Proliferation accurately identifies the high-risk patients among small, low-grade, lymph node-negative invasive breast cancers

J. P. A. Baak1,3,4*, P. J. van Diest1†, E. A. M. Janssen3, E. Gudlaugsson3, F. J. Voorhorst1,2, E. van der Wall5†, J. B. Vermorken6 & other collaborators of the Multicenter Morphometric Mammary Carcinoma Project (MMMCP)

1Departments of Pathology; 2Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands; 3Department of Pathology, Stavanger University Hospital, Stavanger; 4The Gade Institute, University of Bergen, Bergen, Norway; 5Department of Medical Oncology, VU Medical Center, Amsterdam, The Netherlands; 6Department of Medical Oncology, University Hospital, Antwerp, Belgium

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Background: The proliferation factor mitotic activity index (MAI) is the strongest prognosticator in lymph node-negative invasive breast cancer patients under age 71. The question remains, whether this also holds for ‘favourable prognosis’ subgroups.

Patients and methods: The study was a multicentre prospective analysis of the MAI for recurrence-free survival and overall cancer-related survival of grade, MAI, and other prognosticators in 853 long-term follow-up, T1–3N0M0 breast cancer patients under 71 years.

Results: In all tumours together (N = 853), in grade 3 (n = 269), in tumours <1 cm all grades (n = 84), 1–2 cm, grades 1 + 2 (n = 300), and 2–3 cm, grades 1 + 2 (n = 124), the MAI is prognostically superior. Other features [grade, estrogen receptor (ER), diameter, and age] did not enhance its prognostic value except in grades 1 + 2 tumours 2–3 cm diameter with MAI <10, where ER has an additional prognostic value.

Conclusions: In women <71 years with T1–3N0M0 small or low-grade invasive breast cancer usually not receiving systemic treatment, MAI ≥10 accurately identifies those at high risk. These high-risk patients should be considered for adjuvant systemic therapy.

Key words: breast cancer, mitotic index, prognosis, proliferation, small tumours, well-differentiated cancers

Introduction

Approximately, 20%–30% of patients with lymph node-negative (LN−) breast cancers die of recurrent disease. Relative survival improvement of 15%–20% at 10 years resulting from adjuvant systemic therapy (AST) can be expected. With this level of improvement, AST survival benefits and side-effects must be considered simultaneously [1]. Accurate and reliable prognostic markers can help identify high-risk patients.

Many independent studies have shown that proliferation markers exceed the prognostic value of classical prognosticators [2–12]. One of these proliferation markers, the mitotic activity index (MAI), is a powerful, practical, widely available, easily assessable, inexpensive, and well-reproducible prognosticator [4, 5, 7, 9, 10, 12, 13] in women under age 71 at diagnosis, without adjuvant systemic treatment and with long-term follow-up [14]. Moreover, patients with rapidly proliferating tumours significantly benefited from AST, in contrast to those with low proliferation [15–17].

It is unknown whether this prognostic value in patients under age 71 with all T1–3N0M0 invasive breast cancer also holds in special patient subgroups not routinely receiving systemic treatment, MAI ≥10 accurately identifies those at high risk. These high-risk patients should be considered for adjuvant systemic therapy.
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AST for patients with node-negative breast cancer, allowing study of the true biological nature of the cancers in the patient subgroups involved.

