The American Joint Commission Cancer 8th Edition Prognostic Stage Including Oncotype DX[®] Recurrence Score: Impact on Staging of Early Breast Cancer

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Keywords

AJCC · Breast cancer stage · Anatomic TNM stage · Prognostic stage · Oncotype DX recurrence score

Abstract

Background: The American Joint Commission Cancer (AJCC) Cancer Staging Manual 8th edition introduced a breast cancer (BC) Prognostic Stage (PS) that combines tumour grade, oestrogen (ER), progesterone (PgR), and human epidermal growth factor-2 (HER2) receptor status with Anatomic TNM Stage (AS). In a further modification, patients with early BC and an Oncotype DX[®] Recurrence Score (RS) <11 are assigned to PS 1A irrespective of grade and size up to 5 cm. This study profiles the impact of these changes on staging in patients with early BC and RS <11. **Methods:** A total of 127 patients, with primary BC and RS <11, were identified from a consecutive series of 729 patients with ER-positive, HER2-negative, lymph node-negative, primary BC whose tumours were tested using the Oncotype DX[®] 21 multigene assay. Each patient was assigned AS, PS, and RS-modified PS, and staging categories were compared. **Results:** Applying AS, 100 patients were stage IA and 27 IIA. Applying PS, 89 were stage IA, 33 IB, 4 IIA, and 1 IIB. All patients were IA according

to RS-modified PS. Comparing PS to AS, 26.7% of patients ($n = 34$) changed stage, 9.4% ($n = 12$) to a higher and 17.3% ($n = 22$) to a lower stage. RS-modified PS versus AS resulted in downstaging in 21.3% ($n = 27$). Comparing PS modified by RS to PS alone, 29.9% ($n = 38$) were downstaged. **Conclusion:** Application of PS and RS-modified PS results in tumour downstaging in approximately 20% of patients with early BC. Upstaging was observed in 9% of patients when staged according to PS and was primarily due to the impact of high histological grade.

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Introduction

The recently published American Joint Commission on Cancer (AJCC) Cancer Staging Manual, 8th edition [1], introduced into United States clinical practice in January 2018, proposes a new breast cancer (BC) Prognostic Stage (PS) that combines histological tumour grade, oestrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor-2 (HER2) receptor status with traditional Anatomic TNM Stage (AS) [2, 3]. In a further modification, patients with ER-positive, HER2-

negative, lymph node (LN)-negative BC, and an Oncotype DX[®] recurrence score (RS) of <11 are assigned to PS 1A irrespective of histological grade and tumour size up to 5 cm. The changes have been proposed in recognition of the prognostic influence and therapeutic effects associated with these parameters and in attempt to improve personalised patient care. These innovations represent a major departure from traditional practice and a move away from the current harmonised BC staging system agreed by AJCC and Union of International Cancer Control (UICC) [4, 5].

This study assesses the impact on BC staging using the newly proposed AJCC PS, including that modified by low Oncotype DX[®] RS, compared with the traditional AJCC/UICC AS, in a population of patients with early primary invasive BC and RS <11.

Population and Methods

The study population comprised patients with a primary invasive BC Oncotype DX[®] RS <11. The population was identified from a large consecutive series of patients with ER-positive, HER2-negative, LN-negative, primary BC whose tumours were tested using the Oncotype DX[®] multigene assay between November 2011 and December 2016. Patients presented through the Irish National Breast Screening Programme (BreastCheck) or through the symptomatic service and were diagnosed and treated at St. Vincent's University Hospital, Dublin, Ireland.

Therapeutic BC excision (wide local excision or mastectomy) and sentinel and non-sentinel LN specimens were prepared, dissected, and blocks selected according to Royal College of Pathologists (RCPATH), United Kingdom (UK) macroscopy protocols [6]. Tumours were reported in accordance with RCPATH BC minimum datasets [6] that take account of determination of invasive tumour size as defined by AJCC/UICC 7th editions [4, 5, 7] and histological tumour grade using the Nottingham method [8]. All LNs were negative in the study group in accordance with study inclusion criteria.

ER status was determined using immunohistochemistry in accordance with standardised protocols [6]. HER2 status was determined using first-line IHC and reflexive dual-probe HER2/CEP17 fluorescent in situ hybridisation (FISH) methodology in equivocal cases as previously described by our group [9]. During the period of study, PgR studies were not routinely performed on tumours that were strongly ER positive. Information on PgR status was derived from the Oncotype DX[®] report.

