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# An Analysis of Possible Prognostic Features of Long Term and Short Term Survivors of Metastatic Breast Cancer

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**Abstract**—*Factors influencing the extremes of survival in disseminated breast cancer were analysed. From a pool of* 1066 *patients with distant metastatic breast cancer, the* 41 *patients who had survived* 5 *yr or more from first distant recurrence were matched with the* 41 *patients with the shortest survival times. Both groups were compared with the pool and, where relevant, with each other. There were no differences with respect to presentation clinical stage, histological subtype, adjuvant therapy or the likelihood of menopause during the disease-free interval. There were significant differences in age, menopausal status, primary treatment, grade, pathological node involvement, time to recurrence, situation and number of sites of metastatic involvement, and response to treatment. The interpretation of these relationships as causal or casual is uncertain; however, given the magnitude of the survival differences, we expected the associated differences to be much greater than we found.*

## INTRODUCTION

ALTHOUGH the median survival for patients with distant metastatic breast cancer is short (usually less than 18 months) a small proportion of patients [1, 2] survive for relatively long periods. Analysis of factors which may influence survival for all patients with metastatic breast cancer may miss prognostic indices relating to long term survivors in the very small percentage of patients (usually $< 4\%$) who live for longer than 5 yr with distant metastatic breast cancer.

We have therefore examined possible prognostic factors by matching the small subgroup of patients who have survived longer than 5 yr with an identical number of patients who survived for less than 5 months, and comparing both subgroups with the total pool of patients with distant metastatic breast cancer who have been treated at the Royal Marsden Hospital, Sutton, since 1970.

## PATIENTS AND METHODS

All patients who presented with, or developed, distant metastatic breast cancer at the Royal Marsden Hospital since 1970, were identified from the cancer registry and Royal Marsden Hospital breast unit records. Information regarding age, date of presentation, primary clinical and histological staging, menopausal status, types of primary surgical, radiotherapeutic and adjuvant systemic therapy, and basic follow up data was obtained from the South West Thames Cancer Registry. Further information regarding sites, treatment and response of metastatic disease and checks on follow up data was made by retrieval of all the clinical case records. In some respects, full information was not available and this is reflected in variations in the group size of the pool.

All these data were included in a special analysis program using the Royal Marsden Breast Unit PDP 11 breast programme. Analysis of factors influencing survival were evaluated using life table analysis and significant differences in subgroup identified by $\chi^2$ analysis [3].

Distant metastases included recurrence in any site other than the chest wall, the ipsilateral regional nodes or the conserved ipsilateral breast in those patients who did not undergo mastectomy. The sites of metastatic involvement were identified by clinical and investigative techniques. Definitive clinical and/or radiological evidence (preferably confirmed where possible by histology) was required in order to confirm metastatic relapse

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after primary treatment. Separate lesions within the major site categories were not distinguished.

Survival for 5 yr or more after metastatic relapse was arbitrarily defined as long term survival (long term group or LT). Short term survival was defined as the same number of patients as the LT group within the total pool who died the quickest (short term group or ST). These patients were all dead within 5 months. In subsequent analysis of these groups, the numbers in each group may be less than the total numbers, where information such as detailed primary histology, types of primary treatment, accurate definition of metastatic involvement and success of systemic treatment has not been adequately documented for accurate assessment. Tumour grade was assessed according to the method of Bloom and Richardson [4]. Clinical staging was defined according to the UICC system [5], and the response of metastatic disease to systemic treatment has been assessed according to UICC criteria [6]. Patients were defined as premenopausal if they were within 6 months of their last menstrual cycle.

## RESULTS

The total number of patients with metastatic breast cancer treated at the Royal Marsden Hospital, Sutton, and identified from the cancer registry was 1066. Forty-one of these survived for more than 5 yr after first evidence of metastatic relapse; median survival in this LT group is 76 months (60–125) and six are still alive. Of the 35 in the LT group who are now dead, 33 died from breast cancer. The 41 patients who survived the shortest time from the pool were all dead from their disease within 5 months; median survival is 2 months (0–5). Median survival for the pool is 14 months.

