Original Study

The Impact of the Oncotype DX Breast Cancer Assay on Treatment Decisions for Women With Estrogen Receptor-Positive, Node-Negative Breast Carcinoma in Hong Kong

Roland C.Y. Leung,[1] Thomas C.C. Yau,[1] Miranda C.M. Chan,[2] Sharon W.W. Chan,[3] Terence W.C. Chan,[4] Yvonne Y.Y. Tsang,[5] Ting Ting Wong,[5] Calvin Chao,[6] Carl Yoshizawa,[6] Inda S. Soong,[7] Wing-Hong Kwan,[8] Carol C.H. Kwok,[9] Joyce S.J. Suen,[10] Roger K.C. Ngan,[11] Polly S.Y. Cheung[12]

Abstract

We evaluated the impact of the Oncotype DX assay on adjuvant treatment decisions for Chinese patients with breast cancer in Hong Kong. A comparison of pre-assay and post-assay recommendations demonstrated use of the information for treatment recommendations, resulting in a 27% decrease in chemotherapy usage. In approximately 30% of cases, physicians in the multidisciplinary committee agree/strongly agree that the assay influenced their decision.

Background: The Oncotype DX Breast Cancer Assay is validated to assess risk of distant recurrence and likelihood of chemotherapy (CT) benefit in estrogen receptor-positive ESBC in various populations. In Hong Kong, > 80% of breast cancers are early stage breast cancer (ESBC) and > 60% of these women receive CT. This prospective study measured changes in CT type and recommendations, as well as physician impression of assay impact in a homogenous Chinese population. **Methods:** Consecutive patients with estrogen receptor-positive, T1-3 N0-1mi M0 ESBC were offered enrollment. After surgery, physicians discussed treatment options with patients, then ordered the assay, then reassessed treatment recommendation considering assay results. Changes in treatment recommendation, CT utilization, physician confidence, and physician rating of influence on their treatment recommendations were measured. **Results:** A total of 146 evaluable patients received pre- and post-testing treatment recommendations. CT recommendations (including changes in intensity of CT) were changed for 34 of 146 patients (23.3%; 95% confidence interval, 16.7%-31.0%); change in intensity occurred in 7 of 146 (4.8%). There were 27 changes in treatment recommendations of adding or removing CT altogether (18.5% change; 95% confidence interval, 12.6%-25.8%). CT recommendations decreased from 52.1% to 37.7%, a net absolute reduction of 14.4% ($P < .001$; 27.6% net relative reduction). Pre-assay, 96% of physicians agreed/strongly agreed that they were confident in their treatment recommendation; post-assay, 90% of physicians agreed/strongly agreed with the same statement. Thirty percent of physicians agreed/strongly agreed that the test had influenced their recommendation, similar to the proportion of changed recommendations. **Conclusions:** The Oncotype DX Assay appears to influence physician ESBC adjuvant treatment recommendations in Hong Kong.

Clinical Breast Cancer, Vol. 16, No. 5, 372-8

Keywords: Adjuvant drug therapy, Decision support techniques, Molecular diagnostic techniques, Neoplasms, Risk assessment

R.C.Y.L. and T.C.C.Y. contributed equally to this work as first authors.

[1]Division of Medical Oncology, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Breast Centre, Kwong Wah Hospital, Hong Kong
[3]Kowloon East Cluster Breast Centre, United Christian Hospital, Hong Kong
[4]New Territories Cluster Breast Centre, Northern District Hospital, Hong Kong
[5]St. Paul's Hospital, Hong Kong
[6]Genomic Health, Inc, Redwood City, CA
[7]Pamela Youde Nether Sole Eastern Hospital, Hong Kong
[8]Hong Kong Sanatorium and Hospital, Hong Kong
[9]Princess Margaret Hospital, Hong Kong
[10]Prince of Wales Hospital, Hong Kong
[11]Queen Elizabeth Hospital, Hong Kong
[12]Breast Care Centre, Hong Kong Sanatorium and Hospital, Hong Kong Breast Cancer Foundation, Hong Kong

Submitted: Nov 23, 2015; Revised: Mar 6, 2016; Accepted: Mar 9, 2016; Epub: March 17, 2016

Address for correspondence: Polly S.Y. Cheung, MBBS, Breast Care Centre, Hong Kong Sanatorium and Hospital, Hong Kong
E-mail contact: pollyc@pca.hk

http://dx.doi.org/10.1016/j.clbc.2016.03.002

Introduction

The breast cancer burden in Asia represents one-third of the global burden from this disease.[1] Indeed, in Hong Kong, invasive breast cancer is the most common cancer among women, with an incidence of 91.7 per 100,000 in 2012.[2] Of the cases of breast cancer in Hong Kong, early stage breast cancer (ESBC, defined as stages 0 to II) is the most commonly diagnosed, accounting for > 80% of cases. Tumors that are stage II, hormone receptor-positive, and HER2-negative represent the largest proportion.[3]

Treatment decision-making for women with ESBC disease continues to be challenging. In Hong Kong, the majority of women with breast cancer receive adjuvant therapy: 60.8% receive combination chemotherapy (CT), and 66.7% receive hormonal therapy (HT) following surgery.[2,4] However, adjuvant CT yields only a small reduction of risk of recurrence.[5] Given that CT benefits a small proportion of ESBC patients, it would be ideal if CT could be targeted to those women at highest risk of recurrence, sparing those women who would not benefit from adjuvant chemotherapy. Identifying these women using traditional clinicopathologic criteria is imprecise.

The Onco*type* DX Breast Cancer Assay has been validated to assess the risk of distant recurrence and predict the likelihood of CT benefit in patients with estrogen receptor-positive (ER^+), HER2-negative, lymph node-negative breast cancer. The Onco*type* DX test yields a Recurrence Score result between 0 and 100, which can be used to categorize patients into low- (< 18), intermediate- (18-30), and high-risk (> 30) groups. The prognostic and predictive significance of the test has been validated in several studies,[6-13] and its use is now incorporated into international breast cancer treatment guidelines.[14-18]

Currently in Hong Kong, the decision to give adjuvant CT depends on a combination of clinical, biologic, and pathologic factors, which are often evaluated in the multidisciplinary committee (MDