Breast liver metastases - incidence, diagnosis and outcome

A L Hoe FRCS **G T Royle** MS FRCS **I Taylor** MD *University Surgical Unit, Royal South Hants Hospital, Southampton*

Keywords: breast cancer; liver metastases

Summary

Breast liver metastases are uncommon and have not been well reported. We studied the clinical outcome of 47 patients who developed liver metastases out of 912 breast cancer patients treated between 1982 and 1987, an incidence of 5.2%.

The median disease free interval prior to clinical liver metastases was 20.2 months (range 4-192 months). The most frequent clinical presentations were hepatomegaly (70%) and abdominal pain (34%). The diagnosis was confirmed on ultrasound scan in 72.7% patients.

Thirty-one patients (70.5%) received specific treatment with both hormone and chemotherapy but only six showed any evidence of objective response, the majority of whom had metastases only in the liver.

The median survival of treated patients was 4 months and absence of jaundice, response to treatment and liver metastases only were associated with significantly better survival.

In conclusion breast liver metastases usually present as a manifestation of disseminated disease and have an appalling prognosis. When they occur as an initial site the prognosis is better but very few patients overall respond to conventional treatment.

Introduction

The liver is the most frequent site for blood borne metastases and is involved in up to one-third of metastasising cancers[1]. The main origins are gastrointestinal tumours which drain primarily via the portal circulation, eg colorectal cancer.

Conversely, systemic malignancies, eg breast cancer must first transverse the pulmonary circulation before encountering the liver. Hence the incidence of hepatic metastases from systemic primaries are less than from gastrointestinal malignancies[2].

Most reports of liver metastases concentrate on the gastrointestinal tract. There are few reports dealing with patients with breast hepatic metastases alone. In this study we have reviewed those patients who have specifically developed breast hepatic metastases, concentrating on clinical outcome.

Patients and methods

All patients presenting with breast cancer over a 6 year period (1982 to 1987) were reviewed.

After primary treatment of their breast cancer, all patients were followed up regularly in a specialized Breast Clinic. At each follow-up visit a careful history and physical examination was performed to detect any evidence of metastases. A 'metastatic workup' of liver function tests, chest X-ray, radionuclide bone scan and abdominal ultrasound scan was performed only when there was suspicion of metastatic disease.

All patient details were entered into a computerized breast cancer database which was updated at regular intervals.

Those patients who subsequently developed clinical hepatic metastases were identified from the computer and analysed with particular attention to the following: (1) method of diagnosis (2) clinical presentation, (3) response to treatment and (4) survival.

Survival analysis was performed by the method of Kaplan and Meier[3]. The log rank test of Mantel and Haenszel[4] was used to test the significance of differences in survival of various subgroups of patients.

Results

Of the 912 breast cancer patients treated between 1982 to 1987, 47 subsequently developed clinical liver metastases (an incidence of 5.2%). The median follow-up was 77 months (range 38-106 months). Three patients were excluded from the study because of a lack of clinical details on their hepatic metastases. This analysis is thus based on 44 patients.

Patient details

The mean age was 58.3 years (range 30-84 years). There were 10 premenopausal and 34 postmenopausal patients. Thirty-one patients (70%) had UICC[5] stage I and II cancers at the time of initial diagnosis, 11 (25%) had locally advanced disease (stage III) and 5 (11.4%) had advanced breast cancer (stage IV). Three patients with stage IV breast cancer presented with distant metastases; two of whom had bone metastases and one with liver metastases. Most of the patients with stage I and II breast cancer were treated with mastectomy and axillary clearance, some were also given postoperative radiotherapy and adjuvant hormonal or chemotherapy.

Oestrogen receptor status was available in 20 patients; 14 (70%) were ER positive and six (30%) were ER negative.

The median disease free interval (DFI) measured from the time of treatment of the primary to the onset of the first recurrence (including locoregional recurrence or extrahepatic metastases) was 20.2 months (range 4-192 months).