Long term survivors were significantly ($P < 0.005$) younger (51 +/− 3.3 yr) than short term survivors (59 +/− 3.9 yr) (Table 1). Correspondingly more patients (46%) were premenopausal at primary diagnosis in the long term group than in the short term group (20%) or the pool (21%) ($P < 0.001$). Furthermore, the mean age of post menopausal patients in the long term group was significantly ($P < 0.01$) younger (58 +/− 3.4 yr) than the short term group (63 +/− 2.5 yr) or the pool (63 +/− 0.4 yr).

The primary clinical stage and histological features of the primary tumour are summarized in Table 2. At presentation, the long term group, short term group and pool had a similar distribution of clinical stage and histological subtype of their primary tumours. (Insufficient numbers of patients had oestrogen receptor measured in their primary tumours for this to be included in the analysis.)

There was a significant trend difference ($P < 0.05$) in tumour grade between ST and pool, with ST tending towards higher grade. There was also a significant trend difference between LT and pool in the number of histologically positive axillary lymph nodes; LT tended towards no involvement or fewer involved nodes. With regard to primary treatment significantly ($P < 0.01$) more long term survivors had had a mastectomy of some sort, compared to the short term group and the whole pool (Table 3); however the proportions receiving radiotherapy as part of their initial management were not significantly different.

The sites of involvement of metastatic disease varied significantly amongst the long and short term groups and the pool (Tables 4 and 5). At first relapse none of the long term survivors had liver involvement compared to 16% of the pool and 44% of the short term survivors ($P < 0.001$). Short term survivors also had a significantly higher incidence ($P < 0.001$) of pleural and non-hepatic abdominal involvement compared to the pool and long term groups. Most (63%) long term survivors

*Table* 1. *Menopausal status and age (mean ± S.E. and range in parenthesis) of* 41 *long-term survivors* (> 5 yr), 41 *short term survivors* (< 5 months) *compared to a pool of all* 1066 *patients with metastatic breast cancer*

| | % Premenopausal | | Age at presentation | | |
|---|---|---|---|---|---|
| | At primary diagnosis | At metastatic relapse | All patients | Pre-menopausal | Post menopausal |
| | **** | ** | *** | | ** |
| Long term (41) | 46% | 32% | 51 +/− 3.3 (33–73) | 42 +/− 2.4 (33–51) | 58 +/− 3.4 (46–73) |
| Pool (1066) | 21% | 16% | 57 +/− 0.9 (21–91) | 43 +/− 1.3 (21–59) | 63 +/− 0.4 (44–89) |
| Short term (41) | 20% | 15% | 59 +/− 3.2 (35–88) | 42 ± 3.2 (35–48) | 63 ± 2.5 (47–88) |

**$P < 0.01$
***$P < 0.005$
****$P < 0.001$

*Table 2. Clinical stage and histology (% of total) of 41 long term survivors (> 5 yr), 41 short term survivors (< 5 months) compared to a pool of 1060 patients with metastatic breast cancer. Histological classification was available in only 29 long term, 377 pool and 37 short term patients. Tumour grade was available in 21 long term, 334 pool and 28 short term patients. Eight per cent of long term survivors had an unspecified number of histologically confirmed lymph node involvement*

| | | Clinical stage | | | | | | | | | | Histology | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | T | | | | N | | | M | | | | Grade | | | Axillary node involvement | | | | | |
| | No. | 0/1 | 2 | 3 | 4 | 0 | 1 | 2/3 | 0 | 1 | No. | Infiltrative-ductal | I | II | III | 0 | 1–3 | 4–9 | 10 | | |
| Long term | 41 | 8% | 46% | 31% | 15% | 36% | 52% | 12% | 83% | 17% | 29 | 93% | 5% | 71% | 24% | 44%* | 26% | 19% | 4% | | |
| Pool | 1060 | 13% | 38% | 27% | 22% | 37% | 48% | 14% | 87% | 13% | 377 | 96% | 3% | 60% | 37%* | 26% | 40% | 20% | 14% | | |
| Short term | 41 | 12% | 29% | 32% | 27% | 29% | 61% | 10% | 78% | 22% | 37 | 100% | 0% | 39% | 61% | 18% | 43% | 21% | 18% | | |

*$P < 0.05$.
***$P < 0.005$.

had bone involvement at first relapse (LT vs. pool, $P = 0.06$), but unexpectedly, 7% of the long term group relapsed initially in the brain.

