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# Do we need better prognostic factors in node-negative breast cancer?

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### 1. Introduction

Breast cancer is characterised by its early haematogenous dissemination. Therefore, in addition to local management by surgery and radiotherapy, established treatment of breast cancer consists of systemic application of combination chemotherapy and/or endocrine treatment. Within the past 40 years, substantial benefit with regard to disease-free survival and overall survival has been documented by a large number of randomised trials for those patients who had received systemic adjuvant treatment [1,2].

However, since breast cancer is a heterogeneous disease, the question is open whether all patients should receive adjuvant chemotherapy, or only those who have a high probability of systemic disease at primary diagnosis.

### 2. Where are we now?

According to the present recommendations of the St Gallen Consensus Conference 1998 on Adjuvant Therapy in Breast Cancer, almost every breast cancer patient, node-positive as well as node-negative, should be subjected to adjuvant treatment [3,4]. These recommendations are based on the recently published evaluations of the Early Breast Cancer Trialists' Group suggesting a benefit for almost all patients receiving adjuvant therapy [1,2]. For most patients, administration of both adjuvant chemotherapy and tamoxifen is recommended.

These general treatment recommendations are a matter of debate especially with regard to node-negative breast cancer patients. In summary, there are four hypotheses on which the St Gallen recommendations are founded.

#### *2.1. First hypothesis: adjuvant therapy improves disease-free and overall survival in node-negative breast cancer patients*

Trials on adjuvant therapy which led to this conclusion as well as the meta-analysis appear to be designed to answer the question whether adjuvant treatment is better than no treatment with regard to disease-free or overall survival. Owing to the huge number of patients included into these analyses, high statistical power of the results was guaranteed. The fact is, that following the results of these trials, disease-free and overall survival of patients with node-negative breast cancer in general seem to be improved by administering adjuvant therapy [1,2].

*Antithesis*: Results from high-risk patients with node-negative breast cancer cannot be extended to low-risk patients.

Regarding the results of the meta-analysis showing significant benefit from adjuvant chemotherapy, the baseline risk of untreated patients (disease-free survival of 58.0% for patients aged $<50$ years and 59.9% for patients aged 50 years of age or more) appears to be rather unfavourable. Benefit from adjuvant therapy

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might be expected due to the higher risk. However, this observation also suggests selection effects:

- Node-negative breast cancer patients of the decades between 1970 and 1990 probably had characteristics different from those of patients, who will be diagnosed today or in the next decades. The reasons are:
  - Increasing screening leads to an increasing proportion of patients with early detected, small tumours with low risk of recurrence.
  - Due to the increasing life expectancy the proportion of postmenopausal patients will increase as well. Those patients probably have less benefit from adjuvant chemotherapy.
- Inclusion criteria of many trials on which the meta-analysis is based were designed in order to recruit only patients with unfavourable prognosis (receptor-negative disease, larger tumours). Benefit from therapy could have been expected since treatment effect is higher in receptor-negative disease than in receptor-positive.

In conclusion, since one cannot simply transfer results received in high-risk subgroups to low-risk patients, the benefit from adjuvant chemotherapy in node-negative breast cancer patients remains to be proven.

### 2.2. Second hypothesis: each single patient benefits from adjuvant therapy

Considering the trial results it was concluded that from the statistical mean reduction of risk of recurrence for the entire patient cohort, individual reduction of risk of recurrence for each patient can be derived, by assuming homogeneity of node-negative breast cancer disease.

*Antithesis*: In node-negative breast cancer, 70% of all patients are cured by surgery alone and, therefore, do not need any adjuvant treatment.

Breast cancer is a heterogeneous disease. In node-negative breast cancer more than 70% of patients are cured by local therapy alone and will never develop recurrence of disease. Ideally, only 30% of all node-negative patients should receive adjuvant treatment (Fig. 1). Therefore, uniform recommendations appear not to be reasonable, rather it is necessary to distinguish between patients with localised disease and those with occult systemic disease at primary diagnosis. As a general principle, this idea was recognised by the St Gallen Consensus Panel, too: patients with very small tumours, which are highly differentiated (G1) and steroid hormone receptor-positive, may be spared adjuvant chemotherapy. However, these patients represent less than 10% of all node-negative breast cancer patients. Thus, the St Gallen Consensus does not achieve the aim of risk-adapted adjuvant therapy. Therefore, it seems to be necessary to improve identification of patients who have a very low risk of relapse and, therefore, do not need any adjuvant treatment.