Ten patients (22.7%) presented with hepatic metastases only, 11 patients (25%) had hepatic metastases synchronously with locoregional recurrence and/or extrahepatic metastases and 23 patients (52%) developed hepatic metastases following locoregional recurrence and/or extrahepatic metastases. Thus multiple sites of metastases were seen in 34 patients (77.3%).

Correspondence to: Professor I Taylor, University Surgical Unit, Centre Block, 'F' Level, Southampton General Hospital, Tremona Road, Southampton SO9 4XY

0141-0768/91/120714-03/$02.00/0

Clinical features

Fourteen patients (31.8%) did not have symptoms specific to the liver. The majority had extrahepatic metastases and the presence of hepatic metastases was suspected when hepatomegaly was found, when liver function tests were abnormal or when the ultrasound scan performed as part of the metastatic 'workup' was positive.

Non specific complaints such as malaise, weight loss, nausea and vomiting were noted in 12 patients (27.3%).

The most frequent specific complaint was abdominal pain, a dull ache in the right hypochondrium in 16 patients (36.4%). Only three patients complained of jaundice.

The specific clinical findings were hepatomegaly, jaundice and ascites. Twenty-nine patients (70.5%) had an enlarged liver which was usually hard, nodular with an irregular edge. Eleven patients (25%) were found to be jaundiced while ascites was detected in five patients (11.4%). Thirteen patients (29.5%) had two or more physical signs.

Diagnosis

In 32 patients (72.7%) the diagnosis of hepatic metastases was based on a positive ultrasound scan of the liver. Even though an accurate estimate of the extent of hepatic involvement from the ultrasound scan was not possible, metastatic invasion of both lobes of the liver was seen in 29 patients (90.6% of positive scans).

In nine patients (20.4%) the diagnosis of hepatic metastases was based on the clinical presentation and the liver function tests. Ultrasound scans have not been done in these patients because they presented with advanced disease and were too ill to undergo the procedure.

Invasive techniques were rarely used for the diagnosis of hepatic metastases. Needle liver biopsy was carried out only in one patient and it was positive. Liver metastases were noted at autopsy in one patient in whom both liver function tests and ultrasound scan were reported as normal. In a further patient hepatic metastases were discovered at laparotomy for a perforated duodenal ulcer.

Results of liver function tests were available in 40 patients. Serum alkaline phosphatase was raised in 33 (82.5%) by an average of 3.3×normal. In 20 patients without bone metastases it was raised in 18 patients (90%). Serum aspartate aminotransferase was raised in 28 patients (71.7%), average 4.2×normal. In contrast, a raised serum bilirubin was seen in 14 patients (27.8%). A serum albumin of <3 g/ml was found in nine patients (22.5%).

Survival

The median survival (Figure 1) of treated patients was 4 months compared to 0.5 months for patients with no treament (logrank test $t=12.87$, $P<0.001$). Table 1 lists the median survival of patient subgroups and their corresponding logrank tests. Absence of jaundice, objective response to treatment and liver involvement alone were associated with a significantly better survival in this univariate analysis.

Discussion

The incidence of patients developing clinical liver metastases in this study was 5.2%. Other authors have reported incidences ranging from 1.5% to 20%

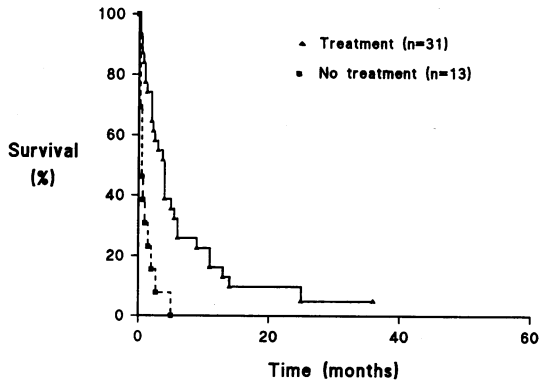

Figure 1. Survival of breast cancer patients with liver metastases comparing treatment versus no treatment

depending on the type of patients, method of diagnosis and the length of follow-up[8-13]. De Rivas *et al.*[8] employing routine ultrasound and scintiscan for patients presenting with breast cancer found positive evidence for hepatic metastases in 1.5% of patients. In practice however liver scan is not routinely performed and the incidence is less. In the present study, only one patient was found to have hepatic metastases at the time of initial diagnosis of breast cancer. With longer follow up the incidence of hepatic metastases will be higher but generally the incidence is $<10\%$ in clinical studies[9,10].

