Prognosis by novel staging systems incorporating tumor biology in estrogen receptor positive and human epidermal growth factor receptor negative breast tumors

Marissa Vane (✉ marissa.vane@gmail.com)

Maastricht Universitair Medisch Centrum+ <https://orcid.org/0000-0003-4514-5329>

Fenna Traa

Maastricht University Hospital: Maastricht Universitair Medisch Centrum+

Lori van Roozendaal

Maastricht University Hospital: Maastricht Universitair Medisch Centrum+

Sander van Kuijk

Maastricht University Hospital: Maastricht Universitair Medisch Centrum+

Sanne Engelen

Maastricht University Hospital: Maastricht Universitair Medisch Centrum+

Marissa van Maaren

IKNL: Integraal Kankercentrum Nederland

Sabine Siesling

Integraal Kankercentrum Nederland

Johannes de Wilt

Radboudumc

Marjolein Smidt

Maastricht University Hospital: Maastricht Universitair Medisch Centrum+

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**Prognosis by novel staging systems incorporating tumor biology
in estrogen receptor positive and human epidermal growth factor receptor negative
breast tumors**

M.L.G. Vane^{1,2}, F. Traa¹, L.M. van Roozendaal¹, S.M.J. van Kuijk³,
S.M.E. Engelen¹, M.C. van Maaren^{4,5}, S. Siesling^{4,5}, J.H.W. de Wilt⁶, M.L. Smidt^{1,2}

¹ Department of Surgical Oncology, Maastricht University Medical Centre, Maastricht, the Netherlands.

² GROW - School for Oncology and Developmental Biology, Maastricht University Medical Centre, the Netherlands.

³ Department of Epidemiology, Maastricht University Medical Center+, Maastricht, The Netherlands.

⁴ Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands.

⁵ Department of Health Technology and Services Research, Faculty of Behavioural, Management and Social Sciences, Technical Medical Centre, University of Twente, Enschede, the Netherlands.

⁶ Division of Surgical Oncology, Radboud University Medical Centre, Nijmegen, the Netherlands.

Corresponding author

Marissa Vane, MD

Department of Surgical Oncology

Maastricht University Medical Centre

P.O. Box 5800

6202 AZ Maastricht

The Netherlands

Phone: +31 43 3881574

Mail: marissa.vane@gmail.com

ABSTRACT

Purpose The prognostic stage group and Bioscore are novel staging systems for breast cancer patients. They provide a better view on five-year disease-specific survival (DSS) compared to the traditional staging system. Five-year follow-up might not be sufficient for ER+HER2- tumors. This study determines five- and 10-year recurrence-free survival (RFS) for the anatomic and prognostic stage group of the 8th AJCC TNM and Bioscore staging system, and compares these systems for ER+HER2- breast cancer patients.

Methods All newly diagnosed ER+HER2- breast cancer patients treated with primary surgery in 2005 were included from the Netherlands Cancer Registry with a ten-year follow-up. All patients were staged according to 8th AJCC TNM (both anatomic and prognostic stage group) and the Bioscore staging system. Five- and 10-year RFS was compared using Kaplan-Meier analysis. The ability to discriminate groups was quantified by the concordance statistic (c-statistic).

Results Five-year RFS ranged from 65.0-91.1% (anatomic) and from 40.9-91.8% (prognostic stage group). The Bioscore staging system ranged from 54.9-92.1%. Ten-year RFS rates were 52.9-84.9% (anatomic stage), 31.8-84.6% (prognostic stage) and 47.1-85.1% (Bioscore). All systems similarly discriminated groups with comparable c-statistic score (five- and 10-year 0.58-0.60). The prognostic stage group identified a group(IIIC) with very poor prognosis (31.8%) which could not be identified using the other staging systems (10-year RFS for 52.8% for anatomic IIIC and 47.1% for Bioscore 6).

Conclusion All three staging systems similarly discriminated groups for ER+HER2- breast cancer patients with a five- and 10-year follow-up. However, the prognostic stage group showed a wider distribution of the 10-year RFS compared to anatomic stage group and Bioscore staging system.

