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Peritoneal disease in breast cancer: A specific entity with an extremely poor prognosis

Mark Tuthill[a,f], *Robert Pell*[a,f], *Rosa Guiliani*[a], *Adrian Lim*[b], *Mihir Gudi*[d], *Kaiyumars B. Contractor*[e], *Jacqueline S. Lewis*[c], *R. Charles Coombes*[a], *Justin Stebbing*[a,*]

[a]*Department of Medical Oncology, Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK*
[b]*Department of Radiology, Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK*
[c]*Department of Surgery, Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK*
[d]*Department of Histopathology and Cytology, Imperial College Healthcare NHS Trust, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK*
[e]*MRC Cylotron Building, Imperial College NHS Trust, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK*

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ABSTRACT

Background: Peritoneal metastases are now a significant cause of morbidity and mortality in patients with advanced breast cancer. There are few published data regarding the prognosis, clinical characteristics and management of individuals with peritoneal metastases from breast cancer.

Methods: The electronic database at Imperial College Healthcare NHS Trust (Charing Cross Hospital) was searched for the terms 'breast', 'cancer' or 'tumour', 'peritoneal' and 'ascites' from 2000 to 2008. Those with confirmed peritoneal disease from breast cancer, as described on ultrasound or staging CT reports with a clinico-pathologic confirmed diagnosis, were included.

Results: A total of 1628 patients were screened and initially 168 patients were identified. A subsequent total of 44 individuals (2.7% of the cohort) were defined as having breast cancer with peritoneal secondaries and were included in the analysis. Of these, the majority (77%) had invasive ductal carcinomas (IDCs). While the median survival from the diagnosis of metastatic breast cancer measured 20.5 months (range 0.1–125 months), the median survival of patients with peritoneal disease was 1.56 months (range 0.2–27 months).

Conclusions: These data demonstrate that the median survival of patients with peritoneal breast cancer metastasis is surprisingly poor, with only a minority surviving more than 6 months. A specific association with invasive lobular carcinoma (ILC) was not observed. The dismal outcome of these individuals, despite further active therapy, merits their inclusion into clinical trials designed specifically for this group of patients.

1. Introduction

The pattern of metastases from breast cancer, the commonest malignancy in females, is changing, probably due to improved systemic and local therapies.[1–4] Although a specific association between invasive lobular carcinoma (ILC) and intra-peritoneal secondaries has been previously described,[5–8] breast cancer with peritoneal disease is rarely reported in the literature.

* Corresponding author: Address: The Hammersmith Hospitals NHS Trust, Charing Cross Hospital, Department Medical Oncology, 1st Floor, E Wing, Fulham Palace Road, London W6 8RF, UK. Tel.: +44 208 7468295; fax: +44 208 8461433.
E-mail address: j.stebbing@imperial.ac.uk (J. Stebbing).
[f] M.T. and R.P. are equal contributors.
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We have observed that peritoneal metastases are a significant cause of morbidity and mortality from both invasive ductal carcinoma (IDC) and ILC. Such patients with advanced disease often require frequent admission for drainage of recurrent ascites and we have estimated that around 10% of the in-patient admissions for patients with advanced breast cancer to our centre, are related to complications of peritoneal metastases.

Information on the management and prognosis of these individuals is scarce and under-represented in the literature. Herein, we describe our experience of the characteristics, management and prognosis of patients with peritoneal metastases from breast cancer from our cancer centre. The results suggest that this disease pattern represents a specific entity, with a very poor outcome.