However in patients who develop metastatic breast cancer the incidence of hepatic metastases is 15-20% on liver scanning[11,12] and 34.5% at laparotomy[13]. Autopsy studies have shown the incidence of liver metastases to be as high as 61%[14]. The liver at autopsy in such patients are normal in size in 30% and the metastases are less than 2 cm in 31%[15]. The disparity in the incidence of breast liver metastases between autopsy and clinical studies is due in part to the limitations of current liver imaging techniques[16]. Moreover by the time hepatic metastes are symptomatic and clinically detectable most of the liver is already replaced by tumour[17]. In our study, 90.6% of patients had involvement of both lobes of the liver.

About 70% of our patients had specific symptoms and signs, most commonly hepatomegaly and abdominal pain. Careful clinical assessment of breast

Table 1. Median survival of patient subgroups and univariate comparison using logrank test

Patients	*Median survival (months)*	*Incidence*
Premenopausal ($n=10$)	3.5	NS
Postmenopausal ($n=34$)	2.0	
ER+($n=14$)	1.75	NS
ER−($n=6$)	3.25	
Jaundice ($n=11$)	0.75	$P<0.025$
No jaundice ($n=33$)	3.0	
Hepatomegaly ($n=31$)	2.0	NS
No hepatomegaly ($n=13$)	4.0	
Ascites ($n=9$)	2.5	NS
No ascites ($n=35$)	2.0	
Objective response ($n=6$)	13.5	$P<0.001$
Disease progression ($n=24$)	2.4	
Liver metatases alone ($n=10$)	8.5	$P<0.01$
Multiple sites ($n=34$)	2.0	
Albumin >3 g% ($n=30$)	2.6	NS
Albumin <3 g% ($n=9$)	1.0	

cancer patients suspected of hepatic metastases is thus important, a view shared by others[12,17].

The majority of patients (82.5%) had a raised serum alkaline phosphatase. It is however not specific for liver metastases as it is an isoenzyme found also in the bones, intestines and kidneys[18]. Thus bone metastases contributed significantly to the raised alkaline phosphatase in many patients. However it is still useful in screening for hepatic metastases as a normal value excludes hepatic metastases in over 90% of patients[12]. It is necessary to scan for hepatic metastases only when the alkaline phosphatase is abnormal. De Rivas *et al.*[8] demonstrated that a raised alkaline phosphatase is detected earlier than a positive scintiscan or ultrasound scan.

Abdominal ultrasound scan was most often used in patients. Of 34 ultrasound scans, 32 (94%) were positive. Kamby *et al.*[12] reported that a positive ultrasound diagnosis was confirmed by needle biopsy in 92% of patients. Schreve *et al.*[19] recommend ultrasound rather than either scintiscan or CT scan for detection of liver metastases from gastrointestinal tumours. However breast hepatic metastases are morphologically[2] and scintigraphically[20] different from colorectal metastases and Alderson *et al.*[21] have found CT scan to be more accurate for breast metastases.

Approximately 30% of patients were unsuitable for treatment and their survival was extremely poor (median survival 0.5 month). However, most had extrahepatic metastases also. A previous study on untreated liver metastases has reported similar findings[22].

Even among patients receiving specific treatment the median survival was only 4 months. Patients with breast hepatic metastases have a poor prognosis and the liver as a site of metastases has been referred to as a 'dire prognostic organ'[23]. However, we were able to identify a group of patients who had significantly better survival and response to treatment and they were patients with liver metastases alone. Even though they formed a small proportion of the total number with hepatic metastases it is worthwhile to identify them for aggressive treatment.

