

Success predictors of adjuvant chemotherapy in node-negative breast cancer patients under 55 years¹

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Abstract. *Background:* Adjuvant systemic chemotherapy (ASCT) in lymph node-negative breast (LN-) cancers improves survival. The majority of (LN-) patients receive ASCT when the St. Gallen criteria or its modifications are used, as accurate identifiers which patients benefit from ASCT are lacking. This may imply over-treatment in many patients. *Aim:* To evaluate which patients or primary tumor factors predict ASCT success. *Material and method:* Retrospective analysis by single and multivariate survival analysis of clinical and tumor characteristics in (LN-) breast cancers <55 years, related to ASCT ($n = 125$) or-not ($n = 516$). *Results:* The two patient groups did not differ in age, tumor diameter, grade, type, number of mitoses and other factors. Fourteen-year survival for the ASCT and non-ASCT patients was 83% and 74% (Hazard Ratio = HR = 0.33; $p < 0.0001$, 9% absolute = 12% relative difference). Subgroup analysis showed that the recurrence-free survival = RFS of ASCT treated vs. non-treated patients differed in patients with grade 1 cancers ($p = 0.008$), grade 2 cancers ($p = 0.004$), grades 3 ($p = 0.02$), tumors under and ≥ 2 cm ($p = 0.001$ and 0.0002), oestrogen receptor-positive or -negative tumors ($p = 0.003, 0.04$), MAI < 10 and ≥ 10 ($p = 0.005, 0.003$) and fibrotic focus absent ($p = 0.002$). With multivariate analysis the most important predictor of ASCT effect was the MAI. In patients with slowly proliferating tumors (MAI < 3) no advantage was found between patients treated-or-not with adjuvant chemotherapy (RFS = 92% and 91%, $p = 0.13$, $p = 0.63$ for overall survival), contrasting those with MAI ≥ 3 ($p = 0.0001$; HR = 0.32, 95% CI 0.18–0.58). *Conclusion:* MAI is the strongest predictor of adjuvant systemic chemotherapy success. In patients with MAI < 3 (31% of all patients), ASCT does not improve survival.

Keywords: Breast cancer, proliferation, Mitotic Activity Index, prognosis, therapy

1. Introduction

Trials have shown that adjuvant systemic chemotherapy (ASCT) can improve prognosis in subsets of lymph-node negative (LN-) breast cancers. Consequently in certain countries such as Norway, breast cancers have been treated with adjuvant systemic

chemotherapy (ASCT) for many years. The relative survival improvement due to ASCT in node-negative invasive breast cancer patients was originally estimated to be 25%, but now more recent investigations indicate that it may be lower, 10–15% [16–18]. This makes it questionable whether all node-negative patients should receive ASCT.

The 2003-St.-Gallen classification [23] recommends ASCT for all LN- premenopausal patients except those at 'minimal/low-risk', defined as tumor diameter ≤ 2 cm and grade I and ER+ and/or PR+ and age >35 years. However, general application of this guideline means that more than 85% of all premenopausal

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LN- patients would be treated, while only a relatively small number would develop distant metastases without AST. It has also been argued that the St.-Gallen classification is an inaccurate outcome predictor in patients with node-negative breast cancer and should be used with caution [7]. Moreover, the reproducibility of grade, an important discriminator in LN- patients in this risk classification, is far from perfect, even between leading experts, with only moderate grading consistency using the Nottingham method achieved by 23 European pathologists from 12 countries ($\kappa = 0.53$) [22].

This study therefore evaluates which easily assessable, widely available, clinical and primary tumor factors determine the long-term benefit of ASCT in lymph node-negative invasive breast cancer women, less than 55 years of age, and without previous malignancies.

