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Liver Metastases from Breast Cancer: the Relationship between Clinical, Biochemical and Pathological Features and Survival

Susan M. O'Reilly, Michael A. Richards and Robert D. Rubens

The clinical records of 312 consecutive patients with liver metastases from breast cancer were reviewed. The primary tumours were commonly poorly differentiated, although the majority were steroid receptor positive. At diagnosis of liver metastases, 60% of patients had hepatomegaly, 13% were jaundiced and 7% had ascites. A raised serum aspartate transaminase (AST) was the most common biochemical abnormality (84%), with 54% of patients having an AST of more than twice the upper limit of normal. The median survival from the time of diagnosis of liver metastases was 3.8 months. No feature existing prior to the development of liver metastases influenced subsequent survival. The presence of jaundice ($P < 0.001$), ascites ($P = 0.01$) or hepatomegaly ($P = 0.01$) were all associated with a particularly poor prognosis. While any degree of elevation of bilirubin ($P < 0.001$) or alkaline phosphatase ($P = 0.003$) was unfavourable, a raised AST alone was not predictive of shorter survival. AST only influenced survival significantly when above twice the upper limit of normal ($P < 0.001$), with prognosis then progressively worsening the more elevated the level. Multivariate analysis using the Cox model suggested that the degree of elevation of AST was the single most important prognostic factor for survival after the diagnosis of liver metastases.
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INTRODUCTION

PATIENTS with liver metastases from breast cancer generally have a poor prognosis with a median survival from liver relapse of 2–14 months [1–3]. Treatment of these patients presents a difficult clinical problem. Response to endocrine therapy is uncommon [4], while the administration of chemotherapy can be complicated by the involvement of the liver in the activation or metabolism of several cytotoxic drugs commonly used in the treatment of advanced breast cancer [5, 6]. We report here our experience of all patients with liver metastases from breast cancer seen in this unit over a 13-year period. The clinical and pathological features associated with liver metastases are described and the impact of these features on survival is analysed.

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PATIENTS AND METHODS

Three hundred and twelve patients seen in the ICRF Clinical Oncology Unit at Guy's Hospital between January 1974 and December 1986 had liver metastases from breast cancer diagnosed before death. Liver metastases were diagnosed on radionuclide or ultrasound liver scan in 293 patients (94%). Scanning of the liver was not performed routinely. Liver scans were obtained only if hepatomegaly was detected clinically or if liver biochemistry was abnormal.

Hepatomegaly was assessed clinically. The biochemical profile included serum bilirubin, aspartate transaminase (AST), alkaline phosphatase and albumin. As the laboratory normal range of these biochemical measurements varied during the period covered by this study the results are expressed as a ratio to the upper limit of the normal range at the time of measurement.

Response to treatment for liver metastases was assessed by UICC criteria [7] and refers to response in the liver only. Survival was measured from the date of diagnosis of liver metastases to death. Chi-square analysis was used to assess differences between subgroups of patients and the log-rank test was used to assess the influence of clinical and pathological features on survival

[8]. Multivariate analysis was performed using the stepwise Cox regression model [9].

RESULTS

Patients' characteristics at diagnosis of breast cancer and survival

Two hundred and forty-three patients (78%) had stage I or II disease, 44 (14%) patients had locally advanced disease and 25 (8%) patients had metastatic disease at diagnosis of breast cancer. Infiltrating ductal carcinoma was the most common histological type (229/312), with 58% of these being grade 3 (poorly differentiated) tumours. Oestrogen receptor (ER) status was recorded for 163 tumours and progesterone receptor (PgR) status for 137. One hundred and six patients (67%) had ER positive (≥10 fmol/mg cytosol protein) tumours and 70 patients (51%) had PgR (≥10 fmol/mg cytosol protein) positive tumours.

The median survival from diagnosis of liver metastases was 3.8 months, with 10% of patients alive 1 year after diagnosis. Only two of the 312 patients are currently alive. Survival was not influenced by the stage ($P = 0.4$), degree of histological differentiation ($P = 0.2$), ER status ($P = 0.3$) or PgR status ($P = 0.4$) of the primary tumour.

Patients' characteristics at diagnosis of liver metastases and survival

Survival after liver relapse was not related to the extent of extrahepatic metastatic spread. There was no difference in survival between patients whose disease was confined to liver alone and those who also had bone metastases ($P = 0.7$) or those who had evidence of spread to two or more extrahepatic sites ($P = 0.5$).

