

# Patterns of metastatic breast carcinoma: influence of tumour histological grade

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## KEYWORDS

Breast cancer  
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**AIM:** To assess if the pattern of metastatic spread of carcinoma of the breast varies according to tumour histological grade.

**MATERIALS AND METHODS:** The clinical details, histological features of the primary tumour, and imaging findings at presentation of patients with metastatic breast cancer have been recorded prospectively since 1997. The pattern of metastatic spread, age at metastasis, metastasis-free interval (MFI), and length of survival with metastases were analysed by tumour grade.

**RESULTS:** There was a significant association between histological high-grade tumours and high frequency of intra-pulmonary metastases ( $p = 0.013$ ); liver metastases ( $p = 0.039$ ); para-aortic lymphadenopathy ( $p = 0.022$ ) and metastatic presentation under 50 years of age ( $p = 0.003$ ). A significant correlation was also demonstrated between histological low-grade tumours and increased frequency of pleural disease ( $p = 0.020$ ); increased frequency of bone metastases ( $p = 0.004$ ); prolonged MFI (MFI > 5 years;  $p < 0.0001$ ); and increased length of survival ( $p < 0.0001$ ).

**CONCLUSION:** There is a correlation between patterns of metastatic spread and tumour histological grade. This partly explains the negative prognostic value of high tumour grade, as metastases from grade 3 tumours more commonly occur at sites associated with a worse prognosis. This finding may also prove useful in interpreting imaging in patients who have a history of breast cancer and undergo subsequent imaging because of new symptoms.

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## Introduction

A number of factors have previously been shown to affect pattern of spread of metastatic breast cancer including: oestrogen receptor (ER) status,<sup>1,2</sup> tumour histological type,<sup>3</sup> and use of adjuvant chemotherapy. Multiple papers have shown that tumour histological grade is an important prognostic marker both in primary breast cancer and in women who develop metastatic disease.<sup>4-6</sup> Although some of this effect is due to different

growth rates of metastatic deposits, some of the effect may be due to a difference in metastatic pattern according to tumour histological grade. For example, it is known that prognosis for liver metastases is appreciably worse than for bone metastases.<sup>5,6</sup> So if patients with high-grade tumours develop liver metastases more frequently, this would partly explain the prognostic influence of grade in metastatic disease.

To improve reproducibility there has been steady evolution of the criteria used in assessing the histological grade of breast carcinoma. The method we have used is the Nottingham method,<sup>4</sup> which is proven to have good reproducibility, and is the system recommended in the UK, Europe, and the USA. Tumours are given between 1 and 3 points for

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each of three morphological features: tubule formation, nuclear pleomorphism and mitotic count. These are then added to give a total score between 3 and 9. The higher the points total the higher the histological grade of the tumour (Table 1). There are multiple studies, which despite differences in methodology, have all shown correlation between histological grade and survival<sup>4-6</sup> in both primary and metastatic breast cancer with patients with grade 3 carcinomas having a poorer outcome.

The aim of this study was to correlate the pattern at presentation with metastatic breast cancer with the histological grade of the primary tumour. Such information could be helpful in interpreting imaging findings in women with a history of breast carcinoma and may be useful in understanding the natural history of metastatic breast carcinoma, in particular the mechanisms by which grade influences prognosis.

## Materials and methods

The imaging findings, pathological and survival details of women presenting with metastatic breast cancer in Nottingham have been collected prospectively in a database since 1997. The study group consisted of those women who had had primary breast cancer resected and in whom information on tumour histological grade was available. In the majority of patients presenting with metastatic disease chest and pelvic radiography, bone scintigraphy with plain films of abnormal foci, and either liver ultrasound or abdominal computed tomography (CT) was performed. Magnetic resonance imaging (MRI) was used to further assess equivocal bone findings, or was undertaken in women with normal conventional imaging but a strong clinical suspicion of bone metastases. The patients were followed up post-operatively on an annual basis. The patients were not routinely imaged to detect systemic spread unless symptomatic at follow-up.

Information on survival was routinely collected via hospital information systems. The imaging findings at presentation, metastasis free interval

(MFI), and survival from metastatic presentation were correlated with histological grade. MFI was defined as the interval between the first diagnosis of primary breast cancer and the time of presentation with metastatic disease.

The significance of differences between groups was ascertained using Chi-squared, Fisher's exact test, and Kaplan-Meier survival curves performed with log rank analysis using Statview 5.0 on an AppleMac computer.