2. Materials and methods

This retrospective study of clinical and tumor characteristics in node-negative invasive breast cancers <55 years, analyzed two groups of patients treated without ($n = 516$) and with ASCT ($n = 125$). The non-ASCT group consists of patients from the nationwide Dutch MMMCP study [2]. The ASCT patients were consecutive breast cancers from approximately the same period as the MMMCP study diagnosed at the Stavanger University Hospital, Stavanger, Norway. All patients were treated with modified radical mastectomy or breast conserving therapy (BCT, always with adequate axillary lymph node dissection, see below). Loco-regional radiotherapy was given in cases that underwent BCT or had medially localized tumors. All aspects of this study were approved by local committees in The Netherlands and in Norway by the Regional Ethics Committee, the Norwegian Social Science Data Service, and the Norwegian Data Inspectorate.

Following the general policy in The Netherlands during the enrollment period of the MMMCP, node-negative patients did not receive adjuvant systemic treatment [3]. In contrast, all node-negative breast cancer patients in Norway received ASCT. To get a comparable group of patients as the Dutch MMMCP group, the ASCT Norwegian patients were selected as follows. The archive of the department of pathology at the Stavanger University Hospital provided a total of 1108 breast tumor patients. The following patients were excluded for further study: $n = 81$ with carcinoma *in situ* and 88 with extensive carcinoma *in situ* and a micro-

invasive component less than 1 mm, which is ineligible for mitoses counting. Another 11 had a previous history of breast cancer, 19 had a recurrence within 6 months of follow-up and 41 had a follow-up of less than 6 months. Patients with Paget's disease, $n = 18$, were also excluded as were 23 patients with bilateral breast cancer, 2 male, and 11 other rare non-cancerous breast malignancies. From 14 patients no material was available and 29 patients were lost to follow-up. Leaving a total group of 771 patients, 381 were lymph node-negative, of which 125 were <55 years and received systemic adjuvant chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil (=CMF)), according to the Norwegian Breast Cancer Group (NBCG) protocol. None of the patients received hormonal treatment next to the adjuvant chemotherapy.

Post-surgical size of the tumor (pT) was measured in the fresh specimens; the tumors were cut in slices of 0.5 centimeter thick and fixed in buffered 4% formaldehyde and embedded in paraffin. At least 10 (median: 14) lymph nodes were detected in the axillary lymph node dissection specimens. Four micrometers thick paraffin sections were cut and stained with haematoxylin and eosin (H&E). Histologic type and grade were assessed at review by pathologists with considerable experience in breast pathology (by J.B., P.D., E.G.) according to the World Health Organization criteria [46]. Grade was assessed according to the Nottingham modification [21,22], using MAI 0–5 = 1, 6–10 = 2 and >10 as 3, nuclear atypia as mild = 1, moderate = 2 and marked = 3, and tubular formation as majority (>75% = 1), moderate (10–75% = 2) and little or none (<10% = 3). Grade is the sum of tubular formation + nuclear atypia + MAI class; where Grade I: (Sum = 3, 4, 5), Grade II (Sum = 6, 7) and Grade III (Sum = 8, 9). Estrogen receptor value (ER) was assessed in reference laboratories with the ligand binding charcoal technique (cut off 10 fmol/mg protein).

Many previous studies have shown that the Mitotic Activity Index (MAI) is the strongest prognostic factor in T1-3 node-negative invasive breast cancer patients under 55 years [3], and therefore is described in greater detail here. Following the MMMCP protocol [2,14], the total number of well-defined mitotic figures was counted at $\times 400$ magnification (objective 40, field diameter 450 μm at specimen level) in 10 consecutive neighboring fields of vision in the most poorly differentiated peripheral area of the tumor (= measurement area, representing a total area of 1.59 mm^2). Fields with necrosis or inflammation were avoided and doubtful structures were ignored. The resulting total number

of mitoses in the 10 fields of vision is the mitotic activity index (MAI). An accurate MAI assessment takes 3–5 minutes. Correction of the MAI for the percentage of tissue occupied by stroma or the number of tumor cells was not applied since it was previously shown that this does not substantially improve the prognostic value of the MAI and is much more time consuming [32]. The MAI is a continuous variable, and according to many previous studies, the most important prognostic thresholds are 10, with MAI < 10 indicating favorable prognosis and MAI \geq 10 poor prognosis [4,10,27,33,36,37,41–43] (this threshold is further denoted as MAI10). Patients with MAI < 3 have an especially favorable prognosis [3].

