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Oncotype DX in Bilateral Synchronous Primary Invasive Breast Cancer

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Abstract

Background—Synchronous bilateral breast cancers (BC) frequently share the same estrogen receptor (ER) status, yet may differ in other histopathologic features. We sought to examine concordance rates of Oncotype DX (RS) testing in women with synchronous bilateral ER-positive BC.

Methods—Institutional databases were reviewed to identify patients with synchronous (within 6mos) bilateral primary invasive BC and multiple RS. RS were stratified by risk group (RS<18, low; RS 18–30, intermediate; RS 31, high) and considered discordant if they reflected different risk groups.

Results—From 2005–2014, 115 patients presented with synchronous bilateral invasive BC; 43 (37%) had 2 RS available. Median patient age was 60yrs (42–84); median tumor size was 1.2cm (0.5–3.7), all cases were HER2 negative and node negative. Of 86 RS, 63 (73%) were low risk, 23 (23%) intermediate risk, and 3 (3%) high risk. RS were concordant in 29 (67%) patients. Patients with concordant RS were older (62yrs versus 56yrs) and had median levels of PR expression that were higher and more similar—80% and 85% for bilateral cancers, respectively—as compared to 55% and 75% for bilateral cancers in discordant cases. Discordant RS led to a treatment change in 8/14 (57%) cases.

Conclusions—Among women with synchronous bilateral ER+ HER2- breast cancer, RS were concordant in 67% of cases. Concordance rates may be higher in older women or among those with comparable levels of PR expression. These data suggest that testing of both tumors should be considered in patients who are candidates for adjuvant chemotherapy.

Keywords

bilateral breast cancer; Oncotype DX

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INTRODUCTION

The 21-gene recurrence score, Oncotype DX (Genomic Health, Redwood City, CA) is widely used to assess risk of recurrence and benefit from chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.^{1,2} The 21-gene assay, which measures the relative levels of expression of genes associated with proliferation, invasion, HER2, and estrogen receptor, provides a single recurrence score which corresponds to a point estimate of the 10-year risk of distant recurrence with a 95% confidence interval.³ The prognostic value of this assay has been demonstrated in clinical trials of both node-negative and node-positive breast cancer, and numerous studies have shown that the Oncotype DX recurrence score (RS) affects clinical decision making.⁴⁻⁶

The incidence of synchronous bilateral invasive breast cancer is reported to range from 0.8%–3.0%; largely reflecting differing definitions used for synchronous diagnoses, with cutoffs ranging from within 3–12 months of initial diagnosis.^{7,8} Currently, there are no consistent evidence-based guidelines for the management of synchronous bilateral breast cancer, and treatment decisions are often made based on the primary tumor with the most high-risk features. However there is often considerable similarity in standard histopathologic features and hormone receptor status, making it difficult to differentiate how long-term prognosis is impacted by the presence of two primary tumors. The aim of this study was to determine the concordance rate for RS testing in women with synchronous bilateral primary breast cancer, and to identify clinical and pathologic features predictive of discordant recurrence scores in this population.

METHODS

Prospective institutional databases were retrospectively reviewed to identify patients presenting to Memorial Sloan Kettering Cancer Center (MSKCC) with synchronous bilateral invasive breast cancer from January 2005 to June 2014. This time period was chosen as RS testing for patients with estrogen receptor-positive, HER2 negative, node-negative breast cancer was incorporated into standard clinical practice at our institution in 2005. Estrogen receptor positivity was defined as greater than or equal to 1% nuclear staining. Bilateral invasive diagnoses were considered synchronous if they occurred within 6 months of each other. Patients with a personal history of breast cancer, those with node-positive disease, and those with only one RS were excluded. This study was approved by the institutional review board.

Patient, tumor, and treatment characteristics were abstracted from the medical record. RS were categorized by risk group as originally described: RS < 18, low risk; RS 18–30, intermediate risk; and RS ≥ 31, high risk.³ Patients were considered to have discordant RS if the bilateral tumor RS reflected different risk groups. Comparisons were made between patients/tumors with concordant and discordant risk scores. Due to limited sample size, all analyses are descriptive.

RESULTS

From January 2005 to June 2014, 115 patients presented with synchronous bilateral primary invasive breast cancer; 43 (37%) of whom met eligibility criteria and had 2 RS available. Patient and bilateral breast tumor characteristics are shown in Table 1. Median patient age was 60 years (range 42–84 years), and median tumor size was 1.2 cm for both primary tumors, with minor differences in the range (0.6–3.7 and 0.5–3.1, respectively). The majority of cases represented invasive ductal carcinomas with a similar distribution of progesterone receptor positivity, nuclear grade, and histologic grade between bilateral breast primaries. All cases were node negative; however, lymphovascular invasion was identified in 7% and 21% of bilateral tumors, respectively. Among 86 primaries, 63 (73%) were categorized as low risk, 20 (23%) were categorized as intermediate risk, and 3 (4%) were categorized as high risk by RS testing. There was no difference in median RS between the two groups of primary (bilateral) tumors (Table 1).