### 2.3. Third hypothesis: traditional prognostic factors tumour size, grading and steroid hormone receptor status give sufficient information on prognosis

In node-negative breast cancer, the St Gallen Consensus tried to assess risk of recurrence by using traditional prognostic factors such as tumour size, grading of malignancy, and steroid hormone receptor status. Risk groups were created — minimal risk, intermediate risk, high risk receptor-positive, high risk receptor-negative — and for each group adjuvant treatment recommendations were given — in most cases, chemotherapy plus tamoxifen.

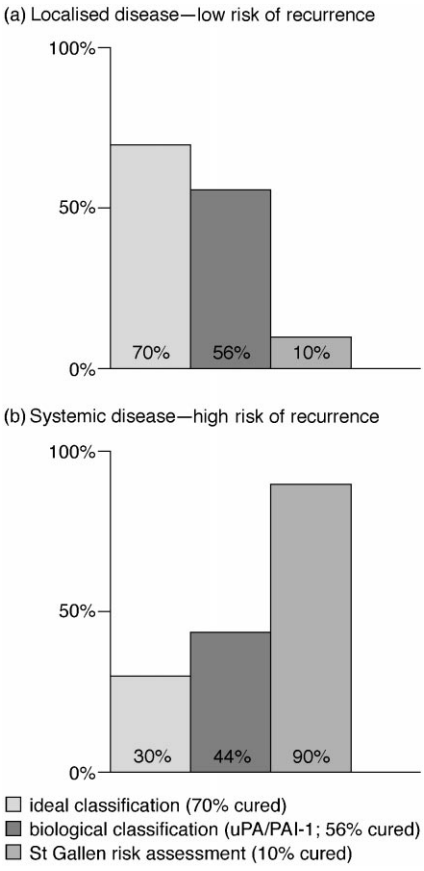


Fig. 1. Comparison of risk classifications: left columns show the real situation (more than 70% of all node-negative breast cancer patients are cured by surgery alone, only 30% will have recurrence), right column the St Gallen classification (only 10% or less of node-negative patients are classified as cured). The middle column shows risk classification as it can be performed by using new prognostic factors uPA and PAI-1: a high proportion (56%) is classified as having a very low risk of recurrence ('cured'), for patients in this group adjuvant therapy should be avoided.

*Antithesis*: Traditional factors such as tumour size, grading and steroid hormone receptor status are not adequate for risk assessment in node-negative breast cancer.

In order to distinguish between patients with high and low risk of recurrence, effective prognostic factors are needed. Traditional prognostic factors such as tumour size, histological grading, and steroid hormone receptor status are integral parts of the St Gallen risk classification, although none of these factors has shown a high and accepted prognostic significance as single factor [5–7].

Tumour size correlates with node-involvement, therefore exhibiting prognostic impact in breast cancer. But, as it has been shown by several analyses within the node-negative group, strong prognostic impact of tumour size has not been proven. An explanation may be that large tumours without axillary node involvement may have biology of local growth only, and thus, a better prognosis [5].

In addition, for histological grading, clinically relevant prognostic impact was not shown in a uniform manner. First, due to substantial interobserver variations, it is difficult to obtain consistent and valid results. Second, most tumours are graded as intermediate (G2) and only 10% are classified as well differentiated (G1) with an excellent prognosis. Therefore, grading should not be used uncritically for risk assessment in node-negative breast cancer [6].

For steroid hormone receptor status, prognostic impact was demonstrated by many authors. However, critical review of these data shows that prognostic impact was demonstrated only in trials with a short observation period. After longer follow-up, the prognostic impact of steroid hormone receptor status is less evident, so that those patients with positive receptor status will have nearly the same prognosis as those with negative receptor status [7–9].

Moreover, even these traditional prognostic factors need standardised evaluation, quality assurance and quality control, in order to receive reliable histopathological and biochemical reports. To date, quality assurance programmes on these parameters have been performed only in part.