The presence of a fibrotic focus (FF) was evaluated [31]. A FF is a scar-like area or areas replacing necrosis in the center of a carcinoma. We previously reported an interobserver concordance of 85% for the estimated relative FF size [11]. When multiple fibrotic foci are present, only the largest one is taken into account.

2.1. Statistical analysis

Comparison of continuous clinicopathologic features between the ASCT and non-ACST was done with the *T*-test, for the discontinuous features the Spearman-test was used. Main endpoints were recurrence and mortality. In analyzing the probability that patients would remain free of distant metastases, we defined recurrence as 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, local or regional recurrences or the development of a secondary primary cancer (including contra-lateral breast cancer). Mortality was defined as any death due to distant metastases

(as evident from clinical, radiologic, histologic or autopsy data) (no patients died from loco-regional disease). If the cause of death was unknown, but a metastasis was previously detected, then death was considered breast cancer related unless explicitly stated otherwise (in line with other studies). If the status during follow-up indicated a confirmed metastasis without a date of recurrence, the date of that follow-up visit was used. Age, time to first recurrence and survival time were calculated relative to date of primary diagnosis. Survival curves were constructed using the Kaplan–Meier techniques. Differences between groups were tested by log-rank tests or tests for trend. The relative importance of potential prognostic variables was tested using Cox-proportional hazard analysis and expressed in Hazards Ratio (HR) with 95% confidence intervals [25]. All variables were tested for proportionality and continuous variables were checked for (non-)linearity and transformed or recoded if necessary (or useful). In all analyses, the threshold for significance (*p*-value) was set at 0.05.

3. Results

Figure 1 shows that the significant survival difference between the treated and the untreated patients at 14 years: 83% for the ASCT and 74% for the non-ASCT patients (9% absolute = 12% relative survival difference Hazard Ratio = HR = 0.33; *p* < 0.0001). The two patient groups did not differ in age, tumor diameter, grade, type, and number of mitoses (*p* > 0.10). Median follow-up in the ASCT-group was longer than in the non-ASCT group; 141 (range: 6–212) vs. 118 (6–198) months (*p* = 0.04) (Table 1).

The effect of ASCT-or-not was analyzed in different subgroups. The distant metastases free survival of

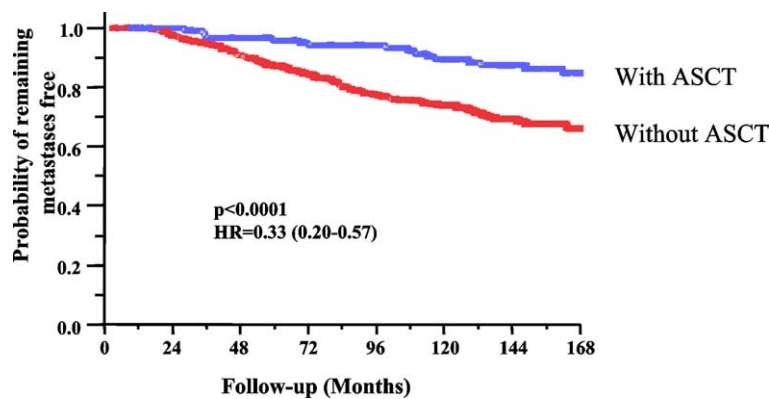


Fig. 1. Survival curves of node negative invasive breast cancer patients <55 years, with and without adjuvant chemotherapy.

Table 1
Recurrence Free Survival in the total population of 639 lymph node-negative patients under 55 years, divided in no chemotherapy vs chemotherapy. For the MAI, only the most significant thresholds are shown.

