Breast Cancer with Low Recurrence Score on Oncotype DX®: Interplay Between Early Recurrence, Lobular Histology and BRCA Mutation

Yonaton Zarbiv · Yael Berner Wygoda · Albert Grinshpun · Tamar Hamburger · Tamar Sella · Shani Breuer · Ofra Maimon · Yakir Rottenberg · Tamar Peretz · Luna Kadouri

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ABSTRACT

Introduction: The 21-gene recurrence score assay Oncotype DX® (ODX) has clear prognostic and predictive value regarding adjuvant chemotherapy. However, recent studies have shown the clinical distinctiveness of both BRCA1/2–driven early breast cancer (EBC) and invasive lobular (ILC) breast cancers. We evaluated the association between BRCA1/2-driven EBC/ILC and Oncotype DX failure despite a recurrence score \( \leq 20 \).

Methods: Here, we describe a small cohort of 16 patients from our center who, despite a low recurrence score (RS) \( \leq 20 \), suffered from early disease recurrence. Clinical parameters of our cohort of patients were compared to a cohort from the general population of Clalit Health Service (CHS).

Results: Median age at diagnosis in our cohort was significantly younger. BRCA mutational status was available in 14 patients in our cohort. A high percentage of these patients had BRCA1/2 mutations (35.7%), either germline (in 3) or somatic (in 2). Half of our cohort was diagnosed with lobular carcinoma (ILC) relative to 10–15% in the general population of BC (\( p = 0.02 \)). The median time to recurrence was 44 months.

Conclusion: BRCA1/2 mutation and ILC are highly represented in this cohort. Although our cohort is small, these data may suggest that a RS \( \leq 20 \) in these subgroups may not reflect a low risk of recurrence.

Keywords: Breast cancer; Recurrence; Recurrence score; BRCA1/2; Invasive lobular carcinoma; Prognostic genomic test; Predictive genomic test
Key Summary Points

| Key Summary Points |
|-------------------|
| Genomic testing is standard to determine benefit of adjuvant chemotherapy in early breast cancer (EBC). |
| The accuracy of these tests in non-invasive ductal carcinoma (IDC) histologies has been questioned. |
| The effect of BRCA on these genomic tests is also unknown. |
| Here, we describe a small cohort of low recurrence score (RS) patients with early recurrence. |
| Despite the small cohort, a significant number of lobular carcinoma and mBRCA patients suffered recurrence. |

INTRODUCTION

Early breast cancer is (EBC) a potentially curative malignancy that is initially treated locally. EBC is defined as local disease that is both operable and without distant metastasis [1]. Adjuvant chemotherapy is administered in high-risk disease and has been shown to reduce the risk of recurrence and improve survival [2, 3]. The risk of recurrence in hormone receptor-positive (HR+) cases can be quantified by the Oncotype DX® 21-gene expression assay (ODX, Genomic Health, Redwood City, CA) and is used to determine the potential benefit of chemotherapy in these patients by determining a recurrence score (RS). Three risk groups were originally defined using archival pathology blocks: low, intermediate and high with RS of < 18, 18–30 and > 30, respectively, corresponding to a 10-year distant recurrence risk of < 10%, 10–20% and > 20% [4]. Extensive population-based studies of SEER [5] and Clalit Health Service (CHS) [6] registries confirmed the prognostic value of ODX among node-negative [5, 6] and node-positive [6, 7] HR+ breast cancer patients. The TailorX, a prospective study among hormone-positive, lymph node-negative breast cancer patients, determined that in a population with an intermediate RS of 11–25, the 9-year distant recurrence rate was approximately 5% irrespective of chemotherapy administration. This finding suggests that endocrine therapy was not inferior to chemoendocrine therapy in this population and therefore adjuvant chemotherapy can be spared in this subgroup [4]. Importantly, patients under 50 years old with an RS of 16–25 seemed to show some benefit from adjuvant chemotherapy. Thus, age determines the risk of recurrence and benefit from chemotherapy, regardless of tumor biology, as assessed by ODX. A further analysis of the data obtained in the TailorX done in young woman under 50 with a score under 20 showed a noninferior benefit of chemotherapy vs endocrine therapy alone, whereas young woman with a score of 21–25 showed a modest but significant advantage with adjuvant chemotherapy treatment [8]. Similar results were recently reported in the RxPONDER study in the node-positive population [9].