**Patients and Methods**

Details of the MMMCP protocol have been described elsewhere [13, 18, 19]. Of the 3479 MMMCP patients registered, 1744 had LN− breast malignancy. The following patients were excluded: 13 males; 86 women with carcinoma in situ (CIS) only or an extensive CIS with a micro-invasive part <1 mm (precluding MAI assessment, see below); three patients with sarcomas; 29 patients ineligible for resection of cancers; two patients with distant metastases at diagnosis; 100 patients with stage T4; 108 patients with previous or synchronous malignancies (other than basal cell carcinoma of the skin or cervical CIS); 16 patients with double-sided carcinoma; 209 women lost to follow-up; and 23 women for whom slide quality was too poor for MAI assessment. The small minority (151) of node-negative patients who received systemic adjuvant hormonal or cytostatic therapies were also excluded. Of the remaining 1004 node-negative patients, 853 were younger than 71 at diagnosis. These patients were treated with modified radical mastectomy or breast-conserving therapy (BCT), always with adequate axillary lymph node dissection. Locoregional radiotherapy was given in patients undergoing BCT or with mediastinally localised tumours. Postsurgical tumour size (pT) was measured in the fresh specimens; tumours were cut in slices 0.5 cm thick, fixed in buffered 4% formaldehyde, and embedded in paraffin. At least six (median: 11) lymph nodes were detected in the axillary lymph node dissection specimens.

Paraffin sections 4 µm thick were cut and stained with haematoxylin and eosin. Histological type was assessed according to the World Health Organisation criteria [20]. Grade was assessed during careful review by two independent pathologists with considerable experience in breast pathology [JPAB and PPvD], according to the Nottingham modification [21], using MAI (see below) = 6 index (i.e. 1–6) of the tumour. The MAI was assessed in each participating laboratory, using the MMMCP protocol [13, 18, 19], as follows. The most poorly differentiated peripheral area (minimum: 1 × 1 mm; maximum: 5 × 5 mm) of the tumour with the highest cellularity and proliferation was demarcated on the slide with a black marker, avoiding necrotic, heavily inflamed, or benign areas. In the measurement area, definitive mitoses were counted at ×400 magnification (objective 40, field diameter 450 µm at the specimen level) in 10 consecutive neighbouring fields of vision in the most cellular area (representing a total area of 1.59 mm² at specimen level); doubtfulness structures and apoptotic bodies were ignored. The total number of well-defined mitotic figures counted in these 10 fields of vision constituted the MAI.

MAI <10 indicates a favourable prognosis and MAI ≥10 a poor prognosis [4, 5, 7, 13, 14]. If 5 < MAI < 15, the MAI was assessed again. If the two assessments were discrepant, but both were either under or >10, the higher count was used. In the rare case of a first MAI count <10 and a second ≥10, two observers, however, carried out a third assessment. Using a discussion microscope, they discussed each putative mitosis, and the resulting MAI was used for analysis. An accurate MAI assessment required ~3–5 min. We did not correct MAI for the percentage of tissue occupied by stroma or the number of tumour cells because this approach does not substantially improve the MAI prognostic value and is more time consuming [22].

**Statistical Analysis**

End points were distant recurrence-free survival (RFS) and mortality resulting from distant metastases [overall survival (OS)]; recurrence was any first recurrence at distant sites. All other patients were censored on the date of the last follow-up visit and included deaths from causes other than breast cancer, whether local or regional recurrences or the development of a secondary primary cancer (including contralateral breast cancer). Mortality was defined as any death due to distant metastases (as evident from clinical, radiological, histological, or autopsy data); no patients died from locoregional disease. If the cause of death was unknown but a metastasis was previously detected, death was considered breast cancer related unless stated otherwise. If status during follow-up indicated a confirmed metastasis without a date of recurrence, the date of that follow-up visit was used.

SPSS version 14 (SPSS, Chicago, IL) was used for the analyses. Age, time to first recurrence, and survival time were calculated relative to the date of the primary diagnosis. The MAI is a continuous variable. Many previous studies have shown that in other patient sets, a binary threshold as MAI <10 versus ≥10 is prognostically the strongest. To analyse once more the best prognostic threshold of the MAI in the current material, all 853 patients were analysed using receiver operating curves (MedCalc Software, Mariakerke, Belgium) and the values/thresholds with the objectively best sensitivity and specificity, designated by the area under the curve was assessed. This confirmed that the previously established prognostic threshold of MAI 10 was best. In addition, previously established other MAI thresholds for three subgroups were also analysed.