2. Patients and methods

The electronic patient database at Charing Cross Hospital, Imperial College Healthcare NHS Trust was searched for the terms 'breast, cancer or tumour, peritoneal and/or ascites'. Patients were treated at Imperial College Healthcare NHS Trust (Charing Cross Hospital site), London, United Kingdom, from January 2000 to November 2008. Individual patient data were obtained from the oncology database, patient records, and all imaging reports were reviewed according to a previously published protocol.[9]

The date of diagnosis of metastatic disease was taken as the date at which pleural, bone, liver, lymph node or peritoneal disease was first noted on imaging or diagnosed at clinical assessment. The age, histological subtype, tumour receptor status, stage and details of, adjuvant and metastatic breast cancer treatments were collected along with the date of diagnosis of peritoneal disease diagnosis and treatment for peritoneal disease. The electronic imaging from patients included in this study was re-read to ensure that reports and scans correlated. A random sampling of 50 scans from the original search was reviewed, to ensure that a significant number of patients were not omitted that should have been included in the analysis. The pathology reports and clinical notes of patients diagnosed by positive cytology alone were reviewed before their inclusion in the analysis.

Data were collected and analysed using Microsoft Excel in combination with the XLSTAT add-in which provides additional statistical analytical capabilities to Excel. Overall survival was calculated using Kaplan and Meier methods using XLSTAT. We compared the overall survival of patients with ILC versus IDC and different breast cancer receptor subtypes such as ER and HER-2 positive and 'triple negative' breast cancers.

3. Results

3.1. Patient characteristics

A search of 1628 individuals with a corresponding number of individual patient scans initially yielded 168 patients, who were screened to confirm breast cancer as the underlying diagnosis and the presence of peritoneal disease, as described on their ultrasound or staging CT reports. A total of 14 patients were initially excluded as they were found not to have breast cancer as their primary cancer diagnosis, and 105 patients were subsequently excluded as they did not have breast cancer with ascites or peritoneal involvement indicated on imaging reports. A further 3 patients who did not have ascites caused by breast metastases to the peritoneum (congestive cardiac failure or hepatic cirrhosis) and 2 patients who moved out of the area to be consequently lost to follow-up were also removed from the study. As a result, 44 patients, comprising 2.7% of the total cohort, were suitable for inclusion in the study.

The median age of the 44 patients at initial presentation of early breast cancer was 50 years (range 23–65) and the median age at presentation with peritoneal disease measured 55 years (range 27–69). A total of 10 out of 44 (23%) patients were presented with breast cancer with stage IV disease of which 3 (7%) had peritoneal disease at presentation; of these one had ILC. A further 4 patients developed peritoneal disease as their initial site of metastatic disease with similar outcomes to the remainder of the cohort. A total of 34 patients (77%) had IDCs, 7 patients had ILC (16%) and 3 patients (7%) had unrecorded histology due to outside referrals (Table 1).

3.2. Treatment data

For the whole cohort, a total number of 75 (for an individual patient: median 3, range 0–5) chemotherapy treatments for metastatic breast cancer were administered prior to the diagnosis of peritoneal disease. A total of 45 hormonal treatments (for an individual patient: median 2, range 0–6) were administered, prior to the diagnosis of peritoneal disease. After peritoneal disease was diagnosed, 25 out of 44 (56%) patients received further chemotherapy, and eight patients received second or third line hormonal treatments. A total of 2 out of 8 patients with HER-2 positive breast cancer received chemotherapy treatment in combination with trastuzumab for peritoneal disease. The majority of patients (38 out of 44; 86%) required at least one paracentesis median 1 (range 0–12). No patients received intra-peritoneal chemotherapy or shunt procedures.

3.3. Outcome data

The median survival of patients with peritoneal disease measured 1.56 months (range 0.2–27 months; Fig. 1). The median duration between detection of metastatic disease and detection of peritoneal spread was 19.2 months (range 0–106 months). The overall median survival of the patients from time of early breast cancer diagnosis in these patients was 74 months (range 7–204 months) and the median survival from diagnosis of metastatic breast cancer measured 20.5 months (range 3–19 months).

Patients with metastatic oestrogen receptor (ER) positive disease had a median survival of 1.4 months (range 0.2–27 months) and patients with human epidermal growth factor receptor-2 (HER2) positive disease had a median survival of 1.4 months (range 0.6–3.4 months) following diagnosis of peritoneal disease. Patients with triple negative breast cancer (negative for ER, progesterone receptor (PR) or HER2 expres-

Table 1 – The histological sub-types and survival of patients with peritoneal disease and breast cancer.