### *2.4. Fourth hypothesis: the higher the risk, the more aggressive the therapy*

Another issue of the St Gallen Consensus focuses on type of adjuvant treatment, suggesting that the efficacy of treatment is dependent on risk of recurrence. According to these recommendations, patients with low risk of recurrence need no therapy or tamoxifen alone, patients with intermediate or high risk need more intense adjuvant therapy (chemotherapy + tamoxifen).

*Antithesis*: Risk of recurrences does not predict sensitivity to therapy.

Efficacy of treatment is dependent on the biology of each single tumour. Thus, individualised treatment requires predictive factors, derived from tumour biology to indicate appropriate adjuvant therapy. The significance of this suggestion is illustrated by the observation that the benefit of adjuvant tamoxifen treatment in breast cancer on disease-free and overall survival is valid only in patients with c-erbB-2-negative tumours. Moreover, in patients with c-erbB-2-overexpressing tumours, tamoxifen had even an adverse effect [10]. Also, the efficacy of adjuvant chemotherapy seems to be dependent on c-erbB-2-status: patients with c-erbB-2-negative tumours have no better survival when anthracyclines are used instead of CMF, whilst for patients with c-erbB-2-overexpressing disease anthracyclines might be more effective than CMF [11]. Thus, tumour biology appears to play a role in resistance to treatment, and it should be considered when adjuvant treatment has to be selected.

### *2.5. Conclusion of St Gallen Consensus Conference 1998 on Adjuvant Treatment in Breast Cancer*

These hypotheses led to the well known recommendations with the uniform conclusion that nearly all patients need combined treatment (chemotherapy plus tamoxifen). However, it was not differentiated when to choose CMF or an anthracycline containing regimen. Obviously, these recommendations were given on the basis of minimal consensus. This all points to one of the most important question still unresolved: do we need better prognostic factors in node-negative breast cancer?

## 3. Synthesis: yes, we do need better prognostic factors!

We know patients with large tumours who will never develop metastases. In these patients, survival will not be altered by the disease. In contrast, some patients present very small, or even undetectable primary breast tumours at first diagnosis, but develop metastases and die within a short interval. Thus, clinical experience evidently demonstrates that breast cancer is a very heterogeneous disease. Localised disease has to be distinguished from (occult) early systemic disease.

Therefore, the question arises whether a heterogeneous disease should be treated by an uniform treatment. The trend of such a strategy is coming more and more into practice [12]. It started in 1988, when the NCI Consensus recommended adjuvant treatment for node-negative disease, stating that patients with a mortality of 30% (after 10-year follow-up) should have adjuvant therapy. In St Gallen, 1995, the recommendation was extended to patients with a 10-year mortality of more than 10%. Now, at the Consensus of 1998, for the majority of the panel of specialists it seemed to be

worthwhile to extend treatment even to low-risk patients with a 10-year relapse rate as low as 10%.

At a risk of recurrence of 30%, as seen in node-negative breast cancer patients, it can be estimated that only 8% of patients benefit from adjuvant treatment. The majority (70%) are cured by surgery alone and would, therefore, be treated unnecessarily. Due to resistance against chemotherapy, 22% of all node-negative patients would be treated in vain. Should we really treat 92 patients unnecessarily or in vain by adjuvant chemotherapy, in order to improve the prognosis in 8 patients? (Fig. 2).

The aforementioned development will lead to substantial overtreatment, for improved awareness concerning health and screening programmes means breast tumours are detected in increasingly smaller shapes and sizes at primary diagnosis corresponding to an increasing frequency of tumour-free axillary lymph nodes. Today, 50–60% of patients are presenting with node-negative disease. In the near future, 70–80% of all patients will be node-negative. In this setting, the majority of all breast cancer patients will be diagnosed without systemic disease. Thus, risk of overtreatment will be a major and relevant issue of future breast cancer management.

Therefore, the burning question is: which patient does not benefit from adjuvant chemotherapy? In which patient can adjuvant treatment be avoided?

In order to resolve these questions we need not just prognostic factors but better prognostic factors.