KEYWORDS breast cancer staging system, Bioscore, 8th AJC TNM system, recurrence-free survival, ER+HER2- tumors

BACKGROUND

Breast cancer is usually staged according to the TNM classification of the American Joint Committee on Cancer (AJCC) system. The anatomic stage group of the AJCC is based on tumor size (T), lymph node status (N), and presence or absence of distant metastasis (M), and is used in breast cancer patients to assess their prognosis and guide their treatment plan (stage 0 to IV). However, tumor biology is not included in this staging system, resulting in a wide variation of prognosis within each TNM stage. Additionally, tumor biology expressed as grade and receptor status have become important prognostic and predictive factors in breast cancer patients (1-3).

The 8th edition of the AJCC TNM staging system recognized the lack of tumor biology and introduced the prognostic stage group. In this staging system, the anatomic stage characteristics (TNM) are combined with tumor grade, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2), and can even include the multigene status (e.g. Oncotype DX) if available. The prognostic stage group identifies several prognostic groups (stage 0 to IV) (4). Another novel staging system is called Bioscore and includes pathologic tumor size, lymph node status, and tumor biology in terms of tumor grade, ER and HER2 receptor status for patients primarily treated with surgery (score 0-7) (5,6). So far, both staging systems are validated for breast cancer patients primarily treated with surgery with a median follow-up of five years (5-7). Although, ER+HER2- tumors have the lowest risk of recurrence of all breast cancer subtypes (10-12), late recurrences (after five years of diagnosis), continue to occur especially in this subgroup (13). Pan et al. showed that recurrences keep occurring in ER+ tumors, even up to 20 years after diagnosis. Hormone therapy in ER+ breast cancer patients potentially postpones these recurrences in several cases (14). Five-year follow-up is therefore not sufficient for ER+HER2- breast cancer patients.

The aim of this study was to determine and compare five- and 10-year recurrence-free survival (RFS) for the anatomic and the prognostic stage group of the 8th edition of the AJCC TNM system and the Bioscore staging system, and to compare these systems for ER+HER2- invasive breast cancer patients primarily treated with surgery.

METHODS

Data were retrieved from the Netherlands Cancer Registry (NCR). The NCR contains data on patient demographics and information regarding the tumor as well as surgery, radiation, systemic treatment, recurrence and survival. Trained data registrars collected the information directly from patients' medical records in all Dutch hospitals, on the basis of a notification from the Pathological Anatomy National Automated Archive. All newly diagnosed ER+HER2- breast cancer patients in the Netherlands in 2005 were included if primarily treated with surgery. Patients were excluded in case of unknown data regarding tumor grade, pathologic tumor status, lymph node status or receptor status (n= 511). Tumors were classified ER+ if at least 10% of the nuclei stained. Tumors were classified HER2 negative if less than 10% of the cells showed membrane staining. In case of 2+ at immunohistochemistry, an amplification test was performed that overruled the results of the immunohistochemistry.

Endpoints

The primary endpoint of this study was five- and 10-year RFS. RFS was defined as the date of surgery until the date of first breast cancer recurrence (local recurrence, regional recurrence, new primary ipsilateral breast cancer, contralateral breast cancer, or distant metastasis), death of any cause, or the date of last observation. Events within 91 days following diagnosis were regarded as synchronous events. Baseline characteristics were presented as mean or median and standard deviation or range, or absolute numbers and percentages.

First, all patients were staged according to the anatomic and prognostic stage group of the 8th edition of the AJCC TNM staging system. The anatomic stage group is based on tumor size (T1-4), lymph node status (N0-3), and presence or absence of distant metastasis (M0-1). The prognostic stage group includes TNM status, tumor grade (I-III), ER status (positive/negative), PR status (positive/negative) and HER2 status (positive/negative) (9). For both stage groups, final staging score ranged from I to IV. Subsequently, patients were staged using the Bioscore staging system. Each tumor characteristic was given a score based on the hazard ratio for DSS: pathological T stage (T1 = 0 and T2 or T3 = 1), pathological N stage (N0, N1mic or N1 = 0, N2 = 2 and N3 = 3), tumor grade (grade I-II = 0 and grade III = 1), ER receptor status (ER+ = 0 and ER- = 1) and HER2 receptor status (HER2+ = 0, HER2- = 1). The Bioscore was calculated by the sum of each tumor characteristic, ranging from 0 to 7 points (7).

