Published in final edited form as:

Ann Surg Oncol. 2018 June ; 25(6): 1530–1535. doi:10.1245/s10434-018-6411-z.

The 21-Gene Recurrence Score in Male Breast Cancer

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Abstract

Background—Given the limited data, systemic treatment of male breast cancer has been extrapolated from female patients. The 21-gene recurrence score (RS) assay estimates the risk of distant recurrence and chemotherapy benefit in early-stage, ER+/HER2– female breast cancer. We aimed to assess the association between RS and type of treatment in male breast cancer.

Methods—We identified male patients with ER+/HER2– breast cancer and available RS results treated at our institution in 2006–2016. We collected data on clinicopathologic features, treatment and outcome. The Institutional Review Board approved the study.

Results—The study cohort consists of 38 male breast cancer patients with a median age of 70 years. Median tumor size was 1.6 cm, and 81.6% (31) were node-negative. RS was low (17) in 26 (68.4%) cases, intermediate (18–30) in 9 (23.7%) cases, and high (31) in 3 (7.9%) cases, comparable to that in female patients at our institution. All patients underwent total mastectomy, and one received radiotherapy. Thirty-four (89.5%) patients received adjuvant endocrine therapy, mostly tamoxifen (81.6%; 31). Five (13.2%) patients with intermediate or high RS were treated with adjuvant chemotherapy. No locoregional recurrence was observed, and one patient developed distant recurrence (median follow-up 34 months).

Conclusion—The RS distribution in male breast cancers was similar to that in females treated at our institution. With limited follow-up, patients with low RS were spared chemotherapy and did not develop recurrence. Our results suggest that the RS may have a clinical utility in male breast cancer patients.

Keywords

Male breast cancer; recurrence score; distant recurrence

Introduction

Male breast cancer is uncommon, accounting for <1% of all cancers in men and <1% of all breast cancers. The incidence of male breast cancer has been rising, with an estimated

annual incidence of 2,470 cases and an annual mortality of approximately 460 cases in the United States [1]. Risk factors include genetics (*BRCA* mutations, Klinefelter's syndrome), lifestyle (obesity, alcohol consumption, exogenous estrogen), race (African-American ancestry), environment (high ambient temperature, exhaust emissions), testicular and liver damage, and radiotherapy to chest [2,3]. Up to 40% of male breast cancer is hereditary, in contrast to only 5–10% of female breast cancer [2,3]. *BRCA2* germline mutations are more common than *BRCA1* mutations [4].

Male breast cancer is usually diagnosed at an advanced stage [2], most likely related to lack of awareness, screening and prevention. Most tumors are hormone receptor positive invasive ductal carcinomas, not otherwise specified (IDC NOS) [2,3]. Treatment of male breast cancer is similar to that of female breast cancer, although mastectomy has been the preferred surgical procedure. Few studies have reported important clinical and genomic differences between males and females [5–7]. Comparison of stage- and subtype-matched patients showed that male breast cancer has a significantly worse overall survival (OS) than female breast cancer [5,6]. Male breast cancer less frequently harbors somatic genetic alterations typically found in ER-positive, HER2-negative female breast cancer, such as *PIK3CA* and *TP53* mutations and 16q loss [7]. Optimal management of male breast cancer patients would benefit from a better understanding of tumor biology and the mechanisms underlying gender-specific differences.

The 21-gene recurrence score (RS) assay (Oncotype Dx™, Genomic Health, Redwood City, CA) is included as a prognostic stage tool in the 8th edition of the Cancer Staging Manual by the American Joint Committee of Cancer (AJCC) [8]. Many studies in female breast cancer patients have reported an association between the RS risk categories and the likelihood of distant recurrence as well as the magnitude of chemotherapy benefits [9–22]. The RS assay results have been reported to significantly change chemotherapy recommendations in as many as >30% of women [11,18]. However, data on the utility of the RS assay in male breast cancer is very limited.

This study aimed to assess the distribution of the RS and to evaluate the benefit of using the RS assay in the management of ER-positive, HER2-negative male breast cancer patients at our institution.