On clinical examination, 187 patients (60%) had hepatomegaly, 42 (13%) were jaundiced and 22 (7%) had ascites. Patients with jaundice had a median survival of 4 weeks compared with 18 weeks for those without ($P < 0.001$). Similarly, patients with ascites at diagnosis of liver metastases had a significantly poorer prognosis than those without ascites (median survival 6 weeks vs. 18 weeks, $P = 0.01$). Patients with hepatomegaly had a median survival of 13 weeks compared with 19 weeks for those patients whose livers were not palpable ($P = 0.01$).

There was biochemical evidence of liver dysfunction in 92% of patients at diagnosis. The most common biochemical abnormality was a raised AST (263/312) with 168 patients (54%) having an AST more than twice normal. Total serum alkaline phosphatase was raised in 237 patients (76%), although this reflects, in part, the presence of bone metastases in the majority of patients. 22% of patients had a raised serum bilirubin. Albumin was less than 35 mg/ml in 75/222 (34%) patients for whom it was recorded. While any elevation of serum bilirubin (Fig. 1) or alkaline phosphatase (Fig. 2) was unfavourable, a raised AST only influenced survival adversely when above twice the upper limit of normal (Fig. 3). Further elevation of AST above this level was associated with a progressive worsening of survival. Patients with an albumin ≥ 35 mg/ml had a significantly better prognosis than those with an albumin <35 mg/ml ($P = 0.01$).

Treatment for liver metastases and survival

Fifty-one patients (16%) received symptomatic treatment only following the diagnosis of liver metastases. Ninety patients (29%) were treated initially with endocrine therapy. In general, these patients were less likely to have markedly deranged liver function than those selected to receive chemotherapy (AST < 2 × normal: 60% vs. 41%, $P < 0.01$). The response rate to first-line endocrine treatment for liver metastases was 9%. Thirty-eight of the 90 patients subsequently received chemotherapy, most commonly (25/38) because of progression of liver metastases. Patients who were given endocrine therapy as initial treatment for liver metastases had a median survival of 4.6 months (range 0–27), but the subgroup who did not subsequently receive chemotherapy had a median survival of only 2.8 months (range 0–24).

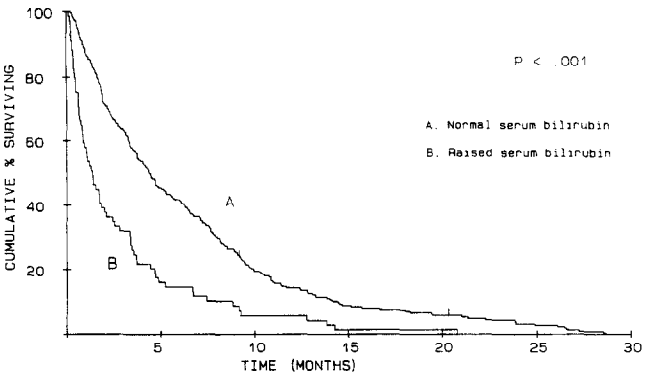

Fig. 1. Survival after diagnosis of liver metastases: normal bilirubin vs. raised bilirubin.

One hundred and seventy-one patients (55%) received chemotherapy as their first treatment for liver metastases and 208 patients (67%) received chemotherapy at some time during treatment. The overall response rate to chemotherapy given as first treatment for liver metastases was 20%. Combination chemotherapy with CMF was the most common regimen used, 102 patients receiving it as their first treatment, with an additional 27 patients being given CMF after an initial trial of endocrine therapy. Patients receiving CMF as first treatment had a 16% response rate to treatment with a median survival of 4.6 months (range 0–28). Forty-one patients were treated with single-agent doxorubicin initially, with 10 further patients receiving doxorubicin later in the course of their disease. These patients had a 39% response rate, with a median survival of 9.6 months (range 1–28). However, patients chosen to receive CMF were significantly more likely to have an AST greater than twice normal compared with patients who received doxorubicin [65/102 (64%) vs. 17/41 (41%), $P = 0.03$].