The relationship between patients with BRCA 1/2 mutations and RS has been previously described [10–13]. ODX RS for a combined 56 BRCA1 and 87 BRCA2 carriers was reported. The distribution of RS in patients harboring BRCA 1/2 mutations was significantly higher than in the BRCA 1/2 WT population, including a ~ threefold RS > 25. These studies suggest a unique molecular profile and question the predictive value of ODX RS in this population. However, long-term follow-up and risk of disease recurrence in this cohort to the best of our knowledge have not been reported.

The distribution of RS in patients with histologies other than IDC, particularly in ILC, has also been previously described [5, 14]. A recent analysis of the National Cancer Database was concordant with previous studies and showed a lower incidence of high RS and higher incidence of intermediate RS in ILC histology [15]. These studies further question the predictive value of ODX RS in predicting the use of adjuvant chemotherapy in patients with ILC.

In our study, we report results from a cohort of 16 patients with a low RS (defined as ≤ 20, in accordance with TailorX 2019) that had disease...
recurrence and compare their clinicopathologic characteristics to the CHS registry. We describe the post-recurrence clinical course, including treatment received after recurrence and response to treatment. Additionally, we report BRCA mutational status of the patients to better define this rare subgroup in 14/16 patients. Our cohort did not include women with locally advanced unresectable disease or metastatic patients.

METHODS

Patients

The Oncotype Dx assay has been used at the Hadassah Medical Center since 2004 on specimens from > 700 patients (true for time of data cutoff). Among these, we identified 16 with ODX RS \leq 20 that had disease recurrence. We chose 20 as a cutoff corresponding to "low risk" in young women based on the TailorX study.

The MammaPrint assay utilizes a profile of 70 genes to stratify hormone-positive breast cancer into high or low risk of recurrence. The prognostic value of this assay was validated in the MINDACT study [16]. We additionally tested four patients for genomic risk profiling with the MammaPrint assay.

Clinical and pathologic characteristics, genetic test results, treatment and outcomes were retrieved from the medical files of these 16 patients and compared to a cohort of 1801 Israeli patients that was published in 2017 [6] and present their clinicopathologic characteristics. This cohort was chosen because it includes a report of ILC frequency, which is highly represented in our cohort. We also reviewed the SEER database [5] and the node-positive cohort from Clalit [17], which did not differ significantly regarding age distribution and pathology.

The statistical comparison is limited because of the small number of cases in our cohort. However, three crucial parameters significantly differ from the CHS group, even in this small cohort. Median age at diagnosis in our cohort was 47 (range 36–71) compared to 59 (52–67) years in the CHS cohort, and the corresponding frequency of those diagnosed at below age 50 was 62.5% (10/16) in our cohort compared to 18% (296/1801) in the CHS cohort (p = 0.0007).

The frequency of ILC (6/16) and combined invasive ductal carcinoma IDC and ILC (2/16) was very high in our group compared to 11.8% (213/1801) in our cohort compared to 18% (296/1801) in the CHS cohort (p = 0.0007).

The frequency of ILC (6/16) and combined invasive ductal carcinoma IDC and ILC (2/16) was very high in our group compared to 11.8% (213/1801) in the CHS cohort (p = 0.02).

Among patients with available genetic information, 5 of our 14 (35.7%) carried a mutation in BRCA1 or BRCA2 genes. A BRCA1 germline mutation (185delAG) was found in two patients and a BRCA2 germline mutation (k332G) in one patient, and two patients had a somatic BRCA2 mutation (a homozygous loss in

RESULTS

We compared the clinical parameters of our cohort of patients with low ODX \leq 20 to a cohort from the general population of Clalit Health Service (CHS) (Table 1). To this end, we used a cohort of 1801 Israeli patients that was published in 2017 [6] and present their clinicopathologic characteristics. This cohort was chosen because it includes a report of ILC frequency, which is highly represented in our cohort. We also reviewed the SEER database [5] and the node-positive cohort from Clalit [17], which did not differ significantly regarding age distribution and pathology.