Materials and Methods

In this retrospective study, we analyzed a cohort of unselected, consecutive male patients with ER-positive, HER2-negative, lymph node-negative and few node-positive invasive breast carcinomas diagnosed and treated at our institution with available 21-gene RS assay results. The RS assay is a reverse transcriptase polymerase chain reaction (RT-PCR) based test that utilizes a recurrence score algorithm to calculate the risk of distant recurrence at 10 years in early-stage, ER-positive, HER2-negative breast cancer. The algorithm integrates the expression of 16 cancer-related genes and 5 reference genes to calculate the RS [9], which stratifies tumors into 3 risk categories: low risk (RS ≤ 17), intermediate risk (RS 18–30) and high risk (RS ≥ 31).

We collected data on clinicopathologic features, treatment and outcome information of our study cohort through a query of our institutional database from a period of February 2006 to August 2016. The clinicopathologic features included age at the time of diagnosis, *BRCA* mutation status, past oncologic history, tumor type and size, lymphovascular invasion (LVI), expression level of ER and PR by immunohistochemistry (IHC), RS, type of local and systemic treatment, follow-up time, and distant and locoregional recurrence.

Clinicopathologic characteristics of the cohort were summarized using descriptive statistics. Analysis of categorical variables was performed using Fisher's exact test. However, due to the small number of events, most analyses were descriptive and exploratory. The Institutional Review Board approved this study.

Results

Clinicopathologic features

We identified a total of 38 male patients with ER-positive, HER2-negative carcinoma (Table 1). The median age at diagnosis was 70 years (range 40–84). The median tumor size was 1.6 cm (range 0.5–5). Most carcinomas (63.2%; 24/38) were IDC NOS, followed by ductal carcinoma with papillary or solid-papillary features (18.4%; 7/38), micropapillary features (15.8%; 6/38), and apocrine morphology (2.6%; 1/38). The majority of tumors were grade 2 (55.3%; 21/38). Only 7/38 (18.4%) tumors had metastasized to lymph nodes, and 26.3% (10/38) had LVI. All tumors were ER-positive, and 34/38 (89.5%) were also PR-positive. The median percentage of ER-positive cells was 95 (range 70–100) and, the median percentage of PR-positive cells was 90 (range 0–100).

Twenty-four patients were tested for *BRCA1* and *BRCA2* germline mutations, and deleterious mutations were identified in 4 patients (10.6%; 2 *BRCA1* and 2 *BRCA2*). Sixteen (42%) patients had a history of prior or subsequent malignancy, the most common of which was prostate cancer (50%; 8/16).

Recurrence Score (RS) assay results and clinical outcome

Of the 38 tumors, 26 (68.4%) had low RS, 9 (23.7%) had intermediate RS, while 3 (7.9%) had high RS. The median patient age was 70 years (range 47–84) in the low RS group, 67 years (range 40–81) in the intermediate RS group, and 74 years (range 74–81) in the high RS group. The median tumor size was 1.6 cm (range 0.5–2.7), 2.1 cm (range 0.5–5), and 1.7 cm (range 1.1–3), in the low, intermediate and high RS groups, respectively. Of the 7 lymph node-positive carcinomas, 4 had intermediate RS and 3 had low RS. There was no association between the RS risk categories and any of the clinicopathologic variables ($p>0.05$). Both *BRCA2* mutation carriers had an intermediate RS. One *BRCA1* mutation carrier had a low RS, while the other carrier had an intermediate RS.

All patients were treated with total mastectomy and one received post-mastectomy radiation therapy. Most patients (34/38; 89.5%) were treated with endocrine therapy, primarily tamoxifen (81.6%; 31/38). Only 3 patients (7.9%) received aromatase inhibitors. Five patients (13.2%) were treated with adjuvant chemotherapy in addition to endocrine therapy, including 3 of 9 in the intermediate RS group, and 2 of 3 in the high RS group. One 74 year-

old patient with a high RS declined chemotherapy due to comorbidity. None of the patients with low RS were treated with chemotherapy.

Median follow-up was 34 months (range 1–133). One patient had a long follow-up of 133 months. He was diagnosed with breast cancer at age of 66 years in 2006, pT1cN0, ER and PR positive (90%), HER2 negative. The RS assay was used to guide adjuvant chemotherapy decision, and the result was low risk (RS=4). He was treated with an aromatase inhibitor and remained free of any recurrence.