To qualify for Oncotype DX[®] testing, the pathological size of the primary tumour must be categorised as T1c (1.1–2.0 cm), T2 (2.1–5 cm), or T1a (<0.5 cm) or T1b (0.5–1.0 cm) with adverse histopathological features, e.g. histological grade 2 or 3 or the presence of lymphovascular invasion.

AS was assigned according to the AJCC Classification of Breast Cancer Staging, 8th edition (unchanged from the 7th edition). PS and PS modified by RS <11 were assigned according to the AJCC 8th edition.

Table 1. Clinico-pathological characteristics of patient population (*n* = 127)

Age, years	
Median	58
Range	35–78
Tumour size category	
T1a	2 (1.6)
T1b	19 (15.0)
T1c	79 (62.2)
T2	27 (21.2)
Histological grade	
Grade 1	14 (11.0)
Grade 2	98 (77.2)
Grade 3	15 (11.8)
Lymph node status	
Positive	0 (0)
Negative	127 (100)
Oestrogen receptor status	
Positive	127 (100)
Negative	0 (0)
Progesterone receptor status	
Positive	126 (99.2)
Negative	1 (0.8)
HER2 receptor status	
Positive	0 (0)
Negative	100 (100)
Data are presented as <i>n</i> (%) or as stated.	

Traditional AS was compared with PS and with Oncotype DX[®] RS-modified PS. Oncotype DX[®] RS-modified PS was also compared with PS alone.

Results

All patients had ER-positive, HER2-negative, and LN-negative primary invasive BC in line with the selection criteria for Oncotype DX[®] testing. 127 of 729 patients had RS <11 and comprised the study group. The mean patient age was 58 years (35–78). The mean tumour size category was 13.6 mm (5–50 mm). 126 patients had PgR-positive tumours. Pathological tumour size was T1a (*n* = 2), T1b (*n* = 19), T1c (*n* = 79), and T2 (*n* = 27). Histological tumour grade was grade 1 (*n* = 14), 2 (*n* = 98), and 3 (*n* = 15). The clinicopathological characteristics are summarised in Table 1.

Applying traditional AS, 100 patients were assigned to BC stage IA (T1N0), and 27 patients to stage IIA (T2N0). Applying PS (without Oncotype DX[®] RS), 89 patients were assigned to stage IA, 33 to stage IB, 4 to stage IIA,

and 1 to stage IIB. Applying PS modified by Oncotype DX® RS of <11, all patients were assigned to stage IA.

Comparing PS alone to traditional AS, 26.7% of patients ($n = 34$) underwent a change in stage, 9.4% ($n = 12$) to a higher stage, and 17.3% ($n = 22$) to a lower stage. Comparing PS modified by RS <11 to traditional AS, 21.3% ($n = 27$) of patients were downstaged. Comparing modified PS to PS alone, 29.9% ($n = 38$) of patients were downstaged. The relative distribution of stage is shown in Table 2.

Discussion

BC has traditionally been staged based on anatomic extent using the TNM classification system specified and agreed by the AJCC and UICC [4, 5]. Anatomic TNM provides information on prognosis, assists decision making regarding adjuvant therapy, provides selection criteria for patient entry to clinical trials and profiles BC epidemiology on a global level. It is relatively simple to apply and is easily understood. However, recent advances in our understanding of the impact of biological indices on prognosis and likely response to therapy have highlighted shortcomings in a purely anatomic-based staging classification system. In an attempt to address this deficit, the AJCC 8th edition has developed a PS that combines histological tumour grade, biomarker status, and the results of the Oncotype DX® 21 multigene assay, in a subset of patients, with AS to more accurately stratify BC patients according to prognosis and to further facilitate personalised treatment planning [1–3]. The PS was developed based on a review of the current literature and on an unpublished analysis, by one of the AJCC breast panel members, of 238,265 women diagnosed in 2010 who were included in the US database. Application of PS to that patient series resulted in an overall re-assignment of stage, to a worse or better category, in 41% of patients with BC. Recently published studies comparing AS with PS in varied patient subgroups have reported up to 64.4% stage change [10, 11].