## 4. Development of prognostic factors

At least 100 factors have been described as having prognostic significance in node-negative breast cancer. However, for most of these factors, available data are inconsistent. Frequently, correlations to classical prognostic factors have been shown, even a prognostic impact in univariate analyses. But most of these factors failed to maintain independent prognostic impact in multivariate analyses.

In the last two decades, tumour biology research has been utilised to try to find clinically relevant prognostic factors. Basic implications of this type of research have been stated by McGuire and Clark and modified by Jänicke and Graeff [13–15]. The following prerequisites are required before transfer of a prognostic factor into clinical routine:

- availability of a biological model supporting the possible role of a factor
- simple and validated method of factor determination
- statistical planning of analyses
- conduction of a prospective study
- univariate and multivariate analyses
- confirmation by a second patient panel
- prospective trial in order to check the predictive value.

Invasion and metastasis in solid tumours require the action of tumour-associated proteases. Urokinase-type plasminogen activator (uPA) and its inhibitor PAI-1 seem to play a key role in the activation and regulation of tumour-associated proteolysis. Clinical studies have demonstrated that the antigen content of uPA and PAI-1 in breast cancer tissue extracts may serve as remarkable prognostic factors since they are strongly correlated with disease-free and overall survival [16]. These findings were confirmed by more than 15 different groups without contradictory results [17]. In a prospective study [18] not only a prognostic differentiation was shown, but also a rather effective grouping: 56% of all node-negative patients were assigned to a low-risk group (less than 10%); only 44% of all patients should be forwarded to adjuvant treatment. (Fig. 1).

In order to confirm the prognostic significance of risk assessment by these new factors, a second prospective

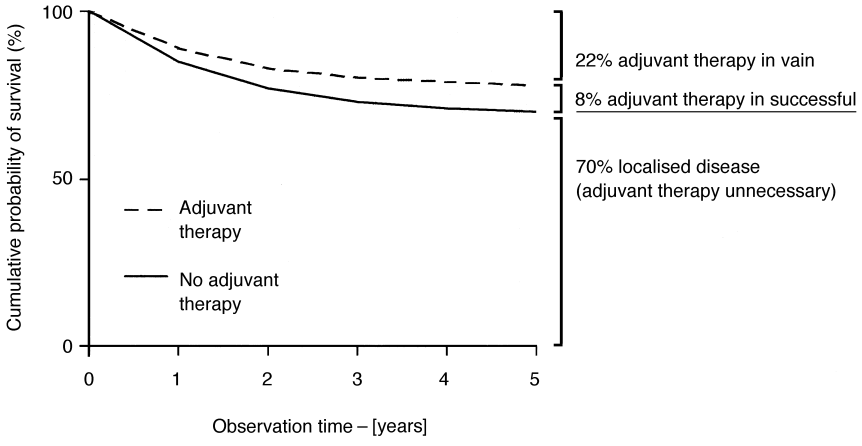


Fig. 2. Efficacy of adjuvant therapy in node-negative breast cancer patients. Owing to the high proportion of patients with localised disease (70%) and chemoresistance (22%), only 8% of all patients benefit from adjuvant chemotherapy.

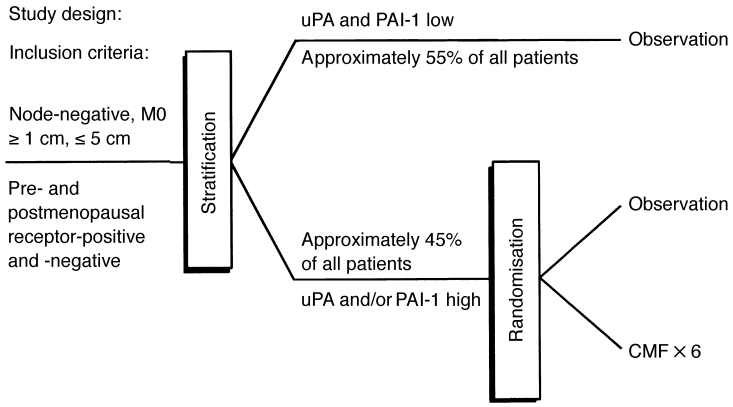


Fig. 3. Study design of the German multicentre trial on risk-adapted adjuvant chemotherapy in node-negative breast cancer patients guided by tumour-biological factors (uPA, PAI-1). CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

and multicentric trial was started (Fig. 3) [19]. Meanwhile, more than 650 node-negative breast cancer patients were recruited for this study. Data of the first interim analysis will be published soon. Moreover, in this multicentre study the feasibility of uPA- and PAI-1-testing at a high level of quality (GLP, good laboratory practice) was demonstrated by performing an externally controlled quality assurance programme [20].