None of the 38 patients developed locoregional recurrence. Only 1 patient (2.6%) developed distant metastasis. This was a 63-year-old man with node-positive IDC and intermediate RS who received adjuvant endocrine therapy combined with chemotherapy. He developed distant recurrence at 29 months. At the time of the study, this patient was alive with disease. All other patients (97.4%; 37/38) had no evidence of disease at the last follow-up. One patient with low RS died of unknown cause within 2 years of the initial diagnosis.

Discussion

Male and female breast cancers have been suggested to be biologically different [23]. Gene expression profiling revealed a different transcriptomic landscape in female and male breast cancers underpinned by genes involved in energy metabolism, regulation of translation, matrix remodeling and immune response [24]. Another study of 220 male breast cancers identified 2 clinically significant subtypes different from the 4 intrinsic subtypes of female breast cancer, including prognostically unfavorable luminal M1 tumors with low expression of genes involved in ER signaling, and prognostically favorable luminal M2 tumors with higher expression of ER-associated and immune response genes [25]. Due to the low incidence of male breast cancer and the subsequent lack of randomized clinical trials, systemic treatment of male breast cancer has primarily been extrapolated from female breast cancer patients. Male breast cancer patients have been shown to benefit from endocrine therapy with tamoxifen in a cohort of 257 patients [26] and adjuvant chemotherapy in a smaller study of 135 patients [27]. However, in a large comparative series of >3,500 age- and stage-matched male and female patients, only 27% of male breast cancer patients received adjuvant chemotherapy compared to 41% of female breast cancer patients [28]. In addition to successfully using the RS risk categories for adjuvant treatment selection in early-stage, ER-positive, HER2-negative female breast cancer patients [11,18], the RS assay is increasingly being incorporated in decision making for node-positive patients [29–32]. Given the lower incidence of chemotherapy despite the advanced clinical presentation of male breast cancer, the RS assay may allow a better selection of adjuvant systemic therapy in male patients.

Our study describes the association between RS and type of treatment in a cohort of 38 male breast cancer patients. None of the 26 male breast cancer patients with low RS received adjuvant chemotherapy, and none developed locoregional or distant metastasis after a relatively brief median follow-up. In a study of 65 male breast cancer patients from Israel 44.6%, 41.5% and 13.9% had low, intermediate and high risk scores, respectively [33], in contrast to 68.4%, 23.7% and 7.9% in our study. Our patient cohort included fewer node-

positive patients (18.4% versus 35.4%), suggesting a more stringent use of the original indications (early-stage breast cancer) for requesting the RS assay at our institution.

Additionally, our study confirms that the RS distribution in male breast cancer is similar to that recently reported in a cohort of 2,326 female breast cancer patients from our center [34]. Namely, the distribution of RS was 60%, 33.4% and 6.6% in female breast cancer versus 68.4%, 23.7% and 7.9% in male breast cancer in low, intermediate and high RS groups, respectively [34]. The rate of distant and locoregional recurrence was very low in female breast cancer patients: in the 3 RS risk groups, the cumulative incidence at 48 months was 0.41%, 1.77% and 3.6% for distant recurrence (Gray's test $p<0.01$), and 0.84%, 2.7% and 2.8% for locoregional recurrence (Gray's test $p<0.01$) [34]. Although our current cohort of 38 male breast cancer patients is significantly smaller, no locoregional recurrence was observed. Only one patient with intermediate RS developed distant recurrence.

Our patient characteristics were comparable to male breast cancer patients in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. According to this database between 2003 and 2012, median age of male breast cancer patients was 65 years (range 23–97). Most tumors were IDC NOS (85%), and positive for ER (95.1%) and PR (86%). Most patients (87.2%) were treated with total mastectomy, and 23.7% received adjuvant radiotherapy [35]. The median age of our patients was 70 years (range 40–84) and 63.2% showed pure IDC histology, while the remaining 36.8% were ductal with apocrine, micropapillary or papillary/solid-papillary features. All tumors in our cohort were ER-positive, and 89.5% also expressed PR. All our patients were treated with total mastectomy and only one patient received adjuvant radiotherapy. The high rate of total mastectomy most likely explains the low rate of radiotherapy in our cohort as total mastectomy and breast conserving surgery with radiotherapy are both equally acceptable options for surgical management [36].