One of the major criticisms of the AJCC 8th edition-proposed modifications to BC stage is the disparity between AS and PS and the potential for loss of information internationally due to variable access to biomarker studies [12]. Comparing AS to PS in the current study of 127 patients with the same ER, HER2, and LN profile, 34 patients (26.7%) underwent a change in stage. Twelve patients (9.4%) were upstaged and 22 (21.3%) were downstaged. In the group of patients who were upstaged, 11 of 12 moved from AS IA to PS IB due to histological tumour grade 3. One patient was upstaged from AS IIA to PS IIB

Table 2. Breast cancer stage distribution according to Anatomic Stage, Prognostic Stage and Prognostic Stage modified by Oncotype DX Recurrence Score <11 ($n = 127$)

Breast cancer stages	<i>n</i> (%)
AS	
Stage IA (T1N0)	100 (78.7)
Stage IIA (T2N0)	27 (21.3)
PS	
Stage IA	89 (70.1)
Stage IB	33 (26.0)
Stage IIA	4 (3.1)
Stage IIB	1 (0.8)
PS modified by Oncotype DX RS <11	
Stage IA	127 (100)
PS vs. AS	
Moved to higher stage	12 (9.4)
Moved to lower stage	22 (17.3)
RS-modified PS vs. AS	
Moved to lower stage	27 (21.3)
RS-modified PS vs. PS alone	
Moved to lower stage	38 (29.9)

AS, Anatomic Stage; PS, Prognostic Stage; RS, Recurrence Score.

due to negative PgR status. The impact of histological grade on PS underscores the prognostic power of Nottingham tumour grade independent of biomarker and LN status, previously validated in several studies [13, 14]. Tumour grade is a key component of the Nottingham Prognostic Index that has both prognostic and predictive value in BC management [15–17]. We have recently reported a strong correlation between the Nottingham Prognostic Index and Oncotype DX® testing in identifying low-risk patients [18]. In the current study, no patient was downstaged solely due to histological grade. This reflects the relatively low-risk tumour profile of the study group that specified ER-positive and HER2-negative biomarker profile and negative LN status.

All 22 patients who were downstaged moved from AS IIA to PS IB. This was due to the effects of positive hormone receptor (ER and PgR) and negative HER2 biomarker profile in conjunction with histological grade 1 or 2 and negative LN status. Positive hormone receptor status strongly correlates with response to adjuvant endocrine therapy and is also an independent favourable prognostic indicator, particularly in the first 5–7 years following diagnosis [19]. Positive PgR receptor status is associated with improved overall and disease-free 5-year survival, with a more pronounced effect in low-grade tu-

mours [20]. Positive PgR status is also highly predictive of a low Oncotype DX[®] RS [21, 22]. HER2 positivity is usually observed in high-grade invasive BC and, in the absence of treatment, is associated with an adverse outcome [23, 24]. Inclusion of HER2 status in PS reflects the adverse impact of positive status on otherwise low-risk tumours but the overall improved prognosis of patients with HER2-positive tumours due to the development of trastuzumab and other anti-HER2-based chemotherapeutic regimes [25]. The impact of biological indices (grade and biomarker profile) and a low Oncotype DX[®] RS is further highlighted by consideration of the fact that a patient with tumour pathological stage pT2N0 equal to AS IIA may be assigned to any one of five PS categories (IA, IB, IIA, IIB, IIIA) depending on the results of these parameters.

The AJCC acknowledges the likely impact on staging of multigene tests and does not endorse any particular assay. The decision to incorporate the results of the Oncotype DX[®] 21 multigene assay [26–30] into PS in a selected subset of patients is supported by level 1 evidence, available at the time of writing, from the TAILORx trial (Trial Assigning Individualised Options for Treatment [Rx]). The trial, sponsored by the National Cancer Institute (NCI) and coordinated by the Eastern Cooperative Oncology Group (ECOG), reported 99.3% distant relapse-free survival, 93.8% invasive disease-free survival, and 98% overall survival at 5 years in patients with a low Oncotype DX[®] RS (<11) [30]. In the current study, 21% of patients (27 of 127), classified as AS IIA due to invasive tumour size T2 (>20 and ≤50 mm), were reassigned to PS 1A due to RS <11. All patients in the current study had ER-positive, HER2-negative, LN-negative tumours, not exceeding 50 mm, in line with TailorX selection criteria and our institutional requirements for Oncotype DX[®] testing. Reassignment to PS 1A due to Oncotype DX[®] RS <11 is restricted to this subset and is independent of PgR status.