Statistical analyses

Five- and 10-year RFS for the 8th edition of the AJCC TNM system (anatomic and prognostic stage group separately) and Bioscore staging system were compared using Kaplan Meier analysis. The ability of these systems to discriminate groups based on risk of a recurrence was quantified by the concordance statistic (c-statistic) after fitting the staging systems separately in a Cox proportional hazards regression model. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 26.0 and R version 3.3.3.

RESULTS

In total, 4,229 ER+HER2- breast cancer patients primarily treated with surgery were included. Median follow-up was 9.6 years (range 0.1 – 12.0). Patient and tumor characteristics are summarized in Table 1.

Using the anatomic stage group of the 8th edition of the AJCC TNM staging system, 2,041 (48.3%) patients were classified as stage I (A and B), followed by stage IIA in 1,209 (28.6%), stage IIB in 499 (11.8%), stage IIIA in 323 (7.6%) and stage IIIC 157 (3.7%) of the patients. None of the patients were staged with IIIB (T4N0-2M0) or stage IV tumors (M1).

Using the prognostic stage group of the 8th edition of the AJCC TNM staging system, 2,821 (66.7%) patients were classified as stage I (A and B), followed by stage IIA in 815 (19.3%), stage IIB in 254 (6.0%), stage IIIA in 154 (3.6%), stage IIIB in 163 (3.9%) and stage IIIC in 22 (0.5%) of the patients.

Using the Bioscore staging system, 2,179 (51.5%) scored 1 point, 1,222 (28.9%) scored 2 points, 453 (10.7%) scored 3 points, 169 (4.0%) scored 4 points, 155 (3.7%) scored 5 points and 51 (1.2%) scored 6 points. None of the patients scored 0 points or 7 points, since only ER+HER2- patients were included in this study (Table 2).

Five-year RFS was 88.6% in the overall population. Using the anatomic stage group of the 8th edition of the AJCC TNM staging system, RFS ranged from 65.0 to 91.1% for the subgroups (Table 2). For the prognostic stage group, five-year RFS ranged from 40.9 to 91.8%. Using the Bioscore staging system, RFS ranged from 54.9 to 92.1% for the subgroups (Table 2).

Ten-year RFS was 80.6% in the overall population. Using the anatomic stage group of the 8th edition of the AJCC TNM staging system, RFS ranged from 52.9 to 84.9%. For stage I, IIA, IIB, IIIA and IIIC, this was 83.4%, 84.9%, 75.2%, 68.4% and 52.9%, respectively (Table 2).

Using the prognostic stage group of the 8th edition of the AJCC TNM staging system, survival

ranged from 31.8 to 84.6%. For stage I, IIA, IIB, IIIA and IIIC, this ranged from 84.6% to 31.8%, respectively (Table 2). Using the Bioscore staging system, 10-year RFS ranged from 47.1% to 85.1%. For Bioscore 1, 2, 3, 4, 5 and 6 this ranged from 85.1% to 47.1%, respectively (Table 2, Figure 2B).

The c-statistic score for the anatomic and prognostic group of the 8th AJCC was 0.58 and 0.59 compared to 0.59 using the Bioscore staging system, in a five-year follow-up period and 0.58, 0.60 and 0.60 in a 10-year follow-up period.