	No chemotherapy Events, Numbers at risk (percentage censored)	Chemotherapy Events, Numbers at risk (percentage censored)	p-value	Hazard ratio	95% CI
Age					
≤45 yr	71/231 (69)	14/63 (78)	0.003	0.37	0.19–0.72
>45 yr	63/283 (78)	7/62 (89)	0.002	0.28	0.12–0.67
T2					
T ≤ 2.0	70/303 (77)	7/61 (89)	0.001	0.28	0.21–0.63
T > 2	64/211 (70)	14/64(78)	0.002	0.35	0.18–0.71
T2–3					
T < 2	70/303 (77)	7/61 (89)	0.001	0.31	0.13–0.72
T2-3	59/195 (70)	12/50 (76)	0.01	0.41	0.20–0.84
T > 3	28/85 (67)	2/14 (86)	0.05	0.17	0.02–1.25
ER					
Pos	68/295 (77)	10/66 (85)	0.003	0.25	0.11–0.56
Neg	63/185 (66)	11/59 (81)	0.04	0.37	0.18–0.74
Grade					
1	42/160 (74)	1/20 (95)	0.008	0.10	0.01–0.74
2	42/191 (68)	5/45 (88)	0.004	0.22	0.07–0.65
3	50/161 (69)	15/60 (75)	0.02	0.49	0.25–0.94
MAI3					
MAI < 3	15/159 (91)	3/39 (92)	0.13	0.36	0.09–1.41
MAI > 2	119/355 (66)	18/86 (79)	0.0001	0.32	0.18–0.58
MAI10					
<10	51/298 (83)	9/78 (88)	0.005	0.34	0.16–0.74
>9	83/216 (62)	12/47 (74)	0.003	0.35	0.17–0.72
MAI 3–9					
MAI < 3	15/159 (91)	3/39 (92)	0.13	0.36	0.09–1.41
MAI3–9	36/139 (74)	6/39 (82)	0.01	0.32	0.13–0.83
MAI > 9	83/216 (62)	12/47 (74)	0.003	0.35	0.17–0.72
FF					
Absent	59/290 (80)	14/105 (87)	0.002	0.36	0.19–0.70
Present	63/158 (60)	7/20 (65)	0.06	0.408	0.15–1.06

the ASCT-treated and non-ASCT patients was significantly better in the grade 1 cancers ($p = 0.008$), the grade 2 cancers ($p = 0.004$), the grade 3 cancers ($p = 0.02$), tumors <2 and ≥ 2 cm ($p = 0.001$ and 0.002), OR positive or negative tumors ($p = 0.003$ and 0.04), MAI $< 3 \geq$ ($p = 0.0001$), and in the patients where a fibrotic focus was absent ($p = 0.002$) (Table 1). In a multivariate analysis for disease specific survival with treatment as strata, the MAI (with thresholds $<10, \geq 10$) was the strongest factor ($p < 0.0001$),

and in a second step the absence of the Fibrotic Focus added some extra value ($p = 0.002$). The strongest single predictor is the MAI with threshold 3, since adjuvant chemotherapy has no treatment advantage in patients with a MAI < 3 (RFS = 92% and 91%, $p = 0.13$ in ASCT treated and non-treated patients). This contrasts those with MAI ≥ 3 (ASCT Hazard Ratio = 0.32, 95% confidence interval 0.18–0.58, 12% absolute survival difference, 16% relative survival difference) (Fig. 2). Once that the threshold of MAI = 3 is used,

Table 2

Overall Survival in the total population of 639 lymph node-negative patients under 55 years, divided in chemotherapy vs no chemotherapy. For the MAI, only the most significant thresholds are shown.