While Anatomic TNM staging provides a more straightforward and easily applied system for classification of BC, the newly developed PS is arguably a more comprehensive approach. PS takes account of major recent advances in our understanding of BC at cellular level and more accurately predicts patient outcome [31–35]. A recent study of deceased patients found that PS separated patients according to overall survival time [36]. The value of incorporating biomarkers with pathological stage into a staging index to improve prognostication has previously been demonstrated by Yi et al. [37] at MD Anderson. This index was developed prior to the routine use of trastuzumab-based chemotherapy for patients with HER2-positive BC and highlights the need for regular updating of a so-called “living index.”

Difficulties with the proposed PS include the complex nature of the staging system with potential for lack of reproducibility [38]. Realisation that certain tumour profiles could not be assigned a PS has been addressed in a recent update [39]. More serious drawbacks include restriction of PS to patients who undergo surgery as their primary treatment in an era where many patients with HER2-positive and triple-negative breast tumours receive neoadjuvant chemotherapy. Disparity in staging and loss of information internationally will inevitably result from unequal access to biomarker studies. Within the more developed countries, variable access to multigene panels and economic considerations [40] will lead to differences in stage even with adoption of this new approach to BC. The availability of multiple genomic assays with varying concordance for individual patients is another confounding factor [41–45]. Inclusion of multigene assay results will necessitate regular updating and reformatting of modified PS as evidence of their clinical validity emerges [44, 46]. Improved understanding of BC heterogeneity at morphological and molecular level with implications for the efficacy of targeted therapy [47] will also need to be considered.

In conclusion, our study demonstrates that application of PS, including that modified by a low Oncotype DX[®] RS, results in tumour downstaging in approximately 20% of patients with early BC. In this series of patient with early BC, upstaging was seen in 9% of patients when staged according to PS and was primarily due to the impact of high histological grade. This new approach to BC staging aims to synthesise the anatomic extent and biological properties of a tumour such that the prognostic implication of a particular stage takes account of the likely response to personalised therapy [48]. Disadvantages include the potential for loss of epidemiological information internationally due to unequal access to biomarker and multigene assays and the need for regular updating as new predictive tests and evidence for their clinical validity emerges.

Statement of Ethics

The authors have consulted the journal policy regarding compliance with ethical standards and state that accepted principles of ethical and professional conduct have been applied to this study.

Disclosure Statement

The authors declare that they have no conflict of interest.

