When to order a biopsy to characterise a metastatic relapse in breast cancer

T. Foukakis1, G. Åström2, L. Lindström1, T. Hatschek1 & J. Bergh1

1Department of Oncology, Radiumhemmet, Cancer Center Karolinska, Karolinska Institutet and University Hospital, Stockholm; 2Department of Radiology, Uppsala University Hospital, Uppsala, Sweden

Today, the diagnosis of metastatic breast cancer is usually based on radiological findings, and therapeutic decisions are made by considering the pathological characteristics and predictive markers of the primary tumour. Accumulating evidence suggests that tumour characteristics, including estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2), are unstable through tumour progression. Several retrospective studies and, recently, two prospective studies have investigated the discrepancies in receptor status between primary tumours and the corresponding metastases in a total of 1773 patients (for ER) and 2845 patients (for HER2). Changes in ER and HER2 status in these studies range from 14.5% to 40% and from 0% to 37.5%, respectively. In the two prospective studies, a different diagnosis, usually non-malignant, was obtained in 3% and 9% of the cases, and the biopsy led to a treatment modification in about one out of seven patients. Here, we review and discuss the currently available data and provide our recommendations on when a metastatic biopsy should be obtained.

Key words: breast cancer, biopsy, heterogeneity, predictive biomarker

introduction

The expression of the estrogen receptor (ER) and overexpression/amplification of the human epidermal growth factor receptor 2 (HER2) are routinely used for the selection of the appropriate targeted therapy in patients with early breast cancer. In the metastatic setting, the expression of these predictive factors together with the other routinely analysed histopathological characteristics of the primary tumours and other factors such as the relapse-free interval and site of relapse is routinely used for therapy decisions. It is widely accepted both in the clinical and scientific community that this is the correct treatment strategy for the vast majority of patients.

Already more than 30 years ago, the first data that receptor inconsistencies exist between the primary tumour and the metastatic lesions were reported [1–3]. These studies, however, did not, in general, influence the management of metastatic breast cancer (MBC) patients, while serious concerns have been raised regarding the methodological consistency of such analyses [4]. Notwithstanding, several modern studies have been carried out during the last few years reporting discordance rates for ER and HER2.

routine work-up at the time of relapse

There is to date no solid data supporting the use of routine radiological assessments in the follow-up of patients with breast cancer. Despite the lack of survival benefit, such routine screens are applied in different institutions. On the other hand, patients at follow-up who demonstrate symptoms and/or signs of local, regional and/or systemic recurrence should be meticulously investigated. After clinical examination supplemented by routine laboratory tests, patients are frequently radiologically assessed by multidetector computerised tomography (CT scan), magnetic resonance imaging (MRI) and/or hybrid techniques such as positron emission tomography–CT (PET–CT). An alternative, less resource-craving strategy could, of course, be the combination of standard X-ray of the lungs, ultrasound of the liver and bone scan. The sensitivities and specificities of dimension techniques are not the subject of this article but to the knowledge of the authors, no formal comparative and randomised study has been run, enabling the proper prospective evaluation of the best available technique for the detection of metastatic disease and location of disease; site-organ involvement probably has a major impact on selection of presumed best technique. Primary HER2-positive breast cancer and triple-negative breast cancer have a higher risk of recurrence in the brain and it is also generally acknowledged that HER2-positive cancers tend to recur more frequently in the liver [5, 6]. Primary endocrine-responsive cancer can have a longer disease-free interval and have a relatively lower frequency of visceral involvement [7].

multifunctional imaging techniques

Multidetector CT, MRI (including diffusion-weighted imaging) and PET–CT have a clearly increased sensitivity in detecting
present strategies for the management of radiologically demonstrated breast cancer recurrence