Histological subtype	Number of patients	Median survival from peritoneal disease diagnosis (median and range in months)
All	44	1.5 (range 0.2–27)
Invasive ductal carcinoma	34	2.36 (range 0.2–9)
Invasive lobular carcinoma	7	2.03 (range 0.9–16.3)
Unknown histology	3	1.5 (range 0.5–27)

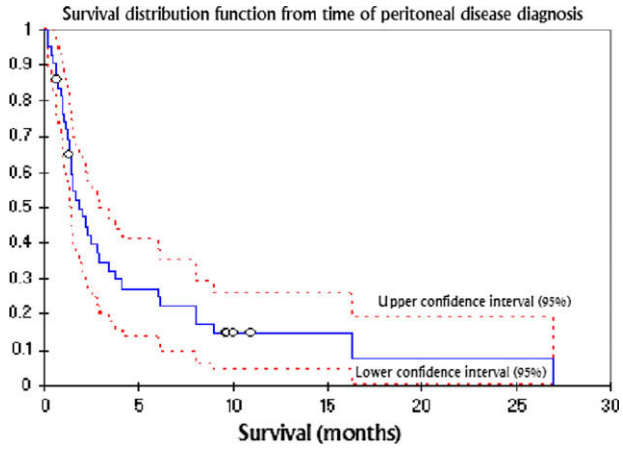

Fig. 1 – A Kaplan–Meier curve with 95% confidence intervals demonstrating the overall survival of 44 patients from date of diagnosis with metastatic peritoneal disease.

sion) had a median survival of 4.2 months on diagnosis of peritoneal disease (range 2.2–6.1 months) (Table 2). The median survival of patients with IDC was 1.4 months (range 0.2–7 months) and the median survival of patients with ILC measured 2.0 months (range 0.9–16.3 months) (Table 1).

None of these factors were statistically significant when compared with either the entire cohort or when different groups (eg. ILC versus IDC; $p = 0.08$) were compared in terms of overall survival.

4. Discussion

We report, for the first time, that the prognosis of patients with breast cancer and peritoneal metastases, is dismal, even considering the fact that the majority of included individuals had advanced metastatic disease and were receiving second line therapy for their breast cancer. In addition, we fail to show any association between ILC and peritoneal disease as the majority of the patients in the cohort (34/44) had peritoneal disease metastasis arising after a diagnosis of IDC. Importantly, no patient or tumour-specific features were found to be associated with peritoneal disease.

The median duration between detection of metastatic disease and detection of peritoneal spread measured 19.2 months suggesting that metastatic disease in the peritoneum occurs late in the clinical course of metastatic breast cancer. The median survival from diagnosis of the patients with metastatic breast cancer was 20.5 months (range 3–119 months) but the median survival of patients with peritoneal disease was extremely poor at only 1.56 months (range 0.2–27 months; Fig. 1). Patients with ER and/or HER-2 positive disease had similarly poor survivals.

The median survival of patients with 'triple negative' breast cancer measured 4.2 months and although numbers were very small, this lends credence to the suggestion that this represents an entirely different form of breast cancer with distinct clinical characteristics and responses to chemotherapy. Our cohort of patients had a median survival of 20.5 months after the diagnosis of metastatic breast cancer and 1.56 months for peritoneal metastasis. These outcomes are in marked contrast with those patients with advanced ovarian cancer who present with a similar pattern of disease but have a survival of over 56 months with optimal treatment.[10]

The majority of our patients with peritoneal disease was extensively pre-treated and had received a median number of 2 prior endocrine and chemotherapy treatments. As opposed to the situation with ovarian cancer, sub-acute bowel obstruction was rarely observed (2 out of 44 cases here) and while it is conceivable that some of these cases may represent second ovarian primaries, these were excluded by a combination of histology, cytology (including ER status on cytology), tumour markers (normal to mildly raised CA125 and

Table 2 – Receptor expression and overall survival.