## Results

The patient and tumour characteristics in the study population of 460 patients are listed in Table 2. The mean age at presentation with primary breast cancer in the study group did not differ significantly with tumour grade. The mean age at presentation with metastatic breast cancer was higher for grade 1 tumours, with fewer women presenting under the age of 50 years. We confirmed that histological grade was a prognostic factor for survival in patients with metastatic breast cancer ( $p < 0.0001$ ), with patients with grade 3 carcinomas having a poorer survival (Fig. 1). Grade 3 tumours were also associated with a shorter MFI ( $p < 0.0001$ ; Fig. 2 and Table 2). The following were found to correlate with high histological grade: high frequency of intra-pulmonary metastases ( $p = 0.013$ ); hepatic metastases ( $p = 0.039$ ); and para-aortic lymphadenopathy ( $p = 0.022$ ). There was a borderline significant correlation between histological grade and multiple liver metastases ( $p = 0.059$ ; Table 3).

Low tumour grade was found to correlate with pleural disease (malignant effusion or solid pleural masses;  $p = 0.020$ ). We compared survival between patients presenting with pleural disease and patients presenting with intra-pulmonary metastases and found no significant difference. Low tumour grade was also associated with increased frequency of bone metastases ( $p = 0.004$ ; Table 3). There was no significant difference in type (sclerotic, lytic or mixed) or multiplicity of bony metastases by grade.

In the study population, grade was not associated with gastric or pericardial metastases. There was a non-significant trend for lymphangitis to occur in grade 1 disease; lymphangitis occurred in three of 30 patients (10%) with grade 1 disease; nine of 140 patients (6%) with grade 2 disease; and 12 of 260 patients (5%) with grade 3 (Table 3).

**Table 1** Tumour histological grade score

Total points	Histological grade
3-5	Grade 1 (low grade)
6-7	Grade 2 (intermediate grade)
8-9	Grade 3 (high grade)

**Table 2** Tumour and patient characteristics in study population

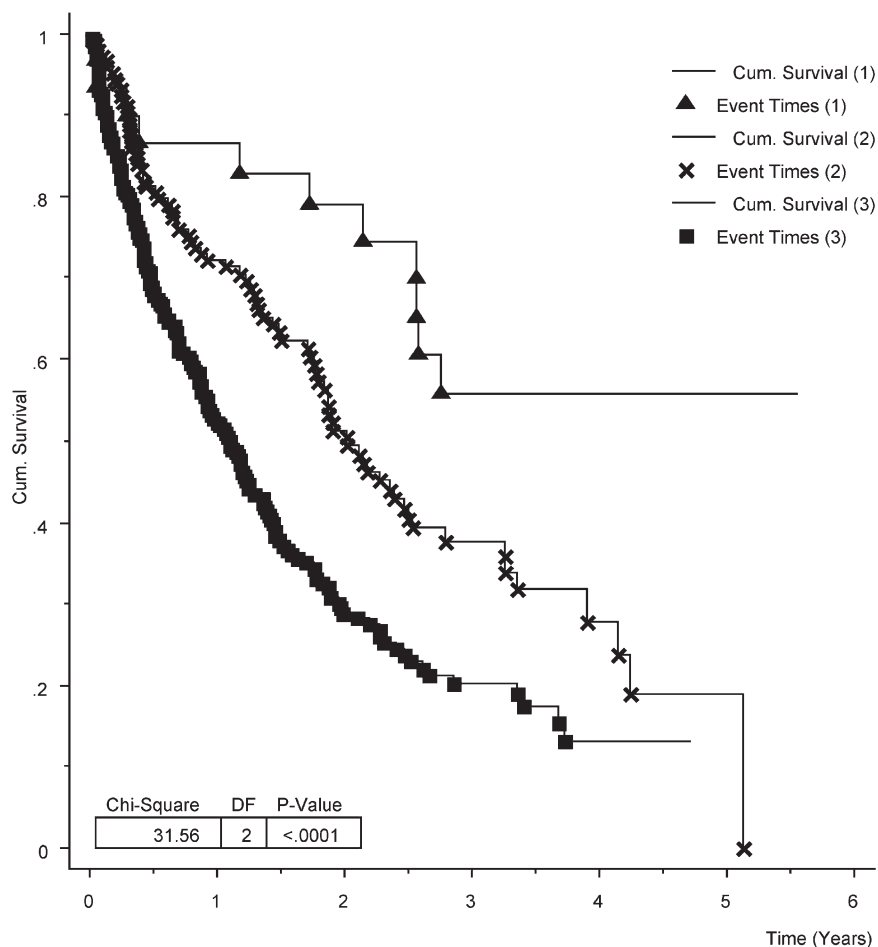
	Grade 1	Grade 2	Grade 3	p Value
Number	30	155	275	Not applicable
Mean age at presentation with primary disease	60.6 Standard deviation (SD)–11.2	55.5 SD–12.6	55.4 SD–13.6	See standard deviations
Mean age at presentation with metastases	69.9 SD–10.9	61.6 SD–12.8	58.7 SD–13.6	See standard deviations
Metastases age < 50 years	0 (0%)	28/155 (18%)	70/275 (25%)	0.003
MFI (at 5 yrs)	27/30 (90%)	89/155 (57%)	72/275 (26%)	<0.0001
Mean age at death if deceased	72.9 SD–11.8	62.2 SD–13.0	59.4 SD–14.1	See standard deviations