Based on the work-up described in the previous paragraph and taking into consideration patient and primary tumour characteristics and previous adjuvant therapies, patients are, in most institutions, treated in the metastatic setting without a biopsy carried out. Therapeutic decision making is also influenced by factors such as the relapse-free interval, metastatic sites and tumour burden, standard laboratory values and patient’s performance status. Thus, in the majority of cases, therapy decisions of the metastatic disease are based on the biological characteristics of the primary tumour, assuming that these are unchanged in the metastasis. A distinct exception is when a patient presents with a single lesion, by which a biopsy is carried out in most institutions to exclude benign changes or another type of malignancy.

retrospective evaluation of ER and HER2

Several groups have carried out retrospective analyses comparing the ER [3, 4, 10–18] and HER2 [4, 10, 13, 19–34] status of primary tumours and their respective relapses. Progesterone receptor (PgR) has also been evaluated in some of the studies; however, methodological and biological concerns do not allow any safe conclusions to be drawn. These are related to the greater uncertainty about the consistency of the biochemical assays and antibodies that have been used for PgR and mainly to the purely biological instability of PgR expression, especially in the context of endocrine therapy that causes a down-regulation of PgR. Thus, this article will focus on ER and HER2.

ER status

Table 1 summarises the studies that report comparisons of ER status between primary tumours and relapses. With the exception of the study by Nedergaard et al. [15] that investigated only regional relapses, the rest of the analyses included both local and systemic relapses or exclusively distant metastases. In summary, all retrospective studies demonstrate discordance of ER status that ranges from 14.5% to 40% (Table 1) and includes both ‘gains’ and ‘losses’ of ER expression.

HER2 status

Table 2 lists all reported studies comparing HER2 status of the primary tumour with that of local relapse, distant metastasis, or in some studies circulating tumour cells after recurrence. Immunocytochemistry or FISH/chromogenic in situ hybridisation was used for determining HER2 status. In general, discordance was not as common as for ER and ranged from 0% to 37.5%.

One critical question is, of course, whether the examination of one metastatic lesion is sufficient to give the full picture of the receptor patterns in the recurrent cancer. The data in this area are, if anything, very scanty. One of the published reports is based on 10 patients who were subjected to immediate autopsies of several metastatic lesions [18]. While heterogeneity was observed between the primary tumour and metastases as well as between metastases, both the ER and PgR tended to be uniformly down-regulated in the metastatic lesions compared with the primary tumour. However, at the time when the biochemical receptor measurements were used, it was relatively well known that warm ischaemia before the time of analysis may have reduced the receptor expression. For HER2, there were no patients with strong HER2 overexpression; however, there was one individual with a low level of HER2 amplification [18]. Lindström et al. [13] compared metastatic biopsies collected from multiple consecutive relapses in the same patient. Information on ER and HER2 was assessed in 119 and 32 cases, showing an individual discrepancy in 33.6% and 15.7% of patients, respectively.
As expected in these retrospective studies, carrying out a metastatic biopsy had an impact on treatment decisions and changes in therapy whenever a discrepancy on receptor status was detected. However, owing to the small size of the individual studies and their retrospective nature, no conclusions could be drawn from these analyses regarding the impact of this practice on survival. Botteri et al. [35] approached this question by comparing 100 patients with liver metastases that were biopsied with an equal number of matched controls with no biopsy carried out. No survival difference was seen for the whole cohorts; however, the 18 patients with discordance on receptor status that led to treatment adjustments had a significant improvement on overall survival compared with controls.

**prospective studies**

Two studies have been reported in which a metastatic tissue biopsy has been carried out prospectively: the Canadian DESTINY study [36] and the British BRITS study [37]. In the former, a single-institution study, 151 women were approached, 137 consented and 121 underwent biopsy. Among those, three had benign disease and one had a second malignancy. Recurrent breast cancer was verified in 117 individuals (97%). For those with verified recurrent breast cancer and sufficient material for IHC, ER was discordant in 16%, PgR in 40% and HER2 in 10%. Both gains and losses were seen for HER2 (6 out of 73 and 2 out of 10, respectively). Biopsy led to a change in treatment in 14% of cases but discordance in receptor status had, in this study, no impact on the failure-free survival or overall survival [36].