The pattern of distribution of sites of metastatic involvement became more characteristic between the groups as the disease progressed. Throughout their disease, significantly more long term survivors had bone involvement (89%, $P < 0.005$) and CNS involvement (29%, $P < 0.01$) and less had liver involvement (17%, $P < 0.05$) than the pool of patients. In contrast, significantly more short term survivors had visceral involvement (44–73%, $P < 0.001$) than the pool (Table 5). (Comparable information regarding metastatic sites was readily available on only 294 pool patients.)

The number of sites of metastases involved at first metastatic relapse and at death varied between the survival groups (Table 6). Long term survivors had an average $1.1 +/- 0.3$ sites involved compared to $1.3 +/- 0.7$ sites for the pool ($P < 0.05$) and $1.8 +/- 0.9$ sites for the short term survivors ($P < 0.001$). Similarly 90% of long term survivors only had one site involved at first relapse compared to 74% of pool patients ($P < 0.005$) and only 41% of short term survivors. Nineteen per cent of short term survivors had three or more sites involved compared to 7% of the pool patients ($P < 0.005$) and none of the long term survivors.

At death the differences in metastatic involvement were maintained with short term survivors having $3.6 +/- 1.5$ sites involved ($P < 0.001$) and 78% having at least three sites involved compared to long term survivors who had a mean of $2.5 +/- 1.4$ sites involved and 63% having less than three sites involved ($P < 0.005$).

Only 6/41 LT survivors remain alive at the time of submission. Four of these have active disease but two are ostensibly disease-free, 5 yr after pulmonary metastasectomy.

Response to treatment of metastatic disease is described in Table 7. Only 61% of short term survivors received endocrine therapy, two of whom (8%) showed evidence of objective response (UICC criteria) compared to 93% of long term survivors who received endocrine therapy, 35 of whom (92%) responded. Similarly, in the short term group only 3 of 20 patients (15%) who received chemotherapy responded compared to 7 of 13 (54%) long term patients. Furthermore only 5 of 11 (45%) of short term survivors responded to palliative radiotherapy compared to 28 of 30 (93%) of long term survivors.

Differences in the growth rate of tumours after metastatic relapse may be reflected in the time taken to relapse (disease free interval or DFI). The DFI for long term survivors was significantly

*Table 3. Primary surgical and radiotherapy treatment for 41 long term (> 5 yr), 41 short term (< 5 months) compared to a pool of 422 patients with metastatic breast cancer*

| | Surgery (%) | | | | Radiotherapy (%) | |
|---|---|---|---|---|---|---|
| | Mastectomy | Tylectomy | Biopsy | None | Yes | No |
| Long term | ** | | | | | |
| (41) | 76 | 7 | 10 | 7 | 63 | 37 |
| Pool | | | | | | |
| (422) | 48 | 26 | 15 | 11 | 55 | 45 |
| Short term | | | | | | |
| (41) | 49 | 24 | 20 | 7 | 66 | 34 |

$^{**}P < 0.01$

*Table 4. % Distribution of sites of first metastatic relapse in 41 long term survivors (> 5 yr), 41 short term survivors (< 5 months) compared to the pool of patients with metastatic breast cancer*

| | Bone | Pleura | Lung | Liver | Abdomen | CNS | Soft tissue (exc. loco-regional) |
|---|---|---|---|---|---|---|---|
| Long term | | | | **** | | | |
| (41) | 63 | 10 | 20 | 0 | 2 | 7 | 7 |
| Pool | | | | | | | |
| (410) | 48 | 10 | 25 | 16 | 6 | 3 | – |
| Short term | | **** | | **** | **** | | |
| (41) | 46 | 34 | 24 | 44 | 20 | 12 | 12 |