Male breast cancer patients have been reported to have up to 41.7% incidence of *BRCA2* germline mutations [37,38]. It has been suggested that germline *BRCA*-associated ER-positive breast cancer may be associated with less favorable biology in females. Studies have found an increased rate of high and intermediate RS among *BRCA1* and *BRCA2* female carriers with ER-positive breast cancer compared to the general population [39,40]. These patients were also more likely to receive adjuvant therapy versus controls ($p=0.002$) [41]. Of the 24 patients tested for *BRCA1* and *BRCA2* germline mutations in our cohort, 10.6% were *BRCA* mutation carriers. However, the small number of patients with *BRCA* mutations precludes a comprehensive analysis of the association between *BRCA* mutation status and the RS data.

Strengths of our study include a population of male breast cancer patients with detailed clinicopathologic variables and clinical outcome data. The main limitations include the retrospective study design, small sample size, limited follow-up (median, 34 months) and low number of events precluding formal statistical analysis of survival functions. Despite the reported genetic differences between female and male breast cancers, and the development and validation of the RS assay in female breast cancer patients, currently there is no

evidence to believe that significant gender-specific clinical differences exist that would significantly limit the utility of the RS assay in male breast cancer [33].

In conclusion, the RS distribution in male breast cancer patients appeared similar to that in female breast cancer patients treated at our institution. With limited follow-up, patients with low risk RS were spared chemotherapy and did not develop recurrence. Our results suggest that the RS may have a clinical utility in male breast cancer patients.

References

1. Society AC. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017. <https://www.ncbi.nlm.nih.gov/pubmed/29035643>
2. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. *Lancet*. 2006; 367(9510):595–604. DOI: 10.1016/S0140-6736(06)68226-3 [PubMed: 16488803]
3. Korde LA, Zujewski JA, Kamin L, Giordano S, Domchek S, Anderson WF, Bartlett JM, Gelmon K, Nahleh Z, Bergh J, Cutuli B, Pruneri G, McCaskill-Stevens W, Gralow J, Hortobagyi G, Cardoso F. Multidisciplinary meeting on male breast cancer: summary and research recommendations. *J Clin Oncol*. 2010; 28(12):2114–2122. DOI: 10.1200/JCO.2009.25.5729 [PubMed: 20308661]
4. Friedman LS, Gayther SA, Kurosaki T, Gordon D, Noble B, Casey G, Ponder BA, Anton-Culver H. Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. *Am J Hum Genet*. 1997; 60(2):313–319. [PubMed: 9012404]
5. Li X, Yang J, Krishnamurti U, Huo L, Ward KC, O'Regan R, Peng L. Hormone Receptor-Positive Breast Cancer Has a Worse Prognosis in Male Than in Female Patients. *Clin Breast Cancer*. 2017; 17(5):356–366. DOI: 10.1016/j.clbc.2017.03.005 [PubMed: 28576631]
6. Greif JM, Pezzi CM, Klimberg VS, Bailey L, Zuraek M. Gender differences in breast cancer: analysis of 13,000 breast cancers in men from the National Cancer Data Base. *Ann Surg Oncol*. 2012; 19(10):3199–3204. DOI: 10.1245/s10434-012-2479-z [PubMed: 22766989]
7. Piscuoglio S, Ng CK, Murray MP, Guerini-Rocco E, Martelotto LG, Geyer FC, Bidard FC, Berman S, Fusco N, Sakr RA, Eberle CA, De Mattos-Arruda L, Macedo GS, Akram M, Baslan T, Hicks JB, King TA, Brogi E, Norton L, Weigelt B, Hudis CA, Reis-Filho JS. The Genomic Landscape of Male Breast Cancers. *Clin Cancer Res*. 2016; 22(16):4045–4056. DOI: 10.1158/1078-0432.CCR-15-2840 [PubMed: 26960396]
8. Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, Weaver DL, Winchester DJ, Hortobagyi GN. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017; 67(4):290–303. DOI: 10.3322/caac.21393 [PubMed: 28294295]
9. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004; 351(27):2817–2826. DOI: 10.1056/NEJMoa041588 [PubMed: 15591335]
10. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, Cronin M, Baehner FL, Watson D, Bryant J, Costantino JP, Geyer CE Jr, Wickerham DL, Wolmark N. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006; 24(23):3726–3734. DOI: 10.1200/JCO.2005.04.7985 [PubMed: 16720680]
11. Lo SS, Mumby PB, Norton J, Rychlik K, Smerage J, Kash J, Chew HK, Gaynor ER, Hayes DF, Epstein A, Albain KS. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010; 28(10):1671–1676. DOI: 10.1200/JCO.2008.20.2119 [PubMed: 20065191]
12. Ademuyiwa FO, Miller A, O'Connor T, Edge SB, Thorat MA, Sledge GW, Levine E, Badve S. The effects of oncotype DX recurrence scores on chemotherapy utilization in a multi-institutional breast cancer cohort. *Breast cancer research and treatment*. 2011; 126(3):797–802. DOI: 10.1007/s10549-010-1329-6 [PubMed: 21197567]

