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Use of a recurrence score in second breast cancers

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ABSTRACT

Introduction: Systemic treatment for second estrogen receptor positive (ER+) invasive breast cancer is controversial. The Recurrence Score (RS) from the 21-gene breast cancer assay (ODX) is used for adjuvant therapy recommendations in primary, early-stage ER+ disease, but has unknown utility in locally recurrent tumors.

Methods: An IRB-approved, single-institution retrospective chart review of a prospective ODX database of was performed. Most patients had ODX performed on an initial invasive breast cancer (1° Cancer); a minority had ODX performed on an ipsilateral local recurrence (2nd Cancer); none had clinical evidence of concurrent regional or distant metastasis at presentation. Eligibility for the ODX assay was based on NCCN guidelines (1° breast cancer) or physician discretion (2nd cancer). Data collected included demographics, clinical-pathologic variables, surgery type, RS, adjuvant treatment and outcomes. Comparisons between 1° breast cancer and 2nd were made by general linear regression model and the exact Wilcoxon Rank Sum Test.

Results: 594 Patients with 1° breast cancer and 7 patients with 2nd breast cancer had ODX and RS. Median invasive tumor size of both 1° cancer and 2nd cancer was 1.5 (range 0.6–2.0 cm). All 1° and 2nd breast cancers were ER+. Median RS was higher in patients with 2nd cancer [25; range 15–40] compared to 1° cancer [16; range 0–63]($p=0.0084$). Categorically, more 2nd cancer patients had a high RS (37.5%) than those with 1° cancer (8.1%) ($p=0.0136$).

Conclusion: Performance of ODX in ER+, locally recurrent breast cancer (2nd breast cancer) should be considered for prognostication and adjuvant systemic treatment recommendations

Introduction

As one of the most common malignancies in women, breast cancer affects approximately one million women per year worldwide, and causes approximately 40,000 deaths yearly in the United States [1–3]. Given the heterogeneity of the disease, a tailored approach to treatment both locally and systemically has markedly improved outcomes in recent years. Multiple factors including tumor size, hormone receptor status, and overexpression of HER-2/neu have been used as prognostic indicators in terms of local-regional and distant recurrence [4,5]. Although our understanding of molecular mechanisms underlying neoplastic processes has improved, the diagnosis and treatment of cancer continues to rely primarily on histopathological and immunohistochemical approaches [5]. This limited insight may result in over or under-treatment of many breast cancer patients.

Multiple attempts have been made to assign molecular signatures to tumors to better guide individualized treatment. Some of these modalities have been validated [6–8] and are being used to guide the treatment of primary breast cancer. One such method is the Oncotype DX (ODX) assay, a 21-gene breast cancer assay which is used for women with ER+, early stage breast cancer and receiving endocrine therapy [9]. This gene expression assay is based on formalin-fixed, paraffin-embedded (FFPE) tumor specimens, and classifies patients into one of three risk categories – low, intermediate or high – for distant recurrence [8]. ODX was developed with the principle of assigning a molecular signature score, called the Recurrence Score (RS), to individual breast cancers and correlating these findings to a 10-year distant recurrence risk as a measure of prognosis. Additional studies performed using

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this assay confirmed prediction of benefit of adjuvant chemotherapy in patients with a "high-risk" recurrence score. Oncotype DX assay currently is an assay that is both prognostic and predictive of benefit from adjuvant treatment.

Though the use of Oncotype DX has been validated for primary tumors, the prognostic value of this assay with respect to in-breast recurrences has yet to be determined. Furthermore, the treatment of recurrent or new second primary breast cancers remains controversial. Per the most recent NCCN guidelines, multiple treatment options exist for local recurrences. These recommendations vary depending on the time course and prior local and systemic treatment. Surgical resection currently remains the preferred treatment for all scenarios in the absence of concurrent distant metastatic disease [7]. However, the role of systemic therapy in patients with isolated in-breast recurrences is an ongoing area of debate, due to the heterogeneity of the patient population and prior therapy [10]. In light of this uncertainty, and the pitfalls of over- or under-treatment, incorporation of a biologically-based, tumor-driven assay such as ODX may significantly impact the selection of appropriate systemic treatment strategies after certain in breast cancer recurrences.

Methods

This is a retrospective, Institutional Review Board approved study of a prospective clinical Oncotype DX database. All patients received surgical intervention by surgical oncologists at a single tertiary cancer center. Abiding by National Comprehensive Cancer Network (NCCN) and institutional protocols, the ODX assay was discussed with and performed on eligible patients as part of postoperative adjuvant treatment planning. In the interest of clarity, and due to the indeterminate nature of a second breast cancer (new primary versus in-breast recurrence), "2nd cancer" is used to describe all of these lesions while index primary breast cancers are labeled as "initial cancers" for the purposes of this study. Of note, if the patient's first presentation to our institution was for a local recurrence or 2nd breast cancer in the ipsilateral breast, the patient would still be considered for ODX eligibility.

