The prognostic effect of histological tumor grade in node-negative breast cancer patients

Martin Schumacher, Claudia Schmoor, Willi Sauerbrei,1 Alfred Schauer, Lucia Ummenhofer,2 Wolfgang Gatzemeier and Helmut Rauschecker3
For the German Breast Cancer Study Group: 1 Institute of Medical Biometry and Informatics, University of Freiburg; 2 Institute of Pathology, University of Göttingen; 3 Department of Surgery, University of Göttingen, Germany

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Summary

The prognostic effect of histological tumor grade was evaluated in 1036 patients with early breast cancer (pT1 pN0 M0) entered into a trial comparing mastectomy and breast preserving treatment. All analyses were adjusted for the factors treatment, patients’ age, and tumor size. Tumor grade was defined according to Bloom and Richardson based on the sum of scores assigned to each of three histological features: 1) degree of differentiation, 2) pleomorphism, and 3) mitotic index. The relative importance of these factors with regard to disease-free survival was evaluated. In univariate as well as in multivariate analyses the pleomorphism was the only factor showing a significant effect (univariate: \( p = 0.0024 \), multivariate: \( p = 0.015 \)). It was investigated how the factors should be combined to define a histological grading score which yields the best possible classification of the patients with respect to prognosis. A new grading system was defined splitting the patients into three groups: 1) pleomorphism 1; 2) pleomorphism 2 or pleomorphism 3 and mitotic index 1; 3) pleomorphism 3 and mitotic index 2 or 3. This yields a good classification of the patients with respect to prognosis (\( p = 0.0004 \)). The prognostic effect of this score was compared with the effects of the grading systems proposed in the literature. According to Bloom and Richardson and in the modified version by Schauer and Weiss, grading is based on the sum of scores of the various histological factors. Therefore, the strong effect of the pleomorphism was diluted in these grading definitions (Bloom and Richardson: \( p = 0.03 \), Schauer and Weiss: \( p = 0.028 \)). The grading system proposed by Le Doussal et al. consists only of the scores of pleomorphism and mitotic index (\( p = 0.014 \)). In summary, the factor pleomorphism showed a stronger effect on disease-free survival by itself than the grading systems proposed in the literature.

Introduction

Although node-negative breast cancer patients are regarded as a group with a quite favorable prognosis, recent studies have shown that also in these patients adjuvant systemic treatment may have a beneficial effect [1–5]. However, about 70% of these patients have long-term survival following surgical and/or radiotherapeutical treatment modalities [6] and would therefore be overtreated by adjuvant therapy. As a consequence, there is the need to identify high-risk node-negative patients for whom further treatment should be recommended [7, 8]. On the other hand, the group of patients with an
extremely favorable prognosis may be overtreated
by standard locoregional treatment modalities such
as radiotherapy following tumor excision. Reliable
prognostic factors are needed which differentiate
between high and low-risk subgroups in node-nega-
tive patients.

The prognostic effect of histological tumor grade
has been shown in several studies [6, 9]. The grading
system most frequently used was established by
Bloom and Richardson (BR) [10]. It is based on the
sum of scores assigned to each of the following
three histological features: 1) degree of differentia-
tion, 2) pleomorphism, and 3) mitotic index. The
BR grade divides the patients into three subgroups
(BR grade I, II, III). Some modifications of the BR
grading system have been suggested. Schauer and
Weiss [11] proposed to subdivide BR grade II into
two subgroups resulting in a total of four different
groups according to tumor grade. Le Doussal et al.
[12, 13] proposed five grading categories based on a
score consisting of the two factors pleomorphism
and mitotic index, ignoring the degree of differentia-
tion.

The aim of this paper is to assess the relative im-
portance of the three single factors degree of differen-
tiation, pleomorphism, and mitotic index, as well
as the prognostic effect of the grading systems pro-
posed so far. Furthermore, we will investigate in
which way the single factors should be combined to
define a histological grading score resulting in the
best possible classification of patients with respect
to prognosis, measured in terms of disease-free sur-
vival. These investigations will be performed within
a study designed to compare the therapeutic effect
of mastectomy and breast preserving treatment in
1036 patients with early breast cancer. In this study,
an analysis of the structural relationship among var-
ious prognostic factors was performed earlier [14].
In a multivariate model tumor grade was related to
patients' age, tumor size, and hormone receptor sta-
tus, whereas the other three factors were uncorre-
lated after adjustment for tumor grade. In an analy-
sis of the effects of treatment and of these various
prognostic factors on disease-free survival, tumor
grade was the most predictive prognostic factor [15,
16]. These results emphasize the central role of tu-
mor grade among the prognostic factors.

Patients and methods

In 1983, the German Breast Cancer Study Group
started a prospective multicenter trial on the treat-
ment of early breast cancer (pT1 pN0 M0). Patients
with early breast cancer cT1 cN0 M0 underwent a
complete tumorectomy with clear tumor margins.
A lower axillary dissection (level I and II) with re-
moval of at least 6 lymph nodes was also performed.
The relevant eligibility criterion was the pathohist-
ological stage pT1 pN0 M0. Definitive treatment
consisted of either mastectomy or additional radio-
therapy to the remaining breast (50Gy in 25 frac-
tions plus 12Gy electron boost). In case of a medial
or central tumor location, the parasternal and supra-
clavicular area was also irradiated with 50Gy. A
treatment selection by random – planned initially –
had to be abandoned due to logistic reasons. Nearly
all patients were treated according to their own
choice.

Tumor size was measured microscopically on fro-
zen sections. Hormone receptor content, both es-
trogen (ER) and progesterone (PR), was measured
by a dextran-coated charcoal method according to
Bojar [17] and classified as being positive if the re-
spective value was equal or greater than 20fmol/
mg. With reference to the Bloom and Richardson
[10] grading system (BR) the following histological
features were analyzed:

1) The degree of differentiation was evaluated ac-
cording to the property of the tumor to form tu-
bular, glandular, or papillary structures. If one
of these tumor formations was prevalent in no
less than 75% of the specimen this was scored as
1; with a prevalence of the structures in 10–75%
of the tissue, the score was 2; and it was 3 when
less than 10% were present.

2) Pleomorphism was coded 1 when the nuclei
were regular and similar to normal breast epi-
thelial cells, as 3 when they were markedly ir-
regular and distorted in size, and 2 when their
appearance was intermediate.

3) Mitotic index: In 12 high power fields, the num-
ber of mitoses was counted. After division by 12
to evaluate the mean number of mitoses per
field, 0–1 mitoses were scored 1 point, more