There was no significant difference in survival when patients who received chemotherapy as initial treatment for liver metast-

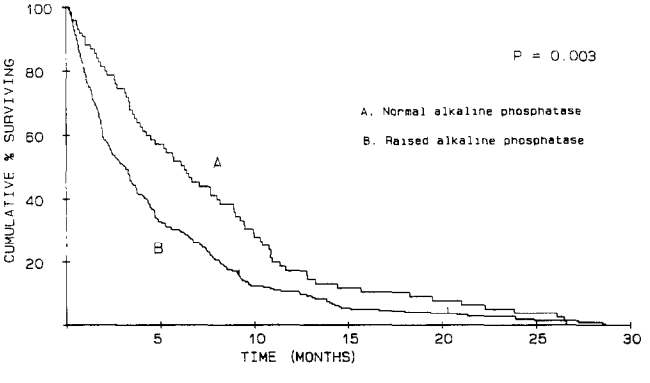

Fig. 2. Survival after diagnosis of liver metastases: normal alkaline phosphatase vs. raised alkaline phosphatase.

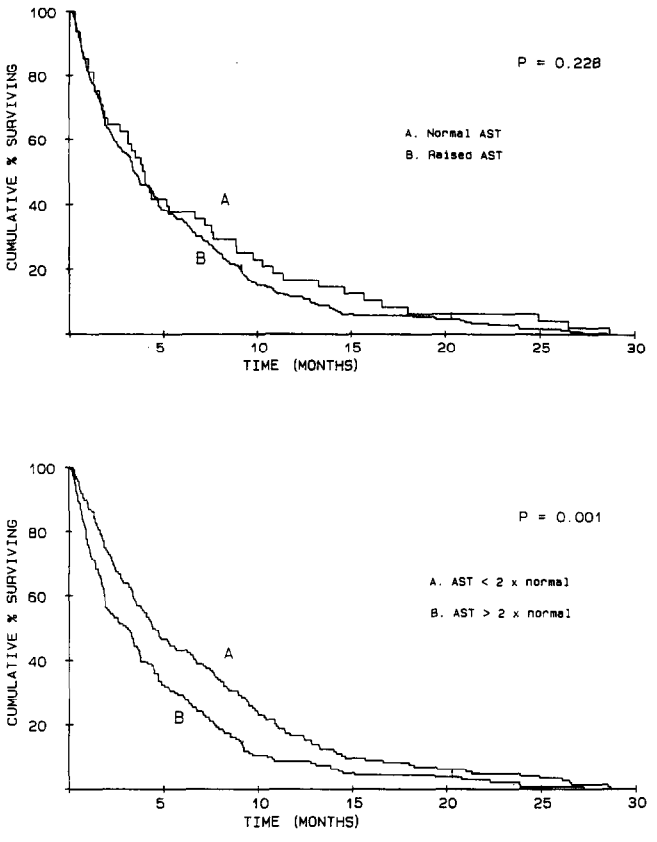

Fig. 3. Survival after diagnosis of liver metastases: (upper) normal AST vs. raised AST; (lower) <2 × normal AST vs. >2 × normal AST.

ases were compared with those who had a trial of endocrine treatment before receiving chemotherapy. The 33 patients who survived more than 1 year from diagnosis of liver metastases were evenly split between those who received first-line endocrine treatment (n = 16) and those who received first-line chemotherapy (doxorubicin n = 7; CMF, n = 10).

Multivariate analysis

The relative prognostic significance of factors that influenced survival on univariate analysis was evaluated using the Cox proportional hazards model. In all analyses, AST was the strongest independent predictor of outcome ($P < 0.001$). Alkaline phosphatase was the only other factor of independent significance ($P = 0.03$).

DISCUSSION

Despite the fact that patients with liver metastases from breast cancer present a common management problem, there is only one major review specifically analysing the clinical course of these patients [3]. Zinser *et al.* reported a median survival of 14 months for 233 patients treated in the M.D. Anderson hospital in the 1970s compared with a median survival of 5 months for 58 patients treated in the 1950s. However, the patient populations in the two studies differ in a number of ways. Firstly, at Guy's hospital routine screening liver scans were not performed, either at diagnosis of breast cancer or during subsequent follow-up. While Zinser *et al.* do not specifically address this point, the high incidence of liver metastases detected at initial diagnosis of breast cancer (15% compared with 2.5% in our series) might suggest that screening was performed. Secondly, a higher proportion of patients treated at Guy's hospital had marked impairment of liver function at diagnosis. Serum AST, which on multivariate analysis was the most important factor predicting outcome in our study, was above twice normal in 54% of our patients compared with 36% of patients in the M.D. Anderson study.