Acknowledgments: A L Hoe is a recipient of an HMDP Fellowship from the Ministry of Health, Singapore. We are grateful to Mary Cross for assistance.

References

1 Sherlock S. Hepatic tumours. In: *Diseases of the liver and biliary system*, 6th edn. Oxford: Blackwell Scientific Publications 1981:460-75
2 Willis RA. Secondary tumours of the liver. In: *The spread of tumours in the human body*. London: Butterworth, 1973:175-83
3 Kaplan EL, Meier P. Nonpapametric estimation from incomplete observations. *J Am Statist Ass* 1958;**53**: 457-81
4 Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. II Analysis and examples. *Br J Cancer* 1977;**35**:1-39
5 Hermanek P, Sobin LH, eds. UICC:TNM *Classification of malignant tumours*, 4th edn. Berlin: Springer, 1987
6 Millar AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47**:207-14
7 Clark CP, Foreman ML, Peters GN, *et al.* Efficacy of peroperative liver function tests and ultrasound in the detecting hepatic metastases in carcinoma of the breast. *Surg Gynecol Obstet* 1988;**167**:510-14
8 De Rivas L, Coombes RC, McCready VR, *et al.* Tests for liver metastases in breast cancer: evaluation of liver scan and liver ultrasound. *Clin Oncol* 1980;**6**:225-30
9 Kamby C. The pattern of metastases in human breast cancer: methodological aspects and influence of prognostic factors. *Cancer Treat Rev* 1990;**17**:37-61
10 Patanaphan V, Salazar OM, Risco R. Breast cancer: metastatic patterns and their prognosis. *South Med J* 1988;**81**:1109-12
11 Zinser JW, Hortobayi GN, Buzdar AU, *et al.* Clinical course of breast cancer patients with liver metastases. *J Clin Oncol* 1987;**5**:773-82
12 Kamby C, Dirksen H, Vejborg I, *et al.* Incidence and methodological aspects of the occurrence of liver metastases in recurrent breast cancer. *Cancer* 1987; **59**:1524-9
13 Nemato T, Dao TL. Significance of liver metastases in women with disseminated breast cancer undergoing endocrine ablative surgery. *Cancer* 1966;**19**:421-7
14 Viadana E, Bross IDJ, Pickren JW. An autopsy study of some routes of dissemination of cancer of the breast. *Br J Cancer* 1973;**27**:336-40
15 Ozarda A, Pickren J. The topographic distribution of liver metastases. Its relation to surgical and isotope diagnosis. *J Nucl Med* 1962;**3**:149-52
16 Smith TJ, Kemeny MM, Sugarbaker PH, *et al.* A prospective study of the hepatic imaging in the detection of metastatic disease. *Ann Surg* 1982;**195**:486-91
17 Fenster LF, Klatskin G. Manifestations of metastatic tumours of the liver. *Am J Med* 1961;**31**:238-48
18 Warnes TW. Alkaline phosphatase. *Gut* 1972;**13**:926-37
19 Schreve RH, Terpstra OT, Ausema L, *et al.* Detection of liver metastases. A prospective study comparing liver enzymes scintigraphy and computed tomography. *Br J Surg* 1984;**71**:947-9
20 Drum DE, Beard JM. Scintigraphic criteria for hepatic metastases from cancer of the breast and colon. *J Nucl Med* 1987;**17**:677-80
21 Alderson PO, Adams DF, McNeil BJ, *et al.* Computed tomography ultrasound and scintigraphy of the liver in patients with colon or breast carcinoma: a prospective comparison. *Radiology* 1983;**149**:225-30
22 Jaffe BM, Donegan WL, Watson F, Spratt JS. Factors influencing survival in patients with untreated hepatic metastases. *Surg Gynecol Obstet* 1968;**127**:1-11
23 Cutler SJ, Asire AJ, Taylor SG. Classification of patients with disseminated cancer of the breast. *Cancer* 1969;**24**:861-9

(Accepted 14 May 1991)