	No chemotherapy Events, Numbers at risk (percentage censored)	Chemotherapy Events, Numbers at risk (percentage censored)	p-value	Hazard ratio	95% CI
Age					
≤45 yr	51/231 (78)	8/63 (87)	0.02	0.41	0.19–0.91
>45 yr	45/283 (84)	6/62 (90)	0.06	0.44	0.18–1.05
T2					
T ≤ 2.0	48/303 (84)	6/61 (90)	0.06	0.43	0.18–1.05
T > 2	48/211 (77)	8/64 (88)	0.01	0.38	0.17–0.85
T2–3					
T < 2	30/234 (87)	6/61 (90)	0.17	0.53	0.21–1.33
T2–3	44/195 (77)	8/50 (84)	0.09	0.50	0.22–1.12
T > 3	22/85 (74)	0/14 (100)	0.03	NS	NS
ER					
Pos	43/295 (85)	8/66 (88)	0.06	0.47	0.21–1.06
Neg	52/185 (72)	6/59 (90)	0.005	0.32	0.14–0.74
Grade					
1	32/160 (80)	1/20 (95)	0.07	0.19	0.03–1.39
2	29/191 (85)	5/45 (89)	0.14	0.47	0.17–1.29
3	35/161 (79)	8/60 (87)	0.07	0.48	0.21–1.07
MAI3					
MAI < 3	9/159 (94)	3/39 (92)	0.63	0.70	0.16–2.99
MAI > 2	87/355 (75)	11/86 (87)	0.003	0.38	0.20–0.74
MAI10					
<10	29/298 (90)	8/78 (90)	0.42	0.72	0.32–1.61
>9	67/216 (62)	6/47 (74)	0.004	0.29	0.12–0.71
MAI3–9					
MAI < 3	9/159 (94)	3/39 (92)	0.63	0.70	0.16–2.99
MAI 3–9	20/139 (74)	5/39 (82)	0.40	0.66	0.25–1.76
MAI > 9	67/216 (69)	6/47 (87)	0.004	0.29	0.12–0.71
FF					
Absent	39/290 (87)	9/105 (91)	0.05	0.50	0.24–1.02
Present	47/158 (70)	5/20 (75)	0.21	0.50	0.17–1.48

none of the other features analyzed, including the Fibrotic Focus, has additional predictive value.

4. Discussion

Previous reports showed that the MAI is the strongest prognostic factor in node negative invasive breast cancer patients less than 55 years of age [8]. The current study shows that the MAI is also the strongest predictor for success when CMF-based adjuvant systemic chemotherapy is used. In patients with low prolifer-

ation (MAI < 3, 31% of all patients, RFS = 91%), ASCT does not improve survival. This result may not be surprising, as due to the nature of ASCT, one would expect that proliferation-related features would have predictive value. These results are in agreement with Volpi et al. [44,45] on the overriding prognostic and therapeutic effect of proliferation factors. They use the Thymidin Labelling Index (TLI), which requires radioactive methods.

Using the mitotic activity index (MAI) as a prognostic and predictive factor in daily practice is practical.

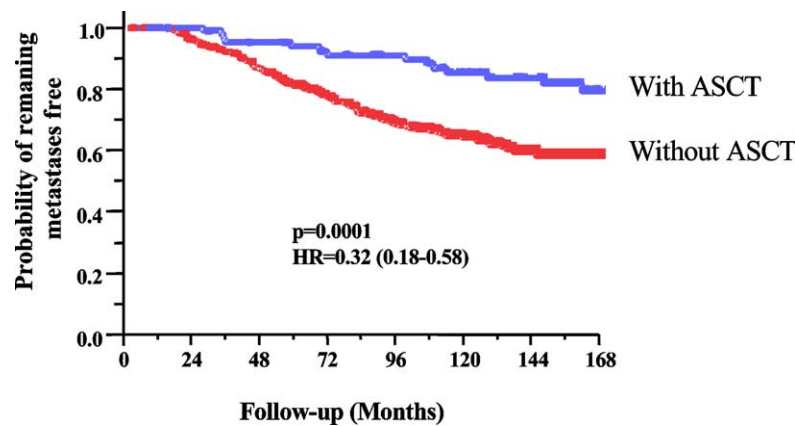


Fig. 2. Survival curves of MAI ≥ 3 in node negative invasive breast cancer patients <55 years with and without adjuvant chemotherapy.