The BRITS study was carried out in 20 British institutions. In this study, 137 out of the initially enrolled 205 individuals had a paired sample of both the primary tumour and the recurrence site that could be analysed. A discrepancy in receptor status was seen for ER in 14 patients (10.2%), PgR in 34 (24.8%) and HER2 in 4 (2.9%). Eighteen patients (8.8%) did not have a breast cancer recurrence on biopsy, while treatment was modified in 24 patients (17.5%).

A pooled analysis of the two prospective trials has been recently published [38]. In summary, these two important studies indicate that treatment adjustments are carried out in one patient of every seven patients with recurrent breast cancer who undergo a biopsy. Even more importantly, in ~3–9% of the patients, the diagnosis was benign, thus the biopsy spared them from unnecessary treatment.

**why is there discordance in receptor status?**

The multitude of studies carried out (13 studies with 1773 patients for ER and 23 studies with 2845 patients for HER2) unequivocally demonstrate the discrepancy of receptor status between primary tumours and relapses (Tables 1 and 2). However, the reason for this discrepancy is less clear and both technical and biological explanations have been discussed. The use of various methods for ER (biochemical versus IHC assays) and HER2 (IHC versus FISH), the variability caused by sampling methods [fine-needle aspiration (FNA) or core biopsy versus surgical excision in the primary tumour] and differences in analysis of samples from different tissues are all possible technical caveats that could cause a false discrepancy. In the study by Amir et al. [36] discussed above, it was shown that FNA and biopsy of bone led to reduced ability to analyse receptors. Even when the same analytic method is used, the reproducibility is suboptimal, especially for ER determination [39], but to some degree also for HER2 [40], which could lead to a false discrepancy rate.

Tumour heterogeneity is well documented in breast cancer and could also lead to an apparent change in receptor status. This could be caused either by sampling a tumour area by biopsy with different characteristics, or by a clonal selection of tumour cells that grow and give rise to metastasis.

Alternatively, the change in tumour attributes could be a pure biological phenomenon, caused by acquisition of genetic changes either due to genomic instability of the tumour cells or as a result of selection due to treatment, in particular endocrine or trastuzumab. The genetic instability in a subset of tumours is supported by the data of Lindström et al. [13] demonstrating some cases with similar discordance rate in consecutive examinations of up to six metastatic lesions.

Despite the fact that methodological issues do exist, there is accumulating evidence that, at least to some degree, true biological and clinically important changes occur during

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**Table 2.** Studies comparing HER2 status on primary tumours and corresponding relapse

<table>
<thead>
<tr>
<th>Publication/Abstract</th>
<th>Number of patients</th>
<th>Number of patients with discordant HER2 status (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrospective studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broom et al. [10]</td>
<td>100</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Curigliano et al. [11]</td>
<td>172</td>
<td>24 (14.0)</td>
</tr>
<tr>
<td>Edgerton et al. [19]</td>
<td>113</td>
<td>19 (16.8)</td>
</tr>
<tr>
<td>Gancberg et al. [20]</td>
<td>107</td>
<td>10 (9.3)</td>
</tr>
<tr>
<td>Gong et al. [21]</td>
<td>60</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Guarneri et al. [12]</td>
<td>75</td>
<td>12 (16.0)</td>
</tr>
<tr>
<td>Liedtke et al. [4]</td>
<td>528</td>
<td>72 (13.6)</td>
</tr>
<tr>
<td>Lindström et al. [13]</td>
<td>104</td>
<td>15 (14.4)</td>
</tr>
<tr>
<td>Lipton et al. [22]</td>
<td>240</td>
<td>61 (25.4)</td>
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<tr>
<td>Lower et al. [23]</td>
<td>382</td>
<td>127 (33.2)</td>
</tr>
<tr>
<td>Masood and Bui [24]</td>
<td>56</td>
<td>1 (1.8)</td>
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<tr>
<td>Meng et al. [25]</td>
<td>24</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Niehans et al. [26]</td>
<td>30</td>
<td>1 (3.3)</td>
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<tr>
<td>Niikura et al. [34]</td>
<td>182</td>
<td>43 (23.6)</td>
</tr>
<tr>
<td>Pectasides et al. [27]</td>
<td>16</td>
<td>6 (37.5)</td>
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<tr>
<td>Sediko et al. [28]</td>
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<td>2 (4.5)</td>
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<td>Shimizu et al. [29]</td>
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<tr>
<td>Tanner et al. [30]</td>
<td>46</td>
<td>0 (0.0)</td>
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<tr>
<td>Tapia et al. [31]</td>
<td>105</td>
<td>8 (7.6)</td>
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<tr>
<td>Wilking et al. [32]</td>
<td>151</td>
<td>15 (9.9)</td>
</tr>
<tr>
<td>Zidan et al. [33]</td>
<td>58</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td><strong>Prospective studies</strong></td>
<td></td>
<td></td>
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<tr>
<td>Amir et al. [36]</td>
<td>94</td>
<td>9 (9.6)</td>
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<tr>
<td>Thompson et al. [37]</td>
<td>137</td>
<td>4 (2.9)</td>
</tr>
</tbody>
</table>