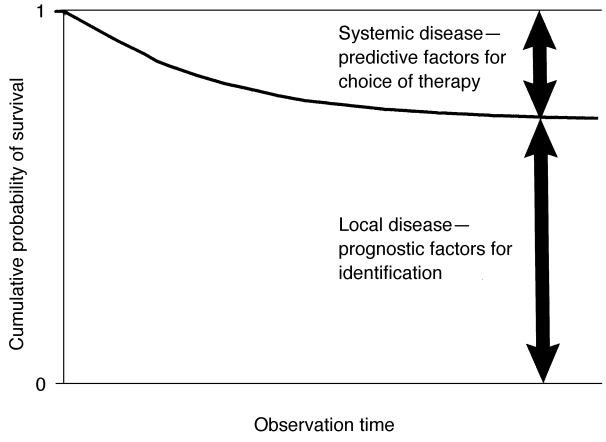


Fig. 4. Prognostic factors are necessary to identify those patients with localised disease and, therefore, very low risk of recurrence, who do not need adjuvant chemotherapy. Predictive factors are required for patients with high risk of recurrence in order to improve efficacy of the adjuvant treatment by selecting the most appropriate regimen.

## 5. Conclusion

### 5.1. Prognostic factors

In conclusion, current modalities of risk assessment in node-negative breast cancer are not effective or sufficient. Better selection is necessary in order to spare adjuvant therapy in those patients who are cured by local treatment alone corresponding to 70% of all node-negative patients. Since breast cancer is a heterogeneous disease, general treatment recommendations are not appropriate. Rather, assessment of risk of recurrence is required for every tumour in order to avoid over-treatment (Table 1).

Therefore, the answer to the question posed in the title of this discussion is: yes, we do need better prognostic factors in node-negative breast cancer.

### 5.2. Predictive factors

Moreover, for those patients who have substantiated risk of recurrence, predictive factors have to be assessed, such that type and aggressiveness of a proper adjuvant treatment can be chosen based on biological data of sensitivity or resistance (Fig. 4).

Consequently, the design of a future trial is aimed at answering the question, whether within the high-risk group of node-negative breast cancer patients as selected

Table 1
Adjuvant therapy in node-negative breast cancer patients: Consensus-approach (St Gallen 1998) versus risk-oriented approach

| Adjuvant treatment according to Consensus recommendations | Adjuvant treatment guided by risk of recurrence |
|---|---|
| • Each patient is at risk for recurrence. | • Discrimination of patients with high risk and low risk of recurrence (< 10% 5-year disease-free survival) is needed. |
| • Each patient benefits from adjuvant chemotherapy. | • The majority (70%) of node-negative patients is cured by local treatment alone |
| • Type of therapy according to risk of recurrence: (low risk: tamoxifen, high risk: chemotherapy) | • Prediction of response for each tumour is required. |
| • Recommendation of a general adjuvant therapy, all patients are treated | • The majority of node-negative breast cancer patients (70%) will be spared adjuvant chemotherapy |

by high uPA and/or PAI-1 values, improved efficacy of an anthracycline-containing regimen in comparison with CMF can be predicted by *c-erbB-2* determination. This prospective randomised trial will be performed within the framework of the BIOMED-2 programme.

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Thanks to intensified effects of screening and early detection the percentage of patients diagnosed with node-negative breast cancer is ever increasing and well beyond 50%. Nodal status is still the strongest factor indicating prognosis. Negative axillary nodes identify a group of patients known to be at lower risk of recurrence and metastasis with approximately two-thirds being cured. However, one-third of node-negative breast cancer patients will eventually relapse. Improving the fate of these patients at risk requires firstly their

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