RS were concordant in 29 patients (67%). Table 2 illustrates the concordance rates for each risk group. There was no significant association between any clinical or histopathologic feature and the likelihood of having concordant or discordant recurrence scores; however, patients with concordant RS were older (62 years versus 56 years) and had median levels of progesterone receptor expression that were higher and more similar when compared to those with discordant scores (Table 3).

RS were ordered at the same time in 34 (79%) patients and in a staged manner in the remaining 9 patients, with no difference in rates of discordance between the two groups (Table 3). The median time between RS testing for those performed in a staged manner was 31 days. Among the 14 patients with discordant scores, 3 had testing performed in a staged manner, and the second score reflected a higher risk group in all 3 cases, leading to a treatment change (recommendation for chemotherapy) in 2 of 3 cases. The time interval between testing in these 3 cases was 3 weeks, 3 weeks, and 10 weeks, respectively. Overall, treatment recommendations were affected by the higher of the two RS in 8 of 14 (57%) patients with discordant risk group scores (Table 4) or 18.6% of the study population (8/43).

DISCUSSION

There are no consistent evidence-based guidelines for the management of synchronous bilateral breast cancer, and treatment decisions are often made based on the primary tumor with the most high-risk features (i.e., hormone receptor status, HER2 status, size, grade, LVI, and others). In the setting of bilateral ER positive, HER2 negative, node-negative breast cancer, this distinction may be difficult as the tumors may appear quite similar by standard histopathologic criteria. There is now a large body of data supporting the use of the 21-gene RS to predict benefit from chemotherapy in the setting of unilateral disease¹⁻⁶; however, published data regarding the RS in the setting of multiple synchronous breast cancers are limited to a single study by Toole et al demonstrating that 2 of 4 (50%) of patients with multiple primary tumors in different breasts, and 4 of 18 (22%) of patients with multiple primaries in the same breast, had RS differences that led to changes in management.⁹ Here we demonstrate that RS were discordant in 33% of women with

estrogen receptor-positive, HER2 negative, node-negative, synchronous bilateral invasive breast cancer, leading to a change in treatment in 57% of these patients. To our knowledge, this is the only study to date examining concordance rates specifically in this population.

Since the first publication of a case series of synchronous bilateral breast cancer by Kilgore in 1921¹⁰, there has been ongoing debate regarding the prognostic significance of bilateral disease. The concept of a time interval to distinguish between synchronous and metachronous bilateral breast cancer was first introduced by Haagensen in 1971.¹¹ He used 6 months as the cutoff for distinguishing these two categories; however, since then, various cut-points have been used to define synchronous bilateral breast cancer, ranging from 0–60 months, making it difficult to draw firm conclusions regarding the impact of bilateral disease on long-term outcomes.¹² Hartman et al¹³ analyzed incidence and mortality rates for bilateral breast cancer in a large nationwide cohort of 123,757 breast cancer patients in Sweden. Compared to women with unilateral disease, women with synchronous bilateral breast cancer (SBBC), defined as a contralateral diagnosis within 3 months, experienced inferior breast cancer specific mortality at 10 years, 45% (95% confidence interval [CI], 41.4–48%) and 33% (95% CI, 32.8–33.5%), respectively, and this difference was strongly influenced by age, whereby a diagnosis of SBBC under 50 years of age was associated with a 120% higher mortality rate when compared to women with unilateral disease. For women with metachronous bilateral breast cancer, the mortality risk was largely dependent on the time interval between the two diagnoses, with those diagnosed more than 10 years later having similar 5-year breast cancer mortality to that of women of the same age with unilateral disease.

A large meta-analysis of 17 studies from 11 different countries, including 8050 synchronous bilateral breast cancers, defined as contralateral diagnosis within 6 months, also reported inferior outcomes for women with SBBC.¹⁴ After adjusting for other known prognostic factors, the diagnosis of synchronous bilateral breast cancer was associated with a pooled HR of 1.37 (95% CI, 1.24–1.50; $p < 0.0001$) for breast cancer mortality compared to unilateral disease. However, among the 4 studies included in the meta-analysis that used a matched approach to compare prognosis between SBBC and unilateral breast cancer, no difference in disease-specific survival was observed⁽¹⁵⁻¹⁸⁾, and in the sensitivity analysis of studies that included lymph node status as a covariate, there was also no difference in breast cancer mortality (pooled HR, 1.18; 95% CI, 0.95–1.48).¹⁴ The overall estimate of increased breast cancer mortality for patients with SBBC in this dataset does suggest, however, that there is room for improvement in determining appropriate adjuvant treatment for this patient subset.