All patients were treated for invasive breast cancer between 2003 and 2012 at a single institution and Oncotype DX was employed for systemic treatment planning. Clinical, pathologic and treatment data points were collected from the patients' medical records. Specific collected data included: date of birth, age, date of diagnosis, gender, menopause status, tumor laterality, type of breast surgery (lumpectomy versus mastectomy), date of surgery, histologic diagnosis and details (tubule, nuclei, mitosis), cancer subtype, grade of cancer, lymphovascular invasion, tumor location, date of local, regional or metastatic recurrence, locations and diagnosis dates of distant disease, treatment type and date of recurrent disease, hormone receptor status, disease status at last follow-up date, and if applicable, date of death.

Type and duration of adjuvant systemic therapy and adherence to hormonal therapy recommendations were also recorded for both initial cancers and 2nd cancers. Adjuvant systemic therapies included chemotherapy and hormonal therapy. Adjuvant radiation was classified as whole/partial breast, chest wall or none. Last follow-up included documentation from surgical oncologists, radiation oncologists and medical oncologists at our institution or from outside physician documentation provided in the medical record. Patients presenting initially with concurrent bilateral breast cancers were excluded.

General linear regression model and the exact Wilcoxon Rank Sum Test were used to compare the RS between initial cancers versus 2nd cancers.

Results

594 patients with initial breast cancers and 8 patients with 2nd cancers (local recurrence vs new primary in a previously treated breast) had documented RS. Recurrence Scores from the 8 patients with 2nd cancers were obtained on the 2nd cancer. One patient in this group had the assay done on both the initial and 2nd cancer and thus was eliminated from the analysis, leaving 7 patients. None of the patients received neoadjuvant chemotherapy for their second/recurrent tumor. The median age of patients at the time of the assay was 58 years (range 27–84) for the initial cancer group and 58.5 years (range 36–63) for the 2nd cancer group ($p=0.411$), respectively. The majority of patients (6/7, 85.8%) with a 2nd cancer had a prior history of breast conservation and received a mastectomy as surgical treatment of the second cancer (Table 1). Median invasive tumor size of initial cancers was 1.5 cm and for second cancers was 1.4 cm; all were ER(+). One 2nd cancer was invasive lobular carcinoma, otherwise all documented initial and 2nd breast cancers had ductal histology. For 2nd cancers, median time from initial breast cancer surgery to diagnosis with a 2nd breast cancer was 92 months (range 13–120) (Tables 2–6).

As a continuous variable, the median RS was significantly higher in patients with 2nd cancers at 22 (range 15–37) compared to initial cancers at 16 (range 0–63) (p-value$=0.03$). Categorically, more 2nd cancer patients had a high RS (28.6%) than those with initial cancers (8.1%), but this was not statistically significant ($p=0.08$). Tumor size, nodal status, degree of ER expression, nuclear grade, number of mitoses, and compliance with endocrine therapy were not significantly different between patients with 2nd cancers compared to those with initial cancers.

Mean follow-up time for initial breast cancers was 37.2 (range 1.2–116.4 months); for the 2nd cancer group, mean follow-up from the 2nd cancer was 44.04 months (range 32.6–66.8 months). For all patients, overall survival was better in patients with initial breast cancers compared to those with 2nd tumors ($p<0.0001$). Due to insufficient events, overall survival stratification by chemotherapy use could not be performed. However, there was a significant difference in overall survival between primary and 2nd cancers in patients that did not receive chemotherapy ($p<0.0001$;

Table 1
Features of second cancer cohort (N=7). DCIS: ductal carcinoma in situ; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma.

Pt #	Original histology	Recurrent histology	Primary surgery	Recurrent surgery	Time to recurrence (mos)	RS of recurrence	Chemotherapy recommended
1	IDC+DCIS	IDC+DCIS	Lumpectomy	Mastectomy	13	15	No
2	DCIS	IDC+DCIS	Lumpectomy	Lumpectomy	60	37	Declined
3	IDC	IDC	Lumpectomy	Mastectomy	120	28	Yes
4	Unknown	IDC	Lumpectomy	Mastectomy	92	22	No
5	IDC	ILC	Partial mastectomy	Mastectomy	120	31	Yes
6	DCIS	IDC+DCIS	Mastectomy	Excision	29	18	No
7	DCIS	IDC+DCIS	Lumpectomy	Mastectomy	120	17	Yes