$^{****}P < 0.001$

*Table 5. % Distribution of all sites of metastatic disease from relapse to death in 35 long term survivors (> 5 yr), 41 short term survivors (< 5 months) compared to a pool of 294 patients with metastatic breast cancer who are now dead*

| | Bone | Pleura | Lung | Liver | Abdomen | C.N.S. | Soft tissue (exc. loco-regional) |
|---|---|---|---|---|---|---|---|
| Long term | *** | | | * | | ** | |
| (35) | 89 | 17 | 23 | 17 | 14 | 29 | 49 |
| Pool | | | | | | | |
| (294) | 65 | 11 | 38 | 34 | 16 | 12 | 47 |
| Short term | | **** | | **** | **** | | |
| (41) | 71 | 44 | 51 | 73 | 49 | 10 | 54 |

$^{*}P < 0.05$
$^{**}P < 0.01$
$^{***}P < 0.005$
$^{****}P < 0.001$

longer ($P < 0.005$) and for short term survivors significantly shorter ($P < 0.005$) than for pool patients (Fig. 1). These differences are maintained when M1 patients are excluded (data not shown).

DFI depends in part on the particular site of relapse (because of variable case of detection); site distribution at first relapse is different for the groups (Table 4). We controlled for this by comparing DFI in those patients who initially relapsed in the same site; only in bone were there sufficient numbers to permit a statistical analysis. The differences were maintained (Fig. 2) but only the ST vs. pool difference was statistically significant ($P < 0.01$).

*Table 6. Number of sites involved at first metastatic relapse for 41 long term survivors, 41 short term survivors compared to the pool of 410 patients with metastatic breast cancer. Also total number of sites involved throughout metastatic illness till death for 35 long term survivors, 41 short term survivors, compared to a pool size of 294 patients with metastatic breast cancer who have died*

| | At metastatic relapse | | | | | By death | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean number per patient +/− S.E. | Number of sites | | | | Mean number per patient +/−S.E. | Number of sites | | | |
| | | 1 | 2 | 3 | 4+ | | 1 | 2 | 3 | +4 |
| | * | *** | | | | | | *** | | |
| Long term | 1.1 +/− 0.3 | 90% | 10% | 0% | 0% | 2.5 +/− 1.4 | 20% | 43% | 26% | 11% |
| Pool | 1.3 +/− 0.7 | 74% | 20% | 5% | 2% | 2.2 +/− 1.2 | 32% | 31% | 22% | 14% |
| | **** | | | *** | | **** | | | *** | *** |
| Short term | 1.8 +/− 0.9 | 41% | 39% | 17% | 2% | 3.6 +/− 1.5 | 2% | 20% | 37% | 41% |

*$P < 0.05$
***$P < 0.005$
****$P < 0.001$

*Table 7. Number (%) of long term survivors (> 5 yr) vs. short term survivors (< 5 months) with metastatic breast cancer who received and responded to systemic endocrine therapy, chemotherapy and/or palliative radiotherapy*

| | Endocrine therapy | | Chemotherapy | | Radiotherapy | |
|---|---|---|---|---|---|---|
| | Number (%) received of total | Number (%) responders of recipients | Number (%) received of total | Number (%) responders of recipients | Number (%) received of total | Number (%) responders of recipients |
| Long term (41) | 38 (93%) | 35 (92%) | 13 (32%) | 7 (54%) | 30 (73%) | 28 (93%) |
| Short term (41) | 25 (61%) | 2 (8%) | 20 (49%) | 3 (15%) | 11 (27%) | 5 (45%) |

