

Information regarding adjuvant treatment, follow-up, and prognostic indicators including age, menopausal status, number of metastatic axillary lymph nodes, metastatic nodes by axillary level, pathological tumour size, histological grade, and ER status, were obtained from the medical records of the patients. The first metastasis to the bone was classified as solitary or multiple if metastases were initially confined to solitary or multiple bones. The first metastasis to a visceral site at the initial diagnosis was defined as visceral metastasis. Coexistence of skeletal and visceral metastases was classified as visceral metastasis. Exclusion of six patients with first distant metastasis to soft tissues did not change the results, and were included in the visceral metastasis. Metastasis-free interval (MFI) was defined as the time (in months) between surgery and the diagnosis of the first distant metastasis, and was categorised as < 12 months, 12–60 months, or > 60 months. The follow-up interval was calculated in months, and defined as the time between surgery and date of death or last follow-up. OS was calculated based on the follow-up interval, and survival after metastasis was calculated based on the time interval between the first metastasis and time of death or last follow-up.

Survival analysis was performed using the Kaplan-Meier method, and log-rank test was used for comparisons. Stepwise Cox multivariate analysis was used to calculate hazard ratios and 95% confidence intervals (CI) for the risk of death from breast cancer.[15,16] For the selection of independent prognostic factors for OS age, axillary level of invasion, number of metastatic nodes, tumour size, menopausal status, grade, ER status, systemic treatment, and radiotherapy were entered in the multivariate analysis as categorical covariates (Table I). Along with the above-mentioned covariates, the MFI was also entered in the multivariate analysis for survival after the development

Table IV. Independent prognostic factors for survival after distant metastasis in multivariate analysis.

	Hazard ratio (95% CI)	p-value
Invasion by level		
0 (node negative)	1*	
Apex axillary	2 (1.49–2.77)	< 0.001
No. metastatic lymph nodes		
0	1*	
4–9	1.5 (1.09–2.14)	0.013
≥ 10	1.7 (1.22–2.33)	0.002
Pathological node status†		
pN0	1*	
pN3	1.95 (1.43–2.65)	< 0.001
Stage††		
I	1*	
IIIC§	1.9 (1.44–2.72)	< 0.001
Grade		
1	1*	
3	1.8 (1.24–2.55)	0.001
ER status		
Negative	1*	
Positive	0.65 (0.50–0.84)	< 0.001
Metastatic site		
Solitary bone	0.54 (0.35–0.82)	0.004
Multiple bone	1*	
Visceral	2.2 (1.69–3.03)	< 0.001
Metastasis-free interval (months)		
< 12	3.6 (1.60–8.18)	0.002
12–60	2.3 (1.10–5.01)	0.027
> 60	1*	

* reference value

† When included in the analysis, instead of invasion level and metastatic nodes

†† When included in the analysis, instead of invasion level and metastatic nodes

§ Hazard ratios for stage I, IIA, IIB, IIIA are 0.5, 0.54, 0.65, and 0.9, if IIIC is taken as reference ($p = 0.77$ for IIIA compared to IIIC; $p < 0.001$ for the other comparisons).

of metastasis. Because patients with level III invasion or ≥ 10 positive nodes were classified as pN3, and pN3 was categorised as stage IIIC according to the current 2002 AJCC staging system as described above,[13] pN status or stage includes also invasion level and number of metastatic nodes. Therefore, pN status, or stage was separately entered in the multivariate analyses instead of invasion level and number of metastatic nodes to prevent the elimination of these factors from the analysis due to the constant or dependent variable. Comparisons of metastatic sites by patient characteristics and prognostic, predictive, and treatment factors and comparison of radiotherapy by deaths due to cardiac and respiratory failures were made by chi-square or Fisher's exact test. Comparisons of metastatic sites by total number of removed lymph nodes and age were made by Mann-Whitney U test. Statistical analysis was performed using the Statistical Package for Social Sciences version 10.0 (SPSS Inc, Chicago, IL, USA). p-values < 0.05 were considered to be significant.

RESULTS

The median age was not different for solitary skeletal, multiple skeletal and visceral metastases (Table I). The median number of totally-removed axillary lymph nodes was 19 (range 6–51) for all patients, and was 20, 18, and 19 for solitary, multiple skeletal and visceral metastasis, respectively. Of the 470 patients with distant metastasis, 184 (39%) had skeletal metastasis and 286 (61%) had visceral metastasis. Of the 184 patients with skeletal metastasis, 79 (43%) had solitary, and 105 (57%) had multiple skeletal metastases. Solitary bone metastasis was significantly less in patients with level III invasion, 4–9 and ≥ 10 positive nodes, pN3 status, stage IIIC, grade 3 tumours, and negative ER (Table I). Nodal status was not correlated to skeletal and visceral metastases ($p = 0.25$). Compared to visceral metastasis, skeletal metastasis was significantly lower in patients with grade 3 ($p < 0.001$), and ER-negative tumours ($p = 0.04$). The median metastasis-free interval was significantly longer in patients with skeletal metastasis (Table I). Eight patients who died of cardiac and respiratory failure also had radiotherapy. However, there was no significant difference between patients with or without radiotherapy among those who died from cardiac and respiratory failures ($p = 0.11$).

In the univariate analysis, five-year OS was significantly better for patients with solitary bone

metastasis (73%) compared to patients who had multiple bone (46%), and visceral (22%) metastases ($p < 0.0001$; Fig. 1 and Table II). Patients with level III invasion, 4–9 and ≥ 10 positive nodes, pN3, stage IIIC, ≥ 50 years of age, grade 3 tumour, negative ER, premenopausal patients and patients treated with chemotherapy alone showed significantly worse OS (Table II). Of the variables entered into the multivariate analysis, apex axillary invasion, 4–9 and ≥ 10 positive nodes, grade 3, ER negativity, and visceral metastasis were found to have independent detrimental influence on survival. pN3 status influenced survival adversely, and stage IIIC had independently worse survival compared to stage I ($p = 0.014$), IIA ($p < 0.001$), IIB ($p < 0.001$), and IIIA ($p = 0.001$). Solitary bone metastasis and radiotherapy affected survival independently and favourably (Table III).