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| Clinical characteristics | Patients with low RS and disease recurrence (n = 16) | CHS cohort (n = 1801) | p value |
|--------------------------|---------------------------------------------------|-----------------------|---------|
| Age years, median (Range) | 47 (36–71)                                        | 295 (18%)             | p < 0.001 |
| < 50                     | 11 (68.7%)                                        | 2 (185delAG)          |         |
| BRCA1 mutation           | 3 (somatic in 2)                                  |                       |         |
| BRCA2 mutation           | 9*                                                |                       |         |
| WT                       | 2                                                 |                       |         |
| Lymph node: 0            | 12 (75%)                                          | 1801 (100%)           |         |
| Tumor size               |                                                   |                       |         |
| ≤ 2 cm                   | 6 (42.8%)                                         | 1396 (77.5%)          | p = 0.01 |
| > 2 cm                   | 8 (57.1%)                                         | 405 (22.5%)           |         |
| Grade (n = 10)           |                                                   |                       |         |
| 1                        | 0                                                 | 205 (14.3%)           |         |
| 2                        | 5 (50%)                                           | 907 (50.4%)           |         |
| 3                        | 5 (50%)                                           | 297 (15.9%)           |         |
| Pathology: IDC           |                                                   | 1461 (81.1%)          | p = 0.02 |
| ILC                      | 8 (50%)                                           | 213 (11.8%)           |         |
| ILC + IDC                | 6 (37.5%)                                         | NR                    |         |
| Other                    | 2 (12.5%)                                         | 127 (3.6%)            |         |
| ER positive              | 16                                                |                       | > 90% [7] |
| PR positive              | 11 (68.75%)                                       |                       |         |
| RS median (range)        | 15.5 (11–18)                                      |                       |         |
| MammaPrint Risk Score (n = 4) |                       |                       |         |
| Low-risk luminal A       | 3                                                 |                       |         |
| High-risk luminal B      | 1                                                 |                       |         |
| Adjuvant chemotherapy    | 2                                                 | 12/880 (1.4%)         |         |
| Hormonal: tamoxifen      | 10                                                |                       |         |

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one patient and a Glu1646fs mutation in the second patient). The genetic evaluation varied among our cohort of nine patients with wild-type BRCA. Three patients were tested for the Ashkenazi founder mutations, three were screened for germline cancer gene panel, and two were evaluated for BRCA1/2 mutations in the tumor. The genetic evaluation was unknown for two of the patients.

Among the five patients with BRCA mutations, only one had lobular histology. Additionally, although loco-regional recurrence was observed in a total of 5/16 patients, only 1 patient with mBRCA was observed.

We additionally tested four patients for genomic risk profiling with the MammaPrint assay. Interestingly, three of the patients with “low risk-luminal A” reported tumors while one patient had a “high risk-luminal B” score. Notably, 3/4 patients received a low-risk genomic score based on two different assays. One patient was reported to have high-risk luminal B score; her tumor had lobular histology and was BRCA1/2 wt.

In our cohort, tumor size was > 2 cm in 8/14 (57.1%) patients, and 38.5% were lymph node-positive (one patient had a microscopic lesion, four patients had one lymph node involved, and one patient had three lymph nodes involved). Tumor grade and Ki67 information were missing for most of our cohort. However, of ten patients with available data, none had grade 1 disease, five (50%) had grade 2, and five (50%) had grade 3 disease. These results are in contrast to the CHS cohort in which only 15.9% had grade 3 disease. Small numbers precluded statistical analyses.

Two of the 16 patients were treated with adjuvant chemotherapy. Three patients that were diagnosed with local recurrence received local treatment and chemotherapy at recurrence. All patients received adjuvant hormonal therapy with tamoxifen, and four also received an aromatase inhibitor. Treatment with ovarian ablation was performed in 5/10 premenopausal patients [oophorectomy in two women and Luteinizing hormone-releasing hormone (LHRH) agonist treatment in three].

### Table 2 Clinical and pathologic characteristics of disease recurrence

| Clinical characteristics | BC recurrence and low RS patients (16) |
|--------------------------|----------------------------------------|
| Median (range)           | 44 (17–118)                            |
| Site of recurrence       |                                        |
| Loco-regional            | 5 (1 developed metastases)             |
| Loco-regional and distant metastases | 3                                     |
| Metastatic               | 8                                      |
| Pathology at recurrence  |                                        |
| ER positive              | 8                                      |
| PR positive              | 5                                      |
| Triple negative          | 1                                      |

*Test performed: germline cancer gene panel in five patients, founder mutation tested in two patients, BRCA1/2 test of the tumor in two patients*
Disease recurrence occurred at a median of 44 (range 17–118) months. In five patients, loco-regional lymph nodal recurrence was found and treated with resection, chemotherapy and irradiation. These patients now have no evidence of disease, except one who had subsequent distant metastatic disease. In the patients with local recurrence, one underwent mastectomy and four underwent lumpectomy with sentinel lymph node biopsy upon disease recurrence.