13. Geffen DB, Abu-Ghanem S, Sion-Vardy N, Braunstein R, Tokar M, Ariad S, Delgado B, Bayme M, Koretz M. The impact of the 21-gene recurrence score assay on decision making about adjuvant chemotherapy in early-stage estrogen-receptor-positive breast cancer in an oncology practice with a unified treatment policy. *Annals of oncology : official journal of the European Society for Medical Oncology/ESMO*. 2011; 22(11):2381–2386. DOI: 10.1093/annonc/mdq769
14. Partin JF, Mamounas EP. Impact of the 21-gene recurrence score assay compared with standard clinicopathologic guidelines in adjuvant therapy selection for node-negative, estrogen receptor-positive breast cancer. *Annals of surgical oncology*. 2011; 18(12):3399–3406. DOI: 10.1245/s10434-011-1698-z [PubMed: 21537874]
15. Albanell J, Gonzalez A, Ruiz-Borrego M, Alba E, Garcia-Saenz JA, Corominas JM, Burgues O, Furio V, Rojo A, Palacios J, Bermejo B, Martinez-Garcia M, Limon ML, Munoz AS, Martin M, Tusquets I, Rojo F, Colomer R, Faull I, Lluch A. Prospective transGEICAM study of the impact of the 21-gene Recurrence Score assay and traditional clinicopathological factors on adjuvant clinical decision making in women with estrogen receptor-positive (ER+) node-negative breast cancer. *Annals of oncology : official journal of the European Society for Medical Oncology/ESMO*. 2012; 23(3):625–631. DOI: 10.1093/annonc/mdr278
16. Joh JE, Esposito NN, Kiluk JV, Laronga C, Lee MC, Loftus L, Soliman H, Boughey JC, Reynolds C, Lawton TJ, Acs PI, Gordan L, Acs G. The effect of Oncotype DX recurrence score on treatment recommendations for patients with estrogen receptor-positive early stage breast cancer and correlation with estimation of recurrence risk by breast cancer specialists. *The oncologist*. 2011; 16(11):1520–1526. DOI: 10.1634/theoncologist.2011-0045 [PubMed: 22016474]
17. Eiermann W, Rezai M, Kummel S, Kuhn T, Warm M, Friedrichs K, Schneeweiss A, Markmann S, Eggemann H, Hilfrich J, Jackisch C, Witzel I, Eidtmann H, Bachinger A, Hell S, Blohmer J. The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. *Annals of oncology : official journal of the European Society for Medical Oncology/ESMO*. 2013; 24(3):618–624. DOI: 10.1093/annonc/mds512
18. Carlson JJ, Roth JA. The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis. *Breast cancer research and treatment*. 2013; 141(1):13–22. DOI: 10.1007/s10549-013-2666-z [PubMed: 23974828]
19. Dinan MA, Mi X, Reed SD, Lyman GH, Curtis LH. Association Between Use of the 21-Gene Recurrence Score Assay and Receipt of Chemotherapy Among Medicare Beneficiaries With Early-Stage Breast Cancer, 2005–2009. *JAMA oncology*. 2015; 1(8):1098–1109. DOI: 10.1001/jamaoncol.2015.2722 [PubMed: 26313372]
20. Levine MN, Julian JA, Bedard PL, Eisen A, Trudeau ME, Higgins B, Bordeleau L, Pritchard KI. Prospective Evaluation of the 21-Gene Recurrence Score Assay for Breast Cancer Decision-Making in Ontario. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015; doi: 10.1200/JCO.2015.62.8503
21. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer CE Jr, Dees EC, Perez EA, Olson JA Jr, Zujewski J, Lively T, Badve SS, Saphner TJ, Wagner LI, Whelan TJ, Ellis MJ, Paik S, Wood WC, Ravdin P, Keane MM, Gomez Moreno HL, Reddy PS, Goggins TF, Mayer IA, Brufsky AM, Toppmeyer DL, Kaklamani VG, Atkins JN, Berenberg JL, Sledge GW. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. *The New England journal of medicine*. 2015; doi: 10.1056/NEJMoa1510764
22. Petkov V, Miller DP, Howlader N, Gliner N, Howe W, Schussler NC, Cronin K, Baehner FL, Penberthy L. Breast cancer specific mortality in patients with early-stage hormone receptor-positive invasive breast cancer and oncotype DX recurrence score results in the SEER database. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016; 34(7_suppl):176.
23. Vermeulen MA, Slaets L, Cardoso F, Giordano SH, Tryfonidis K, van Diest PJ, Dijkstra NH, Schroder CP, van Asperen CJ, Linderholm B, Benstead K, Foekens R, Martens JWM, Bartlett JMS, van Deurzen CHM. Pathological characterisation of male breast cancer: Results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Eur J Cancer*. 2017; 82:219–227. DOI: 10.1016/j.ejca.2017.01.034 [PubMed: 28292559]