Survival curves were constructed using the Kaplan–Meier technique. Differences between groups were tested by log-rank tests. The relative importance of potential prognostic variables was tested using stepwise Cox proportional hazard analysis and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). To understand better the significance of the MAI in the low (i.e. 1 + 2) and high (i.e. 3+) grades, we analysed with multivariate survival analysis the independent additional prognostic value of the three features which together constitute grade [i.e. MAI, tubular formation (TF), and NA].

To simulate age-corrected general mortality, we standardised the patients over different age groups (<35, 35–44, 45–54, and 55–70) using a stratified analysis, indicating that age might be a possible confounder. HRs were then recalculated for each single feature. In these stratified analyses, there was hardly any change in the HRs of the different factors analysed.

**Results**

In all tumours together (n = 853) and in the grade 3 cancers separately (n = 269), multivariate survival showed that the prognostic value of the MAI overshadowed all other features. Not unexpectedly, many grade 3 tumours had a MAI ≥10, but those with a MAI <10 have much more favourable prognosis.

Comparison of the multivariate significance of the MAI, tubule formation, and NA in all the patients together showed that the MAI is included first and once the MAI is selected, TF and NA lose their prognostic significance. In other words, the prognostic significance of grade is due to the MAI and not TF and NA.

Table 1 summarises the survival results stratified in the different subgroups for the most important characteristics.
The discretised values for continuous variables (age, tumour diameter, and MAI) are those that were the most significant; other thresholds for these features with less significant are not discussed further. Special attention was paid to young age as a prognostic factor in this large group of node-negative breast cancer patients. There was a (nonsignificant) trend for slightly worse prognosis in women under 45 years versus older women, but not for women <35 versus the others.

### Table 1. Comparison of grade and MAI for distant metastases-related recurrence and mortality in different subgroups of breast cancer patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Distant metastases-related recurrence</th>
<th>Distant metastases-related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/at risk</td>
<td>P</td>
</tr>
<tr>
<td>Tumours &lt;1 cm, all grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>7/28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>45–54</td>
<td>1/22</td>
<td>0.97</td>
</tr>
<tr>
<td>55–70</td>
<td>3/34</td>
<td>0.04</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>8/53</td>
<td>0.07</td>
</tr>
<tr>
<td>Negative/dubious</td>
<td>3/26</td>
<td>0.07</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1/34</td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>8/33</td>
<td>0.04</td>
</tr>
<tr>
<td>3</td>
<td>2/17</td>
<td>0.02</td>
</tr>
<tr>
<td>MAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>6/69</td>
<td>0.02</td>
</tr>
<tr>
<td>≥10</td>
<td>5/15</td>
<td>0.05</td>
</tr>
<tr>
<td>Tumour diameter 1–2 cm, grades 1 + 2 only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>21/77</td>
<td>0.04</td>
</tr>
<tr>
<td>45–54</td>
<td>25/108</td>
<td>0.04</td>
</tr>
<tr>
<td>55–70</td>
<td>23/115</td>
<td>0.04</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>48/217</td>
<td>0.04</td>
</tr>
<tr>
<td>Negative/dubious</td>
<td>20/64</td>
<td>0.04</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>25/123</td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>44/177</td>
<td>0.04</td>
</tr>
<tr>
<td>MAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>43/243</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>≥10</td>
<td>26/57</td>
<td>0.05</td>
</tr>
<tr>
<td>Tumour diameter 2–3 cm, grades 1 + 2 only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>12/31</td>
<td>0.59</td>
</tr>
<tr>
<td>45–54</td>
<td>10/43</td>
<td>0.59</td>
</tr>
<tr>
<td>55–70</td>
<td>14/50</td>
<td>0.59</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>21/89</td>
<td>0.003</td>
</tr>
<tr>
<td>Negative/dubious</td>
<td>14/31</td>
<td>0.003</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8/36</td>
<td>0.06</td>
</tr>
<tr>
<td>2</td>
<td>28/88</td>
<td>0.06</td>
</tr>
<tr>
<td>MAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>21/92</td>
<td>0.0004</td>
</tr>
<tr>
<td>≥10</td>
<td>15/32</td>
<td>0.3</td>
</tr>
</tbody>
</table>

MAI, mitotic activity index; P, probability of no difference; KM, Kaplan–Meier; CI, confidence interval; HR, hazard ratio; =a, cannot be calculated because of being divided by zero error; ER, estrogen receptor.