Importantly, among 11 patients with distant recurrence, two also had local lymph node disease. Only one of seven patients with axillary lymph node recurrence had a positive sentinel lymph node biopsy (SLNB); six patients had a negative SLNB. Of ten patients with available pathology at recurrence, one was triple negative and three others were PR (progesterone receptor) negative at recurrence. Clinical and pathologic characteristics are described in Table 2.

Outcomes of metastatic disease are shown in Fig. 1. All 12 patients with metastatic ER-positive disease were treated with aromatase inhibitors (1), fulvestrant (1) or both (8), combined with the biologic agents everolimus (in 3 cases) and CDK 4/6 inhibitor (in 7 cases) for a median of 15 (4–55) months and 2-year PFS of 44%. Ten patients that were treated with chemotherapy for metastatic disease had a heterogeneous response. Only two patients experienced a complete response to chemotherapy, specifically carboplatin; both were BRCA positive (one with a germline BRCA1 mutation and one with a somatic BRCA2 deletion).

**DISCUSSION**

We report 16 patients with hormone-positive, low ODX score (RS ≤ 20) breast cancer who developed early disease recurrence. We additionally tested four samples with the MammaPrint assay, three of which were luminal A low-risk score while only one was luminal B high-risk score. The overlap in risk stratification using two different assays was remarkable and suggests that both tests could not identify these patients as having high risk for recurrence. The one patient with discordant results had lobular histology and was BRCA1/2 wt. Due to the small (4) number of patients with both assays, care
must be exercised when interpreting these results.

Next, we referenced this cohort to data available on early breast cancer in the general Israeli population using data published from the Clalit Health Services. Three subgroups are highly represented in our series: premenopausal age at diagnosis, BRCA mutations and ILC pathology. Interestingly, there was no apparent overlap between mBRCA1/2 and lobular histology.

The major limitation of this study is its descriptive and observational nature. Of note, the clinical data for the full cohort of patients who underwent the ODX assay at our institution were not available, critically including treatment failure. As such, they were not used for direct comparison with the study cohort. Our study must therefore be viewed as descriptive and observational in nature and not comparative. Additionally, the major limitation of our study is the small size of our cohort. One cannot derive any final conclusions based on such a limited number of patients. However, we are unaware of a study in a similar population of woman with low RS and disease recurrence. Despite its limitation as a descriptive study, the extremely high incidence of ILC and BRCA 1/2 mutations is striking. This is presumably due to the discordant molecular and genetic signature of classic IDC to ILC and BRCA mutant HR-positive Her2 negative EBC. Further studies are warranted.

The high frequency of BRCA mutated tumors, either germline or somatic, in our cohort suggests BRCA status is possibly an additional factor determining the need for adjuvant chemoendocrine treatment among patients with ER-positive breast cancer. Up to 10% of BC can be attributed to pathogenic mutations in BRCA 1/2 genes [18, 19]. A recent metaanalysis including 105,220 patients with EBC showed a germline BRCA mutation in 3.4%. This study also demonstrates a poorer OS than in BRCA-negative patients [20]. The incidence of BRCA 1/2 carriers among Israeli EBC patients is known only for women of Ashkenazi Jewish descent and not the whole population. Similarly, since the age of the patients included in the Clalit cohort was relatively high, the percentage of BRCA carriers is expected to be disproportionately low. Therefore, a direct comparison of BRCA carriers in Israeli women with EBC was unavailable. However, using the above-mentioned metaanalysis, we found a much higher incidence of total BRCA mutations of 35.7% (5/14 evaluable patients), including 21% germline (3/14) and somatic (in 2), than expected.

We and others previously showed that in BRCA1/2 carriers, RS is significantly higher than in the general population [13] including a threefold increase of RS > 25 and above. Taken together, these findings suggest that hormone-positive breast cancer among BRCA carriers is biologically different than in non-carriers. Indeed, higher response to DNA-damaging agents, including platinum compounds and PARP inhibitors, was reported among carriers [21]. Whether mutation status accounts partly for the higher benefit from adjuvant chemotherapy observed among young breast cancer patients in the TailorX is of interest. The use of oncotype among BRCA1/2 carriers requires further validation. Of note, in our cohort, two patients with BRCA mutations experienced an extended complete response to chemotherapy, suggesting they might have been cured with adjuvant chemotherapy. Therefore, BRCA1/2 mutation analyses, especially in young patients, should be part of evaluation and decisions regarding adjuvant chemotherapy or PARP inhibitors in these patients.