First, it is a prognostically strong, robust, yet-easy-to-assess proliferation-associated factor [3]. Moreover, it can be determined in standard histologic sections and can be very well reproducible if simple quality control criteria are kept [4,32]. Its' prognostic value has been carefully validated in many retrospective and prospective studies. Patients with MAI < 3 have an especially favorable prognosis of 95% 10-year survival [3]. The MAI is not sensitive to fixation delay [6,15] and is already part of different grading systems [19,20,46].

Unfortunately, investigators do not always follow a strict mitoses counting protocol activity as described previously [14] and prescribed by the WHO [19,20], but instead estimate the mitotic index. They apparently believe that tubular formation and nuclear atypia have such strong prognostic value that the *exact* value of the MAI has little additional value and that a rough MAI impression is sufficient. This opinion is not correct [3] and dangerous. An accurately assessed MAI overshadows all prognostic information contained within the other grade components. MAI-protocol violations may result in too low or too high grades and hence differences in the selection of patients for adjuvant therapy. It could also result in wrong prognostic impressions in studies evaluating prognostic factors, especially mitotic activity.

Most agents used as adjuvant chemotherapy have been designed to kill fast proliferating cells, as is also the case for CMF used in the current ASCT treated patients. In this respect it is understandable that the MAI comes out so strongly in our analysis. The fact that tumors with a Fibrotic Focus respond so poorly on adjuvant systemic chemotherapy could be explained by the fact that the Fibrotic Focus is a sign of hypoxia [11]: hypoxic cells are more quiescent and therefore

more insensitive to such agents [25,34]. Poor perfusion may limit drug dissemination to hypoxic regions. In addition, changes in gene expression that enable the survival of cells under hypoxic conditions may influence intracellular and extracellular pH, which can influence the uptake of 5-fluorouracil by tumor cells grown *in vitro* [39].

The ninth St Gallen expert consensus meeting in January 2005 made a fundamental change in the algorithm for selection of adjuvant systemic therapy for early breast cancer [24]. Rather than the earlier approach commencing with risk assessment, the Panel affirmed that the first consideration was endocrine responsiveness. Three categories were acknowledged: endocrine responsive, endocrine non-responsive and tumours of uncertain endocrine responsiveness. The three categories were further divided according to menopausal status. Only then did the Panel divide patients into low-, intermediate- and high-risk categories. The long-term effect of this important strategic therapeutic change remains to be analyzed, but it is unfortunate that proliferation factors have not been used as up-front selection criteria, rather than the classical, less prognostic and less well-reproducible St Gallen risk classifiers.

An important question is the comparative prognostic and predictive value of the MAI and other alternative selection methods for adjuvant chemotherapy, like uPA, PAI-1 and gene expression signatures. Patients with node-negative breast cancer with low antigen levels of uPA and PAI-1 in their primary tumour seem to have a good prognosis, whereas those with elevated uPA/PAI-1 antigen levels carry an increased risk of disease recurrence and a greater benefit from adjuvant chemotherapy than patients with low uPA/PAI-1 levels

[28]. However, comparison of uPA, PAI-1 and proliferation factors has been limited. In one small study with short follow-up [29], uPA and PAI-1 have been compared with S-phase fraction (SPF), Ki-67, p53, HER-2/neu), but not with the MAI, and neither of these proliferation-associated factors is as strong as the MAI. Moreover, no age limit was given, and proliferation is age-dependent as breast tumours arising in older patients have slower growth rates [21]. Finally, the robustness and reproducibility of UPA and PAI-1 determinations have not been studied to the same extent as for MAI [6,14]. Immunohistochemical determinations of UPA and PAI-1 give somewhat blurred staining patterns, with expression both in epithelial cells and stroma. Nevertheless, an adequate prognostic and predictive comparison of MAI with uPA and PAI-1 would be interesting.