In this study, we defined bilateral breast cancer as synchronous if the 2 diagnoses occurred within 6 months of each other; yet the majority of cases (39 [91%]) were diagnosed at the same time, and the remaining 4 (9%) were diagnosed within a 3-month window. This observation likely reflects the increased use of breast MRI for extent of disease in patients with newly diagnosed breast cancer during the time period of this study. It is generally assumed that synchronous bilateral breast cancer represents 2 clonally independent malignancies—a hypothesis that has been tested in clonality experiments by several different groups.¹⁹⁻²¹ However, given the conflicting studies reporting outcome differences

for women with unilateral versus bilateral breast cancer, it is plausible that a small proportion of these cases represent early metastatic events.¹⁶⁻¹⁸ The ability to develop multiple tumors simultaneously may also be suggestive of an underlying genetic variation or susceptibility to malignancy, and some studies of patients with synchronous bilateral breast cancer have suggested a relationship between family history and bilaterality; however, others have not confirmed this finding.²²⁻²⁴

Multiple primary breast cancers share the same host, the same history in regards to metabolic changes, and the same exposure to external influences, yet there are limited data on how these shared characteristics impact concordance in regard to the molecular portrait of tumors. Buggi et al examined 113 multiple (multicentric and multifocal) breast cancers of the same histologic subtype and found differences in grade (18.8%), estrogen receptor status (4.4%), progesterone receptor status (15.9%), and HER2 status (9.7%) in a minority of cases.²⁵ In an analysis of 12 patients with synchronous bilateral breast cancer Saad et al reported similar histologic subtype in 58% of the cases, and similar estrogen receptor, progesterone receptor, and HER2 status in 67% of cases.²⁶ Similar findings were reported by Hungness et al and Coradini et al.^{27,28} Although we selected our patients to have bilateral estrogen receptor-positive, HER2 negative, node-negative breast cancer, there was no significant difference in other traditional markers, such as histologic subtype, size, and grade when comparing the bilateral breast tumors, nor did we observe a significant difference in any of these parameters between tumors with concordant and discordant RS. We did observe a trend for patients with concordant RS to be older (62 years of age versus 56 years) and to have median levels of progesterone receptor expression that were higher and more similar between the two primary tumors when compared to those with discordant scores; however, this finding awaits confirmation in a larger dataset (Table 3).

Toole et al also examined factors associated with discordant RS.⁹ Among 22 patients with either bilateral breast cancer (n=4) or multiple primaries in the same breast (n=18), 8 patients had discordant RS. In the Toole dataset, cases with discordant scores were more likely to differ in tumor histology (p=0.05) and tumor grade (p=0.04) than concordant cases. In patients with concordant scores, tumor histology and grade differed in 18.8% and 6.3% of cases, respectively, as compared to 66.7% and 50% of cases for those with discordant scores. Although not statistically significant, tumors with different RS were also more likely to differ in progesterone receptor status (33.3% vs 18.8%).

In our study, a change in chemotherapy recommendation based on the result of the second RS was made in 8 of 14 cases (57%). In all cases, patients who would have not received chemotherapy based on one tumor score received chemotherapy due to a higher second score. In the cases with discordant RS and no treatment change (6 patients), 4 patients received chemotherapy either due to one of the tumors having a high RS or physician/patient choice, and 2 patients whose bilateral tumors had low and intermediate RS, respectively, received endocrine therapy alone. Changes in treatment recommendations based on discordant RS were also reported by Toole et al where different scores led to a treatment change in 2 of 4 (50%) patients with bilateral disease and 4 of 18 (22%) patients with multiple tumors in the same breast.

In conclusion, Oncotype DX recurrence scores were discordant in 33% of women with estrogen receptor-positive, HER2 negative, node-negative, synchronous bilateral invasive breast cancer; leading to a change in treatment in 57% of these patients. To our knowledge, this is the only study to date examining concordance rates specifically in this population. Given our small sample size, we were unable to find significant clinical or pathologic predictors of discordant results, yet given the high rate of discordance, with the potential for a change in treatment recommendation and the controversy surrounding the prognostic impact of bilateral disease, these data suggest that testing of both tumors should be considered in patients with synchronous bilateral breast cancer who are candidates for adjuvant chemotherapy.

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Synopsis

Oncotype DX testing of synchronous bilateral breast cancers yields different risk group scores in approximately 30% of patients; suggesting that testing of both tumors should be considered in patients who are candidates for adjuvant chemotherapy.