## Discussion

Histological grade is known to be an independent prognostic indicator when a patient presents with primary invasive breast cancer. Patients presenting with a primary tumour of histological grade 3 have a significantly worse prognosis than if the tumour was of grade 1.

Grade is also an important prognostic factor

when a patient presents with metastatic breast disease. Other important prognostic factors in this clinical scenario are MFI, ER status and sites of initial metastatic disease (SIMD).<sup>5,14</sup> Grade, ER status, MFI and SIMD are inter-related, with high-grade tumours being more likely to be ER negative with the result that the prolonged responses seen after treatment with hormone therapy are unavailable to many women with high-grade disease.



**Figure 1** Overall survival from date of metastatic presentation by histological grade. Grade 1,  $n = 30$ ; grade 2,  $n = 155$ ; grade 3,  $n = 275$ .

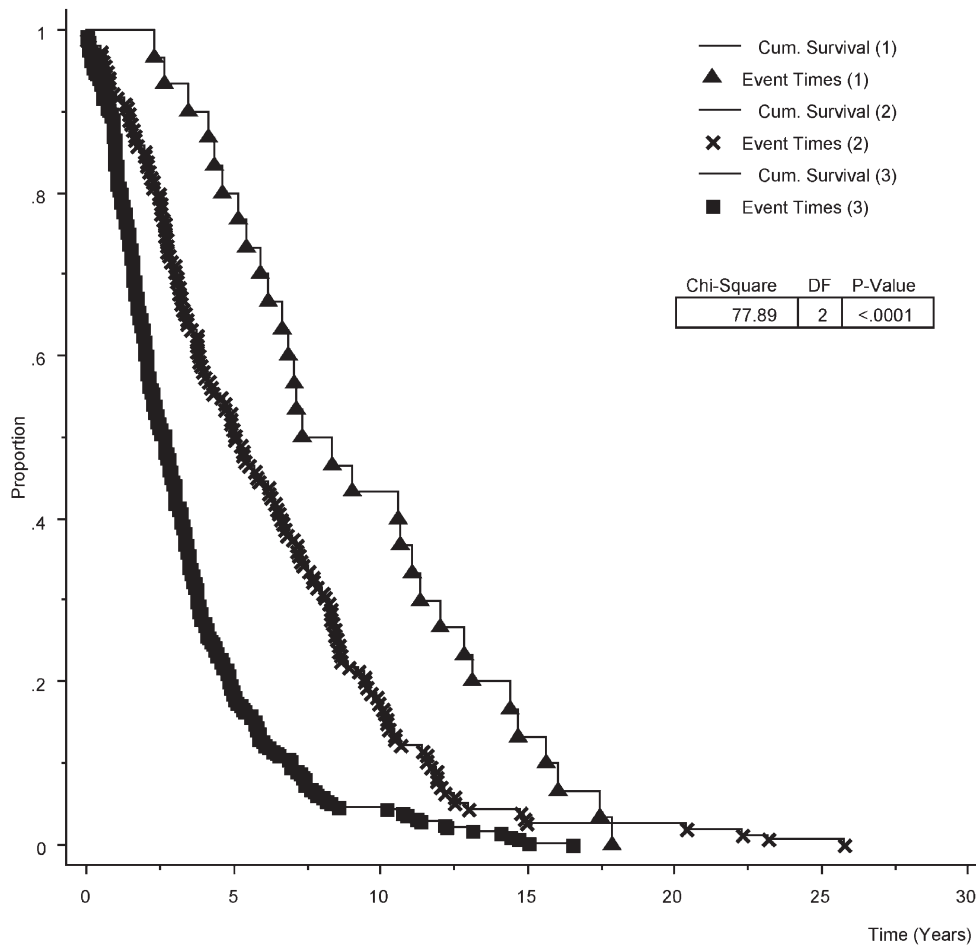


Figure 2 MFI by histological grade. Grade 1, n = 30; grade 2, n = 155; grade 3, n = 275.