References

- Hortobagyi G, Connolly J, D'Orsi C, Edge S, Mittendorf E, Rugo R, et al. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer International Publishing; 2016.
- Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017 Jul; 67(4):290–303.
- Amin MB, Greene FL, Edge SB, Compton CC, Gershengwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin*. 2017 Mar;67(2):93–9.
- Edge SB, Compton CC, Fritz AG, Greene FL, Trotti A, editors. *American Joint Commission on Cancer (AJCC) Staging Manual*. 7th edition. New York: Springer-Verlag; 2010.
- Sobin L, Gospodarowicz M, Ch W, editors. *UICC International Union Against Cancer TNM Classification of Malignant Tumours*. Chichester: Wiley-Blackwell; 2009.
- Ellis I, Al-Sam S, Anderson N, Carder P, Deb R, Girling A, et al. *Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer*. London: Royal College of Pathologists; 2016. Available from <https://www.rcpath.org/resourceLibrary/g148-breastdataset-hires-jun16-pdf.html>.
- Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010 Jun;17(6):1471–4.
- Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology*. 1991 Nov;19(5):403–10.
- Tchrakian N, Flanagan L, Harford J, Gannon JM, Quinn CM. New ASCO/CAP guideline recommendations for HER2 testing increase the proportion of reflex in situ hybridization tests and of HER2 positive breast cancers. *Virchows Arch*. 2016 Feb;468(2):207–11.
- Ibis K, Ozkurt S, Kucuk S, Yavuz E, Saip P. Comparison of Pathological Prognostic Stage and Anatomic Stage Groups According to the Updated Version of the American Joint Committee on Cancer (AJCC) Breast Cancer Staging 8th Edition. *Med Sci Monit*. 2018 May;24: 3637–43.
- Hu H, Wei W, Yi X, Xin L, Liu Y. A Retrospective Analysis of Clinical Utility of AJCC 8th Edition Cancer Staging System for Breast Cancer. *World J Oncol*. 2017 Jun;8(3):71–5.
- Quinn C, Rakha EA. Eight Edition Cancer Staging Manual of Breast Cancer by the American Joint Committee on Cancer: are the new changes to improve staging or a treatment decision tool? *J Clin Pathol*. 2018 Nov; 71(11):1028–29.
- Rakha EA, El-Sayed ME, Lee AH, Elston CW, Grainge MJ, Hodi Z, et al. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. *J Clin Oncol*. 2008 Jul; 26(19):3153–8.
- Rakha EA, Reis-Filho JS, Baehner F, Dabbs DJ, Decker T, Eusebi V, et al. Breast cancer prognostic classification in the molecular era: the role of histological grade. *Breast Cancer Res*. 2010;12(4):207.
- Blamey RW, Ellis IO, Pinder SE, Lee AH, Macmillan RD, Morgan DA, et al. Survival of invasive breast cancer according to the Nottingham Prognostic Index in cases diagnosed in 1990–1999. *Eur J Cancer*. 2007 Jul;43(10): 1548–55.
- Sundquist M, Thorstenson S, Brudin L, Nordenskjöld B; South East Swedish Breast Cancer Study Group. Applying the Nottingham Prognostic Index to a Swedish breast cancer population. *Breast Cancer Res Treat*. 1999 Jan;53(1):1–8.
- D'Eredita' G, Giardina C, Martellotta M, Natale T, Ferraresi F. Prognostic factors in breast cancer: the predictive value of the Nottingham Prognostic Index in patients with a long-term follow-up that were treated in a single institution. *Eur J Cancer*. 2001 Mar; 37(5):591–6.
- Cotter MB, Dakin A, Maguire A, Walshe JM, Kennedy MJ, Dunne B, et al. Comparison of Oncotype DX® Recurrence Score® with other risk assessment tools including the Nottingham Prognostic Index in the identification of patients with low-risk invasive breast cancer. *Virchows Arch*. 2017 Sep;471(3):321–8.
- Duffy MJ, Harbeck N, Nap M, Molina R, Nicolini A, Senkus E, et al. Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). *Eur J Cancer*. 2017 Apr;75:284–98.
- Salmen J, Neugebauer J, Fasching PA, Haerberle L, Huober J, Wöckel A, et al. Pooled analysis of the prognostic relevance of progesterone receptor status in five German cohort studies. *Breast Cancer Res Treat*. 2014 Nov; 148(1):143–51.
- Chaudhary LN, Jawa Z, Szabo A, Visotcky A, Chitambar CR. Relevance of progesterone receptor immunohistochemical staining to Oncotype DX recurrence score. *Hematol Oncol Stem Cell Ther*. 2016 Jun;9(2):48–54.
- Orucevic A BJ, McNabb AP, Heidel RE. Oncotype DX breast cancer recurrence score can be predicted with a novel nomogram using clinicopathologic data. *Breast Cancer Res Treat*. 2017 May;163(1):51–61.
- Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987 Jan;235(4785):177–82.
- Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist*. 2009 Apr;14(4):320–68.
- Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al.; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011 Oct;365(14):1273–83.
- Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004 Dec; 351(27):2817–26.
- Tang G, Shak S, Paik S, Anderson SJ, Costantino JP, Geyer CE Jr, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. *Breast Cancer Res Treat*. 2011 May;127(1):133–42.
- Dowsett M, Cuzick J, Wale C, Forbes J, Mallon EA, Salter J, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol*. 2010 Apr; 28(11):1829–34.
- Nitz U, Gluz O, Christgen M, Kates RE, Clemens M, Malter W, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat*. 2017 Oct;165(3):573–83.
- Zujewski JA, Kamin L. Trial assessing individualized options for treatment for breast cancer: the TAILORx trial. *Future Oncol*. 2008 Oct;4(5):603–10.
- Wong RX, Wong FY, Lim J, Lian WX, Yap YS. Validation of the AJCC 8th prognostic system for breast cancer in an Asian healthcare setting. *Breast*. 2018 Aug;40:38–44.
- Li X, Zhang Y, Meisel J, Jiang R, Behera M, Peng L. Validation of the newly proposed American Joint Committee on Cancer (AJCC) breast cancer prognostic staging group and proposing a new staging system using the National Cancer Database. *Breast Cancer Res Treat*. 2018 Sep;171(2):303–13.