Large-scale gene expression analysis has proved to be a valid strategy for developing gene expression profiles or “signatures”, to classify prognostic subgroups [43]. Unfortunately the method requires fresh tissue for optimal results. Moreover, high throughput analyses methods have been criticized from a statistical point of view. Because of inadequate validation, many studies published overoptimistic results and did not classify patients better than chance [5,38]. Before gene expression profiles are to be clinically implemented the results need to be validated in independent test sets and adequately compared with existing techniques, according to *Good Laboratory Practice guidelines* [1,27], as has been done for the MAI. Vijver et al. [43] have compared their gene expression signature with grade but not with the MAI. This is unfortunate and surprising, as by the time of their publication it was well known that the MAI was much stronger than grade. Moreover, the prognostic differences between the MAI and gene expression profiles do not seem to be very impressive: favourable and unfavourable gene signatures were associated with approximately 96% and 50% survival [43], whereas MAI < 10 versus \geq 10 was associated with nearly comparable long-term survival rates of around 90% and 60% [3]. On the other hand, it is encouraging that a cell proliferation signature is a marker of poor (20%) outcome [12], prognostically similar to the fact that amplification of 3q26 by CGH identifies a very poor prognosis node-negative subgroup with 10% survival [33]. Therefore, it still is a question whether gene expression signatures will perform much better than much less expensive methods. It could well be that simple, widely available well reproducible methods will identify subgroups with an excellent and very poor prognosis.

One could question the age threshold of younger than 55 used by us. The correct gynecological age with formal hormonal determinations would have been preferable, but these were not done in the accrual period of the present material and thus are not available. Most large meta-analyses use 50 years and younger as the age threshold for “young”, which is understandable as the average age of breast cancer patients is around 60 years. Since 1980, in the Netherlands patients younger than 55 years at the time of diagnosis traditionally have been regarded as “young”. An important factor in the evaluation of a laboratory tests is independent prospective validation which typically takes 15–20 years [1]. Changing the threshold from 54 to 50 would put us two decades back in the evaluation of the MAI as a laboratory test. Moreover, the number of patients between 50 and 55 is small. Finally, in our previous large multicenter prospective prognostic study on T_{1–3}N₀M₀ node negative breast cancer, age subgroups as <35, 35–45 and 45–55 did not prove to be significant prognosticators [3].

In some countries like Germany, the vast majority of pre-therapeutic diagnoses are made on minimal invasive biopsy specimens, and many cancers are treated by ASCT before operation (neoadjuvant ASCT). MAI and other important prognostic and diagnostic features cannot be assessed reliably in small minimal invasive biopsy specimens and neoadjuvant ASCT kills many proliferating cells, so that the MAI cannot be assessed afterwards either. It would be preferable to use surrogate markers for mitoses in small pre-treatment biopsies. Ki-67 (MIB-1) has prognostic value [13] but it is not certain if it is prognostically as strong as the MAI (different studies came to conflicting conclusions [8,31]), and Ki-67 certainly has not been validated to the same extent as the MAI. In one neoadjuvant concurrent paclitaxel and radiation in stage II/III breast cancer [9], there was no significant difference in baseline Ki-67 between responders (35%) and non-responders (28%; $p = 0.45$) whereas baseline mitotic index was higher for patients with pathologic complete response over non-responders (27 versus 10, $p = 0.003$). At the current status of knowledge, it therefore seems that tumour proliferation as measured by mitotic activity may serve as the most important indicator of pathologic response in stage II/III breast cancer. Detailed studies comparing the prognostic value of the MAI with alternative surrogate markers remains important.

It has to be admitted that CMF in some countries is no longer the primary choice for ASCT. However,

the big prognostic quantum leap due to ASCT has been from “no adjuvant chemotherapy” to “multiple CMF adjuvant chemotherapy”, not the ASCT modifications afterwards. There is little proof that the real survival benefit of later ASCT schemes is much better than around 7–10% absolute (10–25% relative) survival improvement (comparable to the survival advantage found by us). This makes it likely that the predictive conclusions drawn from the current study therefore are likely to be true for other adjuvant chemotherapy schemes as well.

In conclusion, the current results suggest that patients with a MAI < 3 (31% of all patients) do not benefit from adjuvant chemotherapy and therefore should be considered for non-cytostatic alternative targeted therapy.

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