DISCUSSION

This is the first study comparing the anatomic and prognostic stage group of the 8th edition of the AJCC TNM system and the Bioscore staging system for ER+HER2- invasive breast cancer patients primarily treated with surgery using a ten-year follow-up period. Five-year RFS using the anatomic stage group of the 8th edition of the AJCC TNM system ranged from 65.0-91.1%, using the prognostic stage group this ranged from 40.9-91.8% and 54.9-92.1% using the Bioscore staging system. Ten-year RFS ranged from 52.9-83.4%, 31.8-84.6% and 47.1-85.1%, respectively. All systems similarly discriminated groups according to the risk of recurrence, with comparable c-statistic score at five and 10-years. The prognostic stage group of the 8th AJCC TNM system showed a wider distribution of the 10-year RFS compared to anatomic stage group and Bioscore staging system.

To address the importance of tumor biology, the prognostic stage group was introduced in the 8th edition of the AJCC TNM staging in addition to the anatomic stage group (4, 9, 16, 17). Weiss et al. validated the prognostic stage group using a cohort of 3.327 breast cancer patients primarily treated with surgery diagnosed between 2007-2013. Subsequently, this stage group was validated using the California Cancer Registry (n= 54.727 stage I-IV breast cancer patients). Results showed that the prognostic stage group upstaged 31.0% and downstaged 20.6% of the included patients. Furthermore, the prognostic stage group provided a more accurate five-year DSS stratification compared to anatomic stage group (c-statistic 0.84 versus 0.81) (4). These results were confirmed by this study showing a wider distribution of 10-year RFS ranging from 31.8 to 84.6% using the prognostic stage group compared to 52.9 to 84.9% using the anatomic stage group in ER+HER2- breast cancer patients. An advantage of the prognostic stage group is the incorporation of the gene expression profile Oncotype DX, predicting tumor recurrence and helping to stratify patients who will benefit from chemotherapy in ER + HER2- tumors (4). The Oncotype DX was in this study not available and therefore not included, similar to the study of Weiss et al. Disadvantages of the prognostic stage group are the 170 different groups, making this staging system clinically complex to use (4). Furthermore, some countries do not have access to analysis all these biological factors. For those, the anatomic staging group of the 8th edition of the AJCC TNM system remains recommended (16).

The Bioscore staging system was developed by MD Anderson using the same cohort of 3,327 breast cancer patients as Weiss et al. Several models with different combinations of tumor biology were investigated, and ultimately the Bioscore staging system including anatomic stage, tumor grade, ER and HER2 status was developed. The Bioscore staging system was validated using the California Cancer Registry (n=67,944 patients). Five-year DSS ranged from 33.3% to 100% for different tumor stages using Bioscore, compared to 79.5% to 99.1% using the anatomic stage group of the 7th AJCC TNM staging system (6,7). This present study showed a range of 10-year RFS from 47.1 to 85.1% using the Bioscore staging system compared to 52.9 to 84.9% using the anatomic stage group of the 8th edition of the AJCC TNM staging system in ER+HER2- breast cancer patients. Mittendorf showed that improved stratification was most pronounced in patients with higher Bioscores (five-year DSS of 33.3% for Bioscore 7 versus 79.5% for stage IIIC). This study showed that patients with higher Bioscore had the lowest 10-year RFS (10-year RFS 47.1% for Bioscore 6). However, the prognostic stage group of the AJCC TNM system identified a group of patients with a worse prognosis (stage IIIC, 10-year RFS 31.8%) which could not be identified using the anatomic stage group (stage IIIC, 52.9%) nor Bioscore staging system (Bioscore 6, 10-year RFS 47.1%). The c-statistic score for ten-year RFS for anatomic and prognostic stage group were 0.58 and 0.60 versus 0.60 for Bioscore staging system, implying that staging systems similarly discriminated groups according to the risk of recurrence. This is in contrast to the study of Mittendorf et al. who showed that the Bioscore had a higher c-statistic score (0.81), however this was compared to the 7th AJCC staging system (0.74) and using a five-year follow-up period (6).