- 33 Lee SB, Sohn G, Kim J, Chung IY, Lee JW, Kim HJ, et al. A retrospective prognostic evaluation analysis using the 8th edition of the American Joint Committee on Cancer staging system for breast cancer. *Breast Cancer Res Treat*. 2018 Jun;169(2):257–66.
- 34 Kim JY, Lim JE, Jung HH, Cho SY, Cho EY, Lee SK, et al. Validation of the new AJCC eighth edition of the TNM classification for breast cancer with a single-center breast cancer cohort. *Breast Cancer Res Treat*. 2018 Jun.
- 35 Weiss A, Chavez-MacGregor M, Lichtensztajn DY, Yi M, Tadros A, Hortobagyi GN, et al. Validation Study of the American Joint Committee on Cancer Eighth Edition Prognostic Stage Compared With the Anatomic Stage in Breast Cancer. *JAMA Oncol*. 2018 Feb;4(2):203–9.
- 36 Zombori T, Lehóczy L, Cserni B, Nyári T, Cserni G. [Evaluation of anatomic and prognostic stages of breast cancer according to the 8th edition of the TNM staging system - Retrospective analysis based on data from deceased patients once diagnosed with breast cancer]. *Orv Hetil*. 2017 Sep;158(35):1373–81.
- 37 Yi M, Mittendorf EA, Cormier JN, Buchholz TA, Bilimoria K, Sahin AA, et al. Novel staging system for predicting disease-specific survival in patients with breast cancer treated with surgery as the first intervention: time to modify the current American Joint Committee on Cancer staging system. *J Clin Oncol*. 2011 Dec;29(35):4654–61.
- 38 Cserni G, Chmielik E, Cserni B, Tot T. The new TNM-based staging of breast cancer. *Virchows Arch*. 2018 May;472(5):697–703.
- 39 AJCC AJCoC. Breast Cancer Staging [Available from: <https://cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx>]
- 40 Smyth L, Watson G, Walsh EM, Kelly CM, Keane M, Kennedy MJ, et al. Economic impact of 21-gene recurrence score testing on early-stage breast cancer in Ireland. *Breast Cancer Res Treat*. 2015 Oct;153(3):573–82.
- 41 Dowsett M, Sestak I, Lopez-Knowles E, Sidhu K, Dunbier AK, Cowens JW, et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol*. 2013 Aug;31(22):2783–90.
- 42 Buus R, Sestak I, Kronenwett R, Denkert C, Dubsy P, Krappmann K, et al. Comparison of EndoPredict and EPclin With Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence After Endocrine Therapy. *J Natl Cancer Inst*. 2016 Jul;108(11):djw149.
- 43 Krop I, Ismaila N, Andre F, Bast RC, Barlow W, Collyar DE, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2017 Aug;35(24):2838–47.
- 44 Viale G, de Snoo FA, Slaets L, Bogaerts J, van 't Veer L, Rutgers EJ, et al.; MINDACT investigators. Immunohistochemical versus molecular (BluePrint and MammaPrint) subtyping of breast carcinoma. Outcome results from the EORTC 10041/BIG 3-04 MINDACT trial. *Breast Cancer Res Treat*. 2018 Jan;167(1):123–31.
- 45 Bartlett JM, Bayani J, Marshall A, Dunn JA, Campbell A, Cunningham C, et al.; OPTIMA TMG. Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test Is More Equal Than the Others. *J Natl Cancer Inst*. 2016 Apr;108(9):djw050.
- 46 Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med*. 2018 Jul;379(2):111–21.
- 47 Aleskandarany MA, Vandenberghe ME, Marchiò C, Ellis IO, Sapino A, Rakha EA. Tumour Heterogeneity of Breast Cancer: From Morphology to Personalised Medicine. *Pathobiology*. 2018;85(1-2):23–34.
- 48 Weiss A, King TA, Hunt KK, Mittendorf EA. Incorporating Biologic Factors into the American Joint Committee on Cancer Breast Cancer Staging System: Review of the Supporting Evidence. *Surg Clin North Am*. 2018 Aug;98(4):687–702.