The third major difference between the studies is in the treatment used. All patients in the M.D. Anderson were considered fit for combination chemotherapy using a doxorubicin–containing regimen. In our study, 16% of patients were considered too unwell at diagnosis to receive any specific anti-cancer therapy. 67% of patients were given chemotherapy as treatment for liver metastases, although only 16% of patients received doxorubicin, given as a single agent. There is undoubtedly a large difference in median survival between the two centres. It is difficult to escape the conclusion that this difference is attributable, at least in part, to the different treatment policies.

Liver metastases have been reported to occur more frequently in patients with steroid receptor negative tumours [10]. In this study more than half the patients in whom receptors were measured had tumours that were positive for at least one steroid receptor at initial diagnosis, which confirms the findings of a previous report from this unit [11]. While patients with receptor positive tumours usually have a better prognosis after first relapse [12], in this study survival after relapse in the liver was independent of receptor status at initial diagnosis. This finding, and the low response rate to endocrine therapy, may reflect loss of steroid receptors as disease progresses.

Classification of patients according to extent of extrahepatic spread did not provide useful prognostic information. Patients with disease confined to the liver alone did not survive longer than those with multiple metastatic sites. The extent to which liver function is impaired was the only significant determinant of survival after the development of liver metastases.

This analysis demonstrates that this unselected group of patients with liver metastases from breast cancer has a very poor prognosis, with a median survival of less than 4 months. The outcome for these patients does not appear to relate to the clinical pattern of disease before the development of liver metastases. Rather, spread to the liver determines survival thereafter. Prognostic subgroups can be identified only on the basis of clinical and biochemical features at liver relapse, with serum AST being the most significant single measurement. Patients with liver metastases had a very poor response to either endocrine therapy or CMF chemotherapy in this study, but a higher response rate was seen when doxorubicin was used. Taken in conjunction with the report from Zinser *et al.* [3], this suggests that an anthracycline, probably used in combination with other cytotoxic agents, is necessary to achieve a worthwhile response in these patients.

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CA-15.3, TPA and MCA as Markers for Breast Cancer

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Serum concentrations of CA-15.3, tissue polypeptide antigen (TPA) and mucinous-like carcinoma-associated antigen (MCA) were measured in 327 women: 81 controls, 93 patients with benign breast disease, 46 patients recently diagnosed with breast cancer and 107 patients during breast cancer follow-up. CA-15.3 was elevated in 16% of the controls, in 29% of the patients with benign breast disease, in 65% of the breast cancer patients and in 74% of the follow-up patients. TPA was elevated in 4%, 11%, 36% and 75%, respectively. The corresponding figures for MCA were 10%, 8%, 30% and 64%. The highest sensitivity for cancer detection (74%) was obtained with a combination of CA-15.3 and TPA, while the specificity of this panel was 75%. The negative predictive value of these combined tests was 93%. MCA scored lower values, being only 30% sensitive. The CA-15.3/TPA panel may increase sensitivity compared with single marker tests and provide additional information for clinical evaluation.
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INTRODUCTION

CARCINOMA of the breast is the leading cause of cancer mortality among women in western countries [1]. Early detection will enable prompt treatment and reduce mortality and morbidity. However, in primary breast cancer the 'classic' tumour markers, carcinoembryonic antigen (CEA) [2] and tissue polypeptide antigen (TPA) [3], are neither sensitive nor specific enough to indicate the spread of the disease and its clinical course. Monoclonal antibodies (Mab) techniques are more sensitive and specific than previous assays. Mabs against the milk fat globule membrane (115D8, BC4N154), against enriched fractions of membranes from metastatic breast cancer (DF3), against breast carcinoma cell lines (BC4E 549, b8, b12, b15) and against a high molecular-weight glycoprotein (3×10^5) from human serum (3E 1.2) are used together in several tests. CA15-3 uses 115D8 and DF3 [4]; mucinous-like carcinoma-associated antigen (MCA) uses b12 [5]; MSA uses 3E 1.2 [6]; and CA549 uses BC4E 549 and BC4N154 [7]. With these markers in breast cancer, detection among patients with breast problems sensitivity was at best 45% and specificity 90%.

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