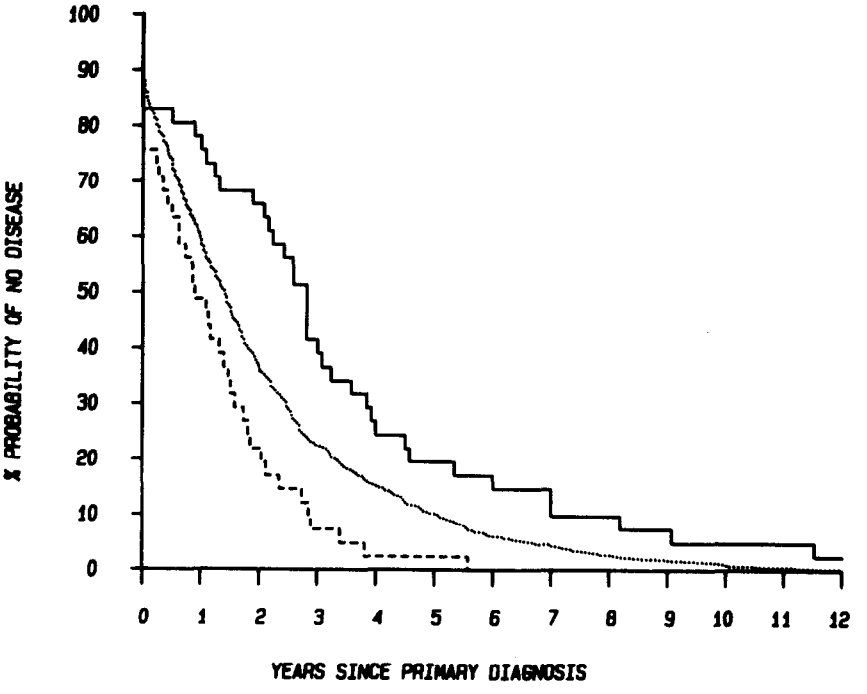


*Fig. 1. Disease-free interval in 988 pool patients (····), 41 long term survivors (——) and 41 short term survivors (----). Differences (LT vs. pool and ST vs pool) are significant ($P < 0.005$).*

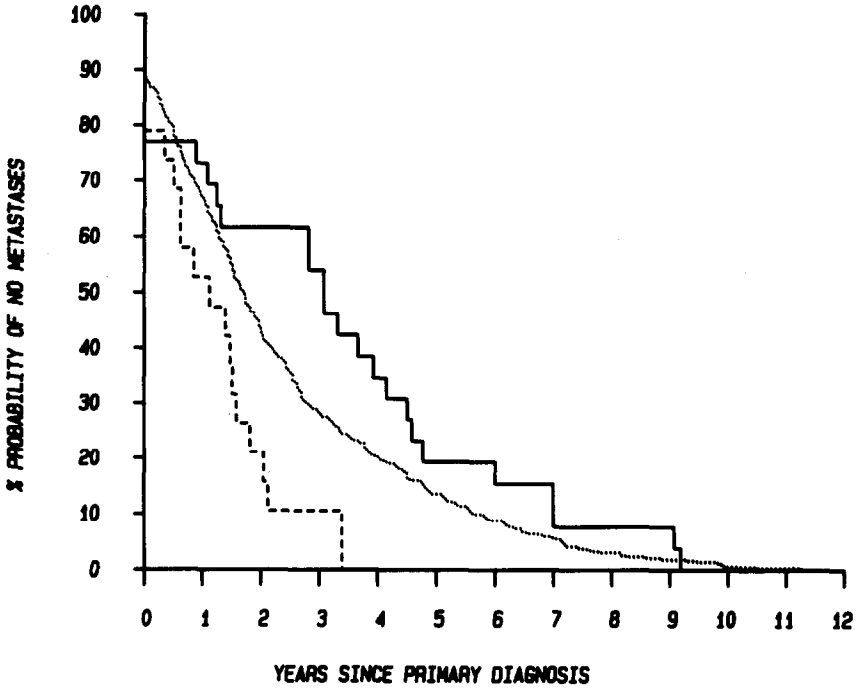


*Fig 2. Metastasis-free interval in 451 pool patients (····), 26 long term survivors (——) and 19 short term survivors (----) who relapsed initially in bone. The ST vs. pool difference is significant ($P < 0.01$).*

## DISCUSSION

Contrary to popular belief [7] it seems that younger patients are more likely to survive 5 yr with metastatic breast cancer than older patients. More long term survivors were premenopausal and even postmenopausal long term survivors were younger than their short term counterparts. These results contrast with studies showing that age has no prognostic significance [2, 8, 9]. There was no difference in the proportion of premenopausal patients who experienced menopause during the disease-free interval.