Median survival time after development of distant metastasis was 50 months (95% CI 28.7–37.2) for solitary skeletal metastasis, 25 months for multiple skeletal metastases (95% CI 20.8–29.1), and 15 months (95% CI 13.6–16.3) for visceral metastasis (Fig. 2; $p < 0.0001$). Median survival after metastasis was also significantly shorter in patients with level III invasion, positive lymph nodes, pN3 status, stage IIIC, < 50 years old, grade 3, and ER-negative tumour, and in premenopausal patients, in patients treated with chemotherapy alone, and patients that did not receive adjuvant systemic therapy. Survival after metastasis was longer in patients with longer metastasis-free intervals (Table II). In multivariate analysis, apex axillary invasion, 4–9 and ≥ 10 positive nodes, grade 3, ER negativity, and visceral metastasis were found to have independent detrimental influence on survival. pN3 status and stage IIIC influenced survival adversely. Solitary bone metastasis and a long MFI affected survival favourably (Table IV).

DISCUSSION

The present study demonstrated that skeletal metastasis had better OS following definitive surgery and survival subsequent to metastasis. Patients with both solitary and multiple skeletal metastases survived longer compared to those with visceral metastasis. Furthermore, solitary bone metastasis had a better outcome than multiple bone metastases. These findings support previous studies, which showed that patients with skeletal metastasis had better OS compared to those with visceral metastasis following surgery,[5] and better survival after metastasis;[4,5,11,17-19] and patients with solitary skeletal metastasis had longer OS following surgery than those with multiple skeletal and visceral metastases,[3] and better survival after metastasis.[9]

The findings of the present study are in accordance with those of other studies, which demonstrated that there was a significant association between low-grade tumours[1,4,5,20] and positive ER,[1,5,10,11,21] and skeletal metastasis as compared to visceral metastasis, and patients with low-grade tumours and ER positive patients had independently favourable prognoses, both for OS after surgery and survival after metastasis.[4,10] These special features associated with the skeletal metastasis may explain the indolent course of the patients with skeletal metastasis. To the best of our knowledge, the present study is the first to demonstrate that the level of axillary invasion and the pN status are correlated to the metastatic site, and are important prognostic factors for survival among patients with metachronous metastasis. Patients with apex axillary invasion and pN3 status had more metastases to multiple bones and viscera, whereas patients with node negative, levels I and II invasion, and pN0–2 status had more metastases to solitary bones. Stage IIIC patients had the worst survival both among patients who developed metastases subsequent to surgery and among patients who had or had not metastasis after surgery,[22-24] and stage IIIC patients had significantly less metastases to solitary bones. In addition to the known prognostic factors such as ER, grade stage IIIC predicts the metastasis site.

Our findings also support the observation that patients with ≥ 4 positive axillary lymph nodes generally have a poor prognosis after the development of metastasis.[4,10,18] Coleman et al pointed out that patients with ≥ 4 positive axillary lymph nodes were more likely to develop the disease outside the skeleton, and tumours with 1–3 or no axillary lymph node involvement are more likely to remain confined to the skeleton.[4] The current finding agrees with those of Solomayer et al who suggested that nodal status was not correlated to skeletal and visceral metastases,[5] but does not agree with the results of Coleman et al.[4] The difference in the results could be due to the evaluation of the first metastases in the present study, whereas Coleman et al analysed metastases confined to the bone and bone plus visceral metastases. The present study also supports the findings of other studies which reported that the number of positive nodes was an independent predictor of length of survival.[3,11] The results of the current work are in contrast with the suggestion that once a patient develops metastatic disease, the lymph node status is not relevant as a predictor of survival.[1,5] However, James et al analysed only the patients with bone metastasis, comparing bone only vs. bone and other distant metastases,[1] and Solomayer et al's series contained significantly more

patients with node negative (31%) than the current series (20%).[5] pN status, grade, and ER were predictive of survival as expected, whereas tumour size was not predictive of survival as suggested.[1,4,18] This data verifies that the intrinsic biological factors of tumours are the indicator of OS in patients with metachronous metastasis following surgery and survival after metastasis.[4,23,24] Increased metastasis-free survival was independently associated with prolonged survival after metastasis, as supported by most of the previous studies.[1,4,5,9,17-19]

Our study has some limitations. First, though the results would not have changed when patients with unknown ER status were excluded in the multivariate survival analysis, 32% of the patients had unknown ER status, which we have presented as a prognostic factor for survival. Second, as in all retrospective studies, adjuvant therapy could have created selection bias. In conclusion, grade and ER status could be used for identifying patients who are likely to have skeletal, or visceral metastasis, and could help in the decision-making process for the treatment of these patients with adjuvant bisphosphonates or other therapies. Our findings confirm that the natural course of the biology of the tumour prevails before and after metastasis. The prognostic factors, as in the current study, could help in the discrimination of the subset of patients with tumours that are likely to metastasise to different sites, which in turn provides an opportunity to apply targeted adjuvant therapy to the bones to reduce metastasis as shown by clinical trials with adjuvant bisphosphonates,[6-8] and to participate in trials to receive novel and aggressive adjuvant therapy for patients with tumours that are prone to visceral metastasis. Thus, patients who want to try new forms of therapy could be encouraged early in the course of the disease, when these therapies are most likely to be effective and the patients have the least to lose if the therapy proves ineffective.[25]

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