HER2, human epidermal growth factor receptor 2.
tumour evolution and metastasis. Gene expression profiling studies demonstrate that, although the majority of genes are similarly expressed in primary tumours and their respective metastases, there is a small subset of genes with differential expression [41]. Furthermore, Norberg et al. [42] have found an increased frequency of p53 mutations in metastatic tissue (41%) compared with the corresponding primary tumours (23%). Finally, a newer whole-genome sequencing study identified both de novo mutations and enrichment of shared mutations in the metastasis, supporting tumour evolution and selection of clones with metastatic potential in the primary tumour [43].

can a biopsy be harmful for the patient?

Although a metastatic biopsy can facilitate and optimise treatment decisions, a physician should always consider the ‘not harm’ principle. In general, the morbidity and complication rate associated with the procedure are minimal in experienced centres. Patient discomfort is sometimes an issue, but it is probably less when an FNA can be carried out instead of a core biopsy. In the DESTINY trial, patient satisfaction was assessed, and while 34% of the patients reported prebiopsy anxiety, and 59% postbiopsy pain, the vast majority (89%) recommended metastatic biopsy to other patients [36]. One of the published retrospective studies has shown a negative impact on survival when a metastatic biopsy was carried out [4]. The authors claimed that discrepancy in receptor status was a methodological artefact and thus patients were suboptimally treated when therapy was based on the results of the biopsy. Nevertheless, none of the other publications (Tables 1 and 2) has confirmed a detrimental effect of metastatic biopsy. A special case is when a liver lesion is resectable and surgical management with curative intention is planned, as it is then widely accepted that a biopsy should be avoided [44]. However, this is usually the case for patients with primary liver cancer or metastatic colorectal cancer; there are no prospective data supporting the added value for liver surgery of breast cancer metastases.

when should a biopsy be carried out when recurrent breast cancer is suspected? recommendations

The existing data described here are strongly indicative of the usefulness of a metastatic biopsy in all cases of suspected recurrence of breast cancer. A biopsy is mandatory when the radiological work-up has identified one single lesion, as well as when the patient has a history of more than one cancer diagnoses and generally when the suspicion of an alternative diagnosis is high. An illustrative example is demonstrated in Figure 1. In the rest of the cases, an effort to achieve histological confirmation and receptor evaluation should be made whenever possible. Patients/samples should be referred to/analysed in institutions with experience in carrying out biopsies and with the infrastructure for image-guided biopsies whenever needed. The metastatic site to be biopsied should be selected considering easy access, low risk for complications and appearance of viable/progressing tumour on radiological examinations. Biopsies from skeletal lesions must be handled with thoughtfulness; decalcification procedures will likely ruin the possibility to detect receptors by IHC, and cytology is probably a superior method in this context. It is also important that cytology material is not alcohol-fixated, but air-dried and fixated in buffered formalin [13]. A biopsy should be avoided when it is not safe and when the results are not expected to lead to any changes in treatment.

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