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TABLE 1

Patient and tumor characteristics (n=86)

	Right breast n=43 n (%)	Left breast n=43 n (%)
Age, years, median (range)	60 (42–84)	60 (42–84)
Tumor size, cm (range)	1.2 (0.6–3.7)	1.2 (0.5–3.1)
ER-expression, %, median (range)	95 (40–100)	95 (50–100)
PR-expression, %, median (range)	80 (0–95)	80 (0–100)
Oncotype DX recurrence score, median (range)	15 (0–35)	12 (2–29)
Subtype		
ER+/PR+/HER2–	40 (93%)	41 (95%)
ER+/PR–/HER2–	3 (7%)	2 (5%)
Histology		
IDC	33 (77%)	35 (81%)
ILC	6 (14%)	5 (12%)
Other *	4 (9%)	3 (7%)
Nuclear grade		
1	6 (14%)	8 (19%)
2	24 (56%)	21 (49%)
3	2 (5%)	6 (14%)
Missing	10 (23%)	8 (19%)
Histologic grade		
1	5 (12%)	6 (14%)
2	13 (30%)	16 (37%)
3	19 (44%)	18 (42%)
Missing	6 (14%)	3 (7%)
Multifocality		
Yes	34 (79%)	31 (72%)
No	9 (21%)	12 (28%)
LVI		
Present	3 (7%)	9 (21%)
Absent	36 (84%)	32 (74%)
Missing	4 (9%)	2 (5%)
Oncotype DX risk		
Low	27 (63%)	36 (84%)
Intermediate	13 (30%)	7 (16%)
High	3 (7%)	0 (0%)

ER, estrogen receptor; PR, progesterone receptor; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion

* tubular and mucinous carcinomas

TABLE 2

Oncotype DX concordance by risk group

Oncotype DX risk right breast	Oncotype DX risk left breast	
	Low (n=36)	Intermediate (n=7)
Low (n=27)	25	2
Intermediate (n=13)	9	4
High (n=3)	2	1

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TABLE 3

Characteristics of concordant and discordant cases

	Concordant Oncotype DX (n=29)	Discordant Oncotype DX (n=14)
	Median (range)	Median (range)
Age (years)	62 (48–84)	56 (42–72)
Tumor 1 size (cm)	1.2 (0.6–3.3)	1.2 (0.6–3.7)
Tumor 2 size (cm)	1.2 (0.5–2.2)	1.1 (0.8–3.1)
ER-expression 1 (%)	98 (40–100)	95 (70–100)
ER-expression 2 (%)	95 (60–100)	96 (50–100)
PR-expression 1 (%)	85 (0–99)	55 (0–98)
PR-expression 2 (%)	80 (0–100)	75 (0–95)
	n (%)	n (%)
Subtype		
ER+/PR+/HER2–	24 (84%)	12 (86%)
ER+/PR–/HER2–	5 (17%)	2 (14%)
Histology		
Concordant	21 (72%)	10 (71%)
Discordant	8 (28%)	4 (29%)
Nuclear grade		
Concordant	12 (41%)	4 (29%)
Discordant	10 (35%)	4 (29%)
<i>Missing</i> *	7 (24%)	6 (42%)
Histologic grade		
Concordant	11 (38%)	8 (58%)
Discordant	13 (45%)	3 (21%)
<i>Missing</i> *	5 (17%)	3 (21%)

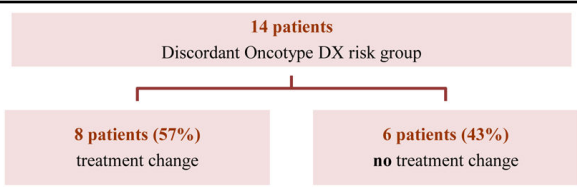
ER, estrogen receptor; PR, progesterone receptor

* due to invasive lobular carcinoma and lack of reporting in those subtypes

TABLE 4

Oncotype scores among those with discordant risk-group scores

Oncotype DX Recurrence Score	Predicted 10yr Risk of Recurrence, %	Risk Group	Recommended Treatment Change
13 22	8 14	Low Intermediate	No
2 34	4 23	Low High	Yes
32 24	21 15	High Intermediate	No
18 and 8 10	8 7	Intermediate Low	Yes
35 13	24 8	High Low	No
3 19	4 12	Low Intermediate	No
11 22	7 14	Low Intermediate	Yes
20 0	13 3	Intermediate high	yes
13 19	9	Low Intermediate	Yes
21 12	14 8	Intermediate Low	Yes
18 11	11 7	Intermediate Low	Yes
19 4	12 4	Intermediate Low	Yes
19 10	12 7	Intermediate Low	No
18 12	12 8	Intermediate Low	No



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