Difference in histological subtype cannot be advanced to account for post-relapse survival trends, and the known irrelevance of presentation clinical stage [8, 10] is confirmed. Contrary to what we expected [10, 11] pathological (but not clinical) axillary nodal status appeared to be important; we also saw a correlation of tumour grade with survival [4].

The prevalence of mastectomy vs. conservation primary treatment varied between the groups; this probably reflects the gradual changes in treatment policy over the period of patient accruel, with long term survivors more likely to have received the older policy treatment of mastectomy. From these data it is not possible to conclude that mastectomy vs. conservation contributed to long term survival with metastatic disease.

The site of distribution of metastases at the time of first distant relapse confirms [2, 7, 10, 12, 13] that visceral involvement, with its consequential life threatening potential, is the most important factor in determining the likelihood of surviving for a relatively long time vs. dying relatively quickly. Similarly, we agree that the presence of bone metastases (especially in relation to response to endocrine therapy) is an important factor for potential long term survival [8]. In particular it was our impression that in those patients with bone disease, this was at least twice as likely to be a dominant feature of their illness in LT compared to ST.

The number of sites involved at first relapse being significantly more in short term vs. long term survivors indicates that extent of metastatic disease is also of major prognostic significance. Curiously, these differences are maintained till death when it might have been supposed that the differences in time to death would have allowed the extent and sites of life threatening disease to be the same.

With regard to CNS disease, there was a significantly increased incidence of CNS involvement at death in LT. In part, it may be argued that patients who live longer have more time to develop metastases in the brain although this does not seem to apply to visceral metastases. Alternatively it may be that CNS disease does not inevitably carry its reputed poor prognosis, which is supported by the 7% incidence for CNS involvement in site of first metastasis in the long term survival group. However, only three patients who presented with CNS disease at first relapse survived more than 5 yr.

The observed increased response to treatment by long term survivors compared to short term survivors may imply survival benefit from successful treatment. Alternatively, patients who would have survived for a longer time without treatment, have more time and opportunity to objectively respond to various treatments without necessarily gaining survival benefit from any response. Nonetheless the two predominant features of long term survival with metastatic disease are a high incidence of bone metastases and a high preponderance of response to treatment.

Finally, as with other studies [2, 7, 8, 11, 12] the analysis of disease-free interval in relation to subsequent survival with metastatic disease indicates that long term survivors took longer to relapse and short term survivors less time to relapse after primary treatment than the general pool of all patients. As few of these patients had adjuvant systemic therapy after primary treatment, it would seem likely that long term survivors with metastatic disease had slower growing tumours and short term survivors faster growing tumours independent of any subsequent treatment. The trend towards higher grade primaries in ST is noteworthy in this respect.

In conclusion, it would seem that there are differences in age, menopausal status, primary treatment, grade, nodal involvement, time to metastatic relapse, sites and extent of metastases and response to subsequent treatment. How much these differences reflect the natural history of the disease, rather than cause and effect relationships, is debatable. In our opinion, given the very large differences in survival for the ST (< 5 months) vs. the LT (> 5 yr) patients, it is surprising that there were not very much more striking differences in the patient/tumour characteristics of the two groups. This would imply that there may be very much more important prognostic features of metastatic breast cancer which have not, as yet, been identified, and whose relationship with the factors we have analysed is at most indirect; however, because of the small numbers of patients in our extreme survival groups, it is hazardous to draw firm conclusions.

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