However, grade, ER status, MFI and SIMD have all been shown to be independent prognostic factors on multivariate analysis for advanced disease. A long MFI and positive ER status are good prognostic factors. Bony metastases have a better prognosis than lung metastases, which in turn have a better prognosis than hepatic metastases.<sup>6,12</sup> Multiple or diffuse hepatic metastases have a worse prognosis than solitary liver metastases.<sup>8</sup>

Part of the prognostic effect of the histological grade in patients with metastatic disease will

obviously be a reflection of the different tumour growth rates. For example grade 3 tumour metastases grow faster with resultant decreased patient survival. However, a number of factors have been shown to influence the metastatic pattern of breast cancer and therefore, as discussed above, to influence prognosis. These include ER status (with ER-positive metastases more likely to occur in bone<sup>1,2</sup>), use of adjuvant chemotherapy and tumour type.<sup>7</sup>

Lobular carcinomas are known to have a different pattern of metastatic spread than ductal

Table 3 Metastatic disease associations with tumour grade

	Grade 1	Grade 2	Grade 3	p Value
Intra-pulmonary	4/30 (13%)	39/149 (26%)	93/260 (36%)	0.013
Hepatic (any)	4/24 (17%)	39/132 (30%)	93/242 (38%)	0.039
Hepatic (multiple)	2/24 (8%)	26/132 (20%)	65/242 (27%)	0.059
Para-aortic	0/30 (0%)	3/155 (1.9%)	20/275 (7.3%)	0.022
Pleural disease	12/30 (40%)	27/149 (18%)	50/260 (19%)	0.020
Bone	14/22 (64%)	100/148 (68%)	127/250 (51%)	0.004
Lymphangitis (CXR)	3/30 (10%)	9/149 (6%)	12/260 (5%)	0.438
Pericardial	0/30 (0%)	3/155 (1.9%)	3/275 (1.1%)	0.615
Gastric	0/30 (0%)	3/155 (1.9%)	1/275 (0.4%)	0.210

carcinomas. Gastrointestinal, gynaecological, peritoneal and retroperitoneal metastatic spread has been found to be more prevalent in lobular carcinomas.<sup>9</sup> Also carcinomas that exhibit tubular features are less likely than ductal carcinomas of no special type to develop liver metastases, particularly multiple liver metastases.<sup>10</sup>

The frequency of breast cancer metastasizing to the central nervous system is related to the use of adjuvant chemotherapy. It is more common for the SIMD to be in the brain in patients who have received adjuvant chemotherapy than in patients who have not.<sup>11</sup> This is likely to be due to the majority of chemotherapy administered for treatment of breast cancer not crossing the blood-brain barrier. This allows the brain to be a sanctuary site for micro-metastases. The aim of this study was to investigate whether histological grade influenced the metastatic pattern of breast cancer, and if so, could this be an explanation for part of the prognostic influence of grade in metastatic disease.

We have found that grade 3 tumours are more likely to spread to metastatic sites that are associated with a poor prognosis, such as the liver and the lung parenchyma. We have shown a trend for liver metastases in grade 3 tumours to be multiple, a pattern with a particularly poor prognosis.<sup>8</sup> The present study also demonstrates a correlation between histological grade 1 tumours and pleural disease. Pleural effusions are more common in the ipsilateral hemithorax.<sup>15</sup> Pleural disease may therefore be a reflection of regional rather than systemic spread. Why such a pattern of spread should be more common in grade 1 disease is unclear. In patients with metastatic breast cancer we have compared survival between patients presenting with pleural disease against patients presenting with intra-pulmonary metastases, and found no significant difference. The present study also confirms the association of low histological tumour grade and increased frequency of bone metastases, which has been reported in a number of previous studies.<sup>12-14</sup>

We have found that the MFI after the diagnosis of primary breast cancer is strongly related to the histological grade. We have confirmed that in metastatic breast cancer high tumour grade is an indicator of poor prognosis. In conclusion the poor prognosis of women with grade 3 invasive breast carcinomas who develop metastatic disease appears to be due to a number of related factors: faster growing metastatic lesions, ER negativity and a tendency to spread to organs that are associated with more rapid death from metastatic disease. The

differing patterns of metastatic spread may also be useful to radiologists interpreting imaging investigations of women presenting with possible metastatic breast cancer.

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