24. Callari M, Cappelletti V, De Cecco L, Musella V, Miodini P, Veneroni S, Gariboldi M, Pierotti MA, Daidone MG. Gene expression analysis reveals a different transcriptomic landscape in female and male breast cancer. *Breast Cancer Res Treat.* 2011; 127(3):601–610. DOI: 10.1007/s10549-010-1015-8 [PubMed: 20625818]
25. Johansson I, Nilsson C, Berglund P, Lauss M, Ringner M, Olsson H, Luts L, Sim E, Thorstensson S, Fjallskog ML, Hedenfalk I. Gene expression profiling of primary male breast cancers reveals two unique subgroups and identifies N-acetyltransferase-1 (NAT1) as a novel prognostic biomarker. *Breast Cancer Res.* 2012; 14(1):R31.doi: 10.1186/bcr3116 [PubMed: 22333393]
26. Eggemann H, Ignatov A, Smith BJ, Altmann U, von Minckwitz G, Rohl FW, Jahn M, Costa SD. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. *Breast Cancer Res Treat.* 2013; 137(2):465–470. DOI: 10.1007/s10549-012-2355-3 [PubMed: 23224235]
27. Giordano SH, Perkins GH, Broglio K, Garcia SG, Middleton LP, Buzdar AU, Hortobagyi GN. Adjuvant systemic therapy for male breast carcinoma. *Cancer.* 2005; 104(11):2359–2364. DOI: 10.1002/ncr.21526 [PubMed: 16270318]
28. Scott-Conner CE, Jochimsen PR, Menck HR, Winchester DJ. An analysis of male and female breast cancer treatment and survival among demographically identical pairs of patients. *Surgery.* 1999; 126(4):775–780. discussion 780–771. [PubMed: 10520928]
29. Peethambaram PP, Hoskin TL, Day CN, Goetz MP, Habermann EB, Boughey JC. Use of 21-gene recurrence score assay to individualize adjuvant chemotherapy recommendations in ER+/HER2–node positive breast cancer-A National Cancer Database study. *NPJ Breast Cancer.* 2017; 3:41.doi: 10.1038/s41523-017-0044-4 [PubMed: 29067357]
30. Mamounas EP, Liu Q, Paik S, Baehner FL, Tang G, Jeong JH, Kim SR, Butler SM, Jamshidian F, Cherbavaz DB, Sing AP, Shak S, Julian TB, Lembersky BC, Wickerham DL, Costantino JP, Wolmark N. 21-Gene Recurrence Score and Locoregional Recurrence in Node-Positive/ER-Positive Breast Cancer Treated With Chemo-Endocrine Therapy. *J Natl Cancer Inst.* 2017; 109(4)doi: 10.1093/jnci/djw259
31. Brufsky AM. Predictive and prognostic value of the 21-gene recurrence score in hormone receptor-positive, node-positive breast cancer. *Am J Clin Oncol.* 2014; 37(4):404–410. DOI: 10.1097/COC.0000000000000086 [PubMed: 24853663]
32. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, Ravdin P, Bugarini R, Baehner FL, Davidson NE, Sledge GW, Winer EP, Hudis C, Ingle JN, Perez EA, Pritchard KI, Shepherd L, Gralow JR, Yoshizawa C, Allred DC, Osborne CK, Hayes DF. Breast Cancer Intergroup of North A. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol.* 2010; 11(1):55–65. DOI: 10.1016/S1470-2045(09)70314-6 [PubMed: 20005174]
33. Grenader T, Yerushalmi R, Tokar M, Fried G, Kaufman B, Peretz T, Geffen DB. The 21-gene recurrence score assay (Oncotype DX) in estrogen receptor-positive male breast cancer: experience in an Israeli cohort. *Oncology.* 2014; 87(1):1–6. DOI: 10.1159/000360793
34. Turashvili G, Chou JF, Brogi E, Morrow M, Dickler M, Norton L, Hudis C, Wen HY. 21-Gene recurrence score and locoregional recurrence in lymph node-negative, estrogen receptor-positive breast cancer. *Breast Cancer Res Treat.* 2017; 166(1):69–76. DOI: 10.1007/s10549-017-4381-7 [PubMed: 28702894]
35. Leone JP, Zwenger AO, Iturbe J, Leone J, Leone BA, Vallejo CT, Bhargava R. Prognostic factors in male breast cancer: a population-based study. *Breast Cancer Res Treat.* 2016; 156(3):539–548. DOI: 10.1007/s10549-016-3768-1 [PubMed: 27039306]
36. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med.* 2002; 347(8):567–575. DOI: 10.1056/NEJMoa020128 [PubMed: 12192016]
37. Chodick G, Struewing JP, Ron E, Rutter JL, Iscovich J. Similar prevalence of founder BRCA1 and BRCA2 mutations among Ashkenazi and non-Ashkenazi men with breast cancer: evidence from 261 cases in Israel, 1976–1999. *Eur J Med Genet.* 2008; 51(2):141–147. DOI: 10.1016/j.ejmg.2007.11.001 [PubMed: 18158280]