### Tumour diameter <1 cm, MAI versus grade

Of the total 853 patients, 84 (10%) had a pT <1 cm (grades 1, 2, and 3). Of these, 11 (13%) developed distant metastases, and nine (11%) died of distant metastatic disease (DOD). Both grade and MAI were prognostic, both for RFS (P = 0.04 and 0.02, respectively) and OS (P = 0.02 and 0.001); 10-year OS rates for MAI <10 versus ≥10 were 94% and 67%, respectively.
significant, while ER was significant (‡ patients with MAI < 10 and 60 (20%) DOD. Of the 243 patients with MAI < 10, 39 of 177 patients (22%) of grade 2 died (‡ was less prognostic: 21 of 123 patients (17%) of grade 1 and = HR the only feature selected (‡ with Cox regression analysis, including age, ER, TF, NA, and MAI, the MAI was the only prognostic factor both for RFS and OS. Figure 1 shows the OS of patients with MAI <10 and ≥10 for this subgroup.

tumour diameter 1–2 cm, grades 1 + 2 only
There were 300 patients with tumours between 1 and 2 cm and grades 1 + 2, with 69 developing distant metastases (23%) and 60 (20%) DOD. Of the 243 patients with MAI <10, 43 recurred (18%) contrasting to 26/57 (46%) of patients with MAI ≥10 (P = 0.00001). Of the 123 patients with grade 1, 25 recurred (20%) and 44/177 (25%) of the grade 2 cancers (P = 0.12). For OS, MAI was again the strongest prognosticator [P < 0.00001; 36/243 (15%) events for MAI <10 and 24/57 (42%) DODs for MAI ≥10] (Figure 1). Grade was less prognostic: 21 of 123 patients (17%) of grade 1 and 39 of 177 patients (22%) of grade 2 died (P = 0.11). Age, ER, TF, and NA were not prognostic. With Cox regression analysis, including age, ER, TF, NA, and MAI, the MAI was the only feature selected (P = 0.0001, for both RFS and OS; HR = 3.9 and 4.3, 95% CI 2.4–6.5 and 2.5–7.3, respectively).

tumour diameter 2–3 cm, grades 1 + 2 only
Among the 124 patients with tumours between 2 and 3 cm grades 1 + 2 only, there were 36 (29%) distant metastases and 33 (27%) DODs. MAI <10 versus ≥10 was the strongest prognostic factor, both for RFS [21/92 (23%) and 15/32 (47%) distant metastases, respectively] and OS [19/92 (21%) and 14/32 (44%) DOD, respectively] (P = 0.0004 and 0.0008; Figure 1). Grade 1 versus 2 was prognostically weaker: for RFS, P = 0.06 (just not significant) but for OS, P = 0.03. Age was not significant, while ER was significant (P = 0.003 for both RFS and OS). This was mostly due to the significance of ER in women <55 years (P < 0.01 both for RFS and OS), while in 55–70 years of age, ER was only (just) significant for OS (P = 0.05). With multivariate analysis, MAI was the strongest prognosticator and only ER had independent prognostic value, but only in women 55–70 years and not <55 years. The additional prognostic value was only in MAI <10 cancers, where ER-positive and -negative cancers had an 83% and 46% survival, respectively, and MAI ≥10 had 58% OS. None other features did not add to its prognostic value of the MAI.

correlation among MAI, tumour diameter, and survival
Patients with MAI ≥10 have a poor prognosis independent of the subgroup analysed, and therefore also independent of tumour diameter. This explains why the prognostic significance of MAI in multivariate analysis overshadows tumour diameter. The percentage of patients with MAI ≥10 and distant metastases is remarkably stable and independent of tumour diameter (43%–47% in all three subgroups).