Receptor expression status	Number of patients	Median survival from peritoneal disease diagnosis (median and range in months)
ER positive	35	1.4 (range 0.2–27)
ER positive and HER-2 positive	5	1.5 (range 1.03–3.4)
HER-2 positive, ER-negative	8	1.42 (range 0.6–3.4)
ER negative tumours	9	2.28 (range 0.6–6.07)
'Triple negative' tumours	4	4.17 (range 2.23–6)

ER positive tumours were defined as $\geqslant$1+ of ER expression on immunohistochemistry (IHC). Human epidermal growth factor receptor-2 (HER2) status was determined by IHC and fluorescence *in situ* hybridisation (FISH) analyses of original tumour blocks. 'Triple negative' tumours were defined as those without expression or oestrogen receptor (ER), progesterone receptor (PR) or HER2 on IHC, respectively.

markedly raised CA15-3) and unremarkable ovarian imaging. Although the association of ILC metastasis to the peritoneum is reported,[5,6,11] these data demonstrate that the features of patients with peritoneal disease and the tumour characteristics are reflective of our large cohort as a whole.

This study has several limitations. First, the small number of patients in the study limits the power to detect differences between the different breast cancer receptor subtypes. Second, the patients are heterogeneous with different treatments, both prior to and for peritoneal disease. In addition, our study criteria are susceptible to selection bias.

We suggest that the dismal outcome of these patients, only analogous to the poor prognosis in lepto-meningeal disease,[12] merits the inclusion of such patients into specific clinical trials. A problem herein will be standard inclusion criteria that normally necessitate an estimated survival of over 3 months and measurable target lesions as opposed to the 'standard' peritoneal streaking observed here (Fig. 2).

It is likely that the development of effective treatment will ultimately involve the identification of the molecular pathways that prevent the dissemination of breast cancer cells to the peritoneum. Studies should consider end-points such as reduced ascitic drainage requirements, as well as the more traditional outcomes and agents that target the mesenchymal-epithelial transition factor (MET) pathway, associated with peritoneal invasion, which may be a promising avenue.[13,14]

Peritoneal breast cancer metastasis is an emerging challenge for oncologists. Understanding the genetic and molecular mechanisms by which breast cancer metastasises to the peritoneum will allow new specific treatments to be developed. We suggest that this subgroup of breast cancer patients with an increasing prevalence, should be a focus of specific clinical trials. As radiological measurement of peritoneal disease is often difficult, this will place an additional challenge for protocols that target such populations.

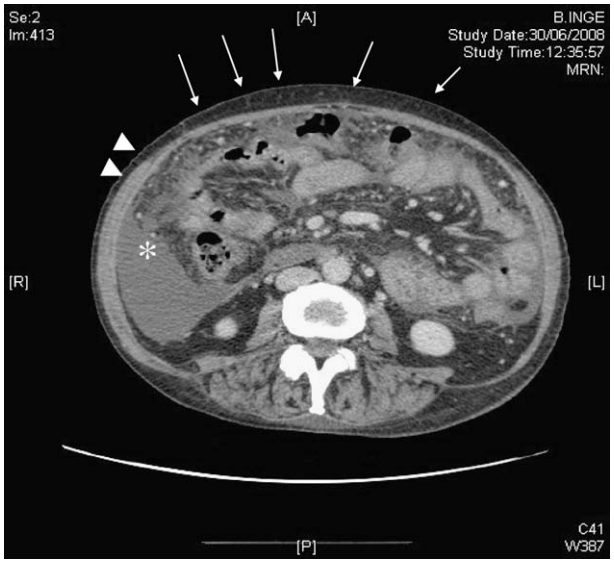

Fig. 2 – An example of typically observed imaging in a representative patient. There is a small amount of ascites in the right paracolic gutter (asterisk*) but the mesentery demonstrates marked stranding as indicated by the arrows indicating peritoneal disease from breast cancer, in the absence of bulky disease. There is also subtle enhancement of the peritoneal lining (arrowheads).

Conflict of interest statement

None declared.

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