The population in our cohort was significantly younger than in the Clalit cohort. TailorX, RxPONDER and MINDACT are all prospective studies which investigated the prognostic and predictive value of mRNA expression based on genomic tests. While all of them suggest low risk of recurrence and benefit from chemotherapy in those with low recurrence tumors, they failed among patients under 50 years. A gain in OS of 1.6% in those with RS of 16–20 and 6.5% in those with RS of 21–25 was found in the TailorX [4]. Similar results were recently reported from the RxPONDER study in a population of node-positive low RS scores. These data show no benefit of adjuvant chemotherapy in postmenopausal women with...
intermediate RS (21–25), yet a small but significant survival advantage was shown in the same group of premenopausal women [9]. A subgroup analysis of the premenopausal cohort in the MINDACT study also found a significant benefit of approximately 5% in disease-free survival with chemotherapy in premenopausal BC patients. It was argued that this benefit is due to ovarian suppression induced by the chemotherapy [4]. Considering these results, the strikingly young median age of our cohort is now expected. Therefore, additional molecular subtyping is required to better tailor adjuvant treatment in premenopausal women. The strikingly high rate of BRCA 1/2 driven tumors may in part explain the younger overall age of our cohort.

Invasive lobular carcinoma (ILC) accounts for 5–15% of all EBCs. Although the TailorX results were not stratified by histologic subtypes, Wang et al. analyzed data available for the SEER database. They reported a 10.8% incidence of ILC [5], and the CHS cohort reported an incidence of 14%. Among our patients with low RS and disease recurrence, a remarkable percentage (54%) had lobular histologic features.

ILC consists of several different subtypes: classic, alveolar, solid, tubulo-lobular and pleomorphic. Histologically, they are characterized by a lack of staining for E-cadherin, an adhesion molecule on the surface of cells. Lobular tumors are more likely to be luminal A type expressing high levels of ER and PR with low histologic grades [22] and low levels of proliferation rates [23]. Clinically, lobular carcinoma has a different metastatic course than invasive ductal carcinoma to unique sites such as the gastrointestinal tract, peritoneal spread and the contralateral breast. Despite advances in research on ILC as a distinct feature, most of it focuses on the most common type, i.e., classic invasive lobular carcinoma. Genomic profile of ILC showed mutation alternations similar to those seen in other subtypes of ILC including 16q loss, 1q gain, CDH1, PIK3CA, ERBB2, RUNX1 and CBFB.

Multiple recent studies have reported a discrepancy in RS of ILC relative to IDC [23]. Kizy et al. reported a high incidence of low and intermediate RS in ILC. Interestingly they showed that while a high recurrence score was shown to have prognostic significance, intermediate and high-risk patients treated with adjuvant chemotherapy did not show a significant survival benefit [14]. Another recent study showed that ILC was three times less likely than IDC to receive a high RS [24].

While there is often a good response to hormonal treatment in ILC, evidence suggests a low response rate to chemotherapy, with various studies reporting 0–11% pathologic complete response (pCR) after neoadjuvant chemotherapy [25]. Similarly, long-term outcomes of ILC were worse than those of IDC [26]. Indeed, our metastatic ILC patients initially responded to endocrine therapy; the response to chemotherapy was varied but generally short lived. Interestingly, one patient had a somatic loss of BRCA2 and a long complete response to carboplatin.

Our findings underline the need to differentiate clearly between ILC and other subtypes of breast cancer. Much recent literature has highlighted the unique clinical and molecular profile of ILC. We suggest that the use of genomic tests such as ODX to guide treatment decision may require further validation in ILC.

CONCLUSIONS

Although the cohort described here is small, the data presented suggest that BRCA mutational status, age and lobular subtype should be considered when interpreting the prognostic and predictive value of the ODX recurrence score and MammaPrint Dx. Prudent clinical judgment must be used while determining the need for adjuvant treatment among HR-positive breast cancer patients with low RS in these subgroups. Considering our cohort as well as the multitude of studies showing a clinical and molecular distinction of mBRCA and ILC EBC, we believe stratification of these subgroups in further studies will be critical. Other adjuvant treatments, such as CDK4/6 inhibitors, platinum compounds or PARPi, may be beneficial.
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Compliance with Ethics Guidelines. The study was conducted at the Sharret Institute of Oncology, after approval by the Institutional review board of the Hadassah Medical Organization, IRB approval number HMO 0346-12. Informed patient consent was obtained for genetic analysis for this study as well as publication. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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