patients <55 years of age
Patients <55 years of age are of special interest because of adjuvant systemic chemotherapy. In this age group, the same results are found for the MAI in the different subgroups as described above for the whole group of patients. Because of the small number of events (n = 6) in patients with tumours smaller than 1 cm, a multivariate comparison of the different features, however, is not reliable.

discussion
Previous studies have shown that proliferation, and especially the MAI, is a widely available, exceedingly strong prognostic and predictive characteristic in node-negative breast cancer. The results of the current study show that the prognostic value of MAI also holds in certain subgroups of node-negative breast cancers under 71 years of age, such as grade 3 tumours separately, or in patients who usually do not get AST, such
as with tumours < 1 cm or with tumours between 1 and 3 cm with grades 1 + 2. Not only in the whole group of 853 patients but also in all subgroups MAI was the strongest prognosticator with univariate and multivariate analyses and both for RFS and OS.

It is striking that MAI ≥10 so accurately identifies patients with a high risk for distant metastases recurrence, independent of tumour diameter and grade. These findings indicate a fundamental common biological process involving metastasis and growth of metastatic colonies. Other proliferation-related measures, such as thymidine labelling index (TLI) and Ki67 [12, 23, 24], are also strong prognosticators and predictors of adjuvant chemotherapy success [23].

Grade 1 versus 2 is a prognostic factor in some, but not all, of the subgroups analysed. Multivariate comparison of the three constituting features of grade (MAI, tubular formation, and NA) shows that MAI is by far the strongest contributor to the prognostic value of grade. Once the MAI is included, NA and tubular formation lose their prognostic value. The fact that MAI is prognostically the most important constituent of grade explains why, over the past five decades, so many publications have identified grade as a major prognosticator. The fact that in most subgroups analysed, the MAI was prognostically strong, but grade was not, however, tells that adding TF and NA to MAI into a composite grade in certain patient groups apparently ‘dilutes’ the prognostic value of MAI.

The poor prognosis in patients with tumours < 1 cm and MAI ≥10 concurs with many years of clinical experience showing that even women with very small tumours can die of distant metastases. In view of the stable percentages of patients with distant metastases when MAI ≥10, independent of tumour diameter, AST for patients with MAI ≥10 seems reasonable, also in patients with a tumour < 1 cm diameter. This treatment may in fact even be more effective for patients with smaller tumours because of the presumably smaller metastatic burden present at the time of operation. The late appearance of distant metastases and the long metastases-free survival of recurrent patients with tumours < 1 cm support this hypothesis.

New technologies can offer exciting and promising approaches for determining prognosis and the benefits of specific therapies for a patient, yet few new technologies have been validated in well-designed, evidence level 1 studies. Patient selection and the effects of systemic therapy often confound the results and are not determined prospectively, not included in analyses, or not reported adequately [25–28]. A straightforward methodological error in propagating new techniques is changing from one study to the other the decision threshold of the test to classify patients as favourable/ unfavourable. It is difficult not to see such a strategy as an attempt to maintain or maximise the prognostic value of the test under study. This can hardly be regarded as a scientifically defendable approach as it carries the serious risk of producing over-optimistic results that are likely not true in clinical routine practice [26, 29]. In this respect, it is important to note that a major advantage of MAI is its confirmed prognostic value in independent validation studies, the mutual confirmation by an independent proliferation test (i.e. the TLI), its reproducibility in large, multicentre studies, and its robustness independent of interlaboratory variations in tissue processing. In addition, the prognostic threshold of < 10 versus ≥10 has been unchanged and consistently evaluated over the past 20 years, both retrospectively and prospectively among different institutions.

In conclusion, in patients < 71 years with T1–3N0M0 invasive breast cancer, MAI ≥10 is the strongest prognosticator in identifying high-risk patients, also in subgroups usually not receiving systemic treatment, i.e. with very small tumours (< 1 cm diameter) or tumours between 1 and 3 cm with grades 1 + 2 only (survival: 53%–67%) which should be considered for AST.

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