38. Deb S, Jene N, Kconfab I, Fox SB. Genotypic and phenotypic analysis of familial male breast cancer shows under representation of the HER2 and basal subtypes in BRCA-associated carcinomas. *BMC Cancer*. 2012; 12:510.doi: 10.1186/1471-2407-12-510 [PubMed: 23146383]
39. Lewin R, Sulkes A, Shochat T, Tsoref D, Rizer S, Liebermann N, Hendler D, Neiman V, Ben-Aharon I, Friedman E, Paluch-Shimon S, Margel D, Kedar I, Yerushalmi R. Oncotype-DX recurrence score distribution in breast cancer patients with BRCA1/2 mutations. *Breast Cancer Res Treat*. 2016; 157(3):511–516. DOI: 10.1007/s10549-016-3836-6 [PubMed: 27225387]
40. Halpern N, Sonnenblick A, Uziely B, Divinsky L, Goldberg Y, Hamburger T, Peretz T, Kadouri L. Oncotype Dx recurrence score among BRCA1/2 germline mutation carriers with hormone receptors positive breast cancer. *Int J Cancer*. 2017; 140(9):2145–2149. DOI: 10.1002/ijc.30616 [PubMed: 28120435]
41. Shah PD, Patil S, Dickler MN, Offit K, Hudis CA, Robson ME. Twenty-one-gene recurrence score assay in BRCA-associated versus sporadic breast cancers: Differences based on germline mutation status. *Cancer*. 2016; 122(8):1178–1184. DOI: 10.1002/cncr.29903 [PubMed: 26859126]

Synopsis

The study reports the association between the 21-gene recurrence score and type of treatment, and suggests that the recurrence score assay may have a clinical utility in male breast cancer patients.