A strength of this study is the large population-based registry of 4,229 ER+HER2- breast cancer patients with complete data on tumor staging and biology and a ten-year follow-up. Subgroups of the staging systems in this present study were not equally divided, especially for higher stage disease which is in line with the population incidence. There were only limited patient numbers for stage IIIA, IIIB and IIIC (7.6%, 0% and 3.7%, respectively) using the anatomic stage group and the prognostic stage group (3.6%, 3.9% and 0.5%, respectively). Subgroups according to Bioscore also revealed low numbers for higher scores 4 to 7 (4.0%, 3.7%, 1.2%, and 0% respectively). This was similar for the cohort of Mittendorf et al., with 0.3% of the patients with lowest DSS of 33.4% with a Bioscore of 7, and highest DSS of 100% in 1.1% of the patients with a Bioscore of 0. Higher stage disease patients are often treated with neoadjuvant systemic therapy and therefore not included in these studies. For this

subset of patients, the Neo-Bioscore staging system was developed (6, 7, 18). While interpreting the current results, it has to be kept in mind that the lower and upper limits of both staging systems are determined by a small subgroup of the overall population.

Due to several differences between the studies, results are difficult to compare.

First, this study used RFS instead of DSS used by Mittendorf and Weis et al. (7, 4), as data on DSS were not available in the NCR database. Breast cancer recurrence occurs more often than death from breast cancer (DSS), and therefore explains the lower rates of RFS in this present study (five-year RFS of 88.6% and 10-year RFS of 80.6%) compared to five-year DSS of 97.9% in the study of Mittendorf et al.

Another difference between the studies was the number of patients treated with adjuvant systemic therapy caused by a different recommendation for adjuvant systemic therapy. Adjuvant systemic therapy was recommended only for patients <35 years and for patients ≥ 35 years with risk factors (i.e. tumor ≥ 3 cm, or tumor ≥ 1 cm and grade III, or tumor ≥ 2 cm and grade II) (15). As a result, only 55.9% of the ER+HER2- patients in this study were treated with HT, whereas all ER+ patients in the study of Mittendorf et al. were advised and 81.2% were treated with HT. Chemotherapy was given in 32.1% in this study compared to 49.2% of the patients from MD Anderson. Since none of the tumors was HER2+ (since it was an exclusion criterium), no indication for trastuzumab existed compared to 9.2% of the patients in the MD Anderson cohort (HER2+ tumors). Kantor et al. compared the prognostic stage group, Bioscore staging system and Risk Score in a large population-based cohort using Surveillance, Epidemiology and End Results program (SEER). Results showed that the c-statistic of each novel staging system was higher than the c-statistic for the anatomic stage group of the AJC TNM staging system (c-statistic 0.83 anatomic stage group versus 0.86 for the prognostic stage group, 0.86 for the Bioscore staging system, and 0.86 for the Risk Score, $p < 0.001$) (19).

In conclusion, this study aimed to determine five- and 10-year RFS for the anatomic stage group and the novel prognostic stage group of the 8th edition of the AJCC TNM system and the Bioscore staging system for ER+HER2- breast cancer patients with a ten-year follow-up. All three staging systems similarly discriminated groups for ER+HER2- breast cancer patients with a 10-year follow-up. The prognostic stage group of the 8th AJCC TNM system showed a wider distribution of the 10-year RFS compared to anatomic stage group and Bioscore staging

system. Therefore, this staging system identified a group with a very poor prognosis (31.8%) which could not be identified using the anatomic stage group of the 8th AJCC (stage IIIC, 52.8%) or Bioscore staging system (Bioscore 6, 47.1%). We would like to suggest that hospitals who have access to analysis of biological factors, use the prognostic stage group in addition to the traditional anatomic stage group of the 8th AJCC TNM staging system to determine a more patient-tailored prognosis.

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Competing interests

M.L. Smidt, has been awarded a grant from Servier Pharma for microbiome research in breast cancer treatment. The remaining authors have no disclosures or conflicts of interest.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by M. Vane and F. Traa, M. van Maaren, S. Siesling, M. Smidt. The first draft of the manuscript was written by M. Vane and F. Traa and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets were analysed during the current study are not publicly available due but are available from the corresponding author on reasonable request.

Ethics approval

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Due to its retrospective design, ethical approval was not obtained.

Consent to participate

Not applicable.

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Supplementary Files

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