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Table 1

Clinicopathologic features of 38 male breast cancer patients.

Clinicopathologic features	Total (n=38)	RS 17 (n=26)	RS 18–30 (n=9)	RS 31 (n=3)
Age at diagnosis, median (range); year	70 (40–84)	70 (47–84)	67 (40–81)	74 (74–81)
BRCA mutation carriers				
BRCA1 mutation	2 (5.3%)	1 (3.8%)	1 (11.1%)	0
BRCA2 mutation	2 (5.3%)	0	2 (22.2%)	0
No mutation	20 (52.6%)	16 (61.5%)	3 (33.3%)	1 (33.3%)
Not tested	14 (36.8%)	9 (34.6%)	3 (33.3%)	2 (66.7%)
History of other malignancies *	16 (42.1%)	11 (42.3%)	4 (44.4%)	1 (33.3%)
Tumor size, median (range); cm	1.6 (0.5–5)	1.6 (0.5–2.7)	2.1 (0.5–5)	1.7 (1.1–3)
Tumor type				
IDC NOS	24 (63.2%)	15 (57.7%)	7 (77.8%)	3 (100%)
Ductal with papillary/solid- papillary features	7 (18.4%)	7 (26.9%)	0	0
Ductal with micropapillary features	6 (15.8%)	4 (15.4%)	2 (22.2%)	0
Ductal with apocrine morphology	1 (2.6%)	1 (3.8%)	0	0
Tumor grade				
Grade 1	3 (7.9%)	3 (11.5%)	0	0
Grade 2	21 (55.3%)	15 (57.7%)	5 (55.6%)	1 (33.3%)
Grade 3	8 (21.1%)	4 (15.4%)	3 (33.3%)	1 (33.3%)
Unknown	6 (15.8%)	4 (15.4%)	1 (11.1%)	1 (33.3%)
LVI	10 (26.3%)	7 (26.9%)	2 (22.2%)	1 (33.3%)
Lymph node positive	7 (18.4%)	3 (11.5%)	4 (44.4%)	0
ER% by IHC, median (range)	95 (70–100)	95 (70–99)	92 (80–100)	90 (80–99)
PR% by IHC, median (range)	90 (0–100)	93 (0–100)	50 (0–100)	0 (0–20)
Radiation therapy	1 (2.6%)	1 (3.8%)	0	0
Endocrine therapy				
Tamoxifen **	31 (81.6%)	21 (80.8%)	7 (77.8%)	3 (100%)
AI	3 (7.9%)	2 (7.7%)	1 (11.1%)	0
No ***	4 (10.5%)	3 (11.5%)	1 (11.1%)	0
Adjuvant chemotherapy	5 (13.2%)	0	3 (33.3%)	2 (66.7%)
Follow-up, median (range); months	34 (1.05–133.4)	36.2 (1.05–133.3)	18.7 (4.3–70.5)	18.5 (7.8–103)
Distant metastasis	1 (2.6%)	0	1 (11.1%)	0
Survival				
NED	36 (94.7%)	25 (96.2%)	8 (88.9%)	3 (100%)
AWD	1 (2.6%)	0	1 (11.1%)	0
DUC	1 (2.6%)	1 (3.8%)	0	0

Abbreviations: AI, aromatase inhibitor; AWD, alive with disease; DUC, died of unknown cause; ER, estrogen receptor; IHC, immunohistochemistry; LVI, lymphovascular invasion; NED, no evidence of disease; PR, progesterone receptor;

* Two patients developed contralateral breast cancer within 2 years of initial diagnosis (not included in the table);

** One patient was treated with AI and switched to tamoxifen;

*** One patient was treated with tamoxifen for 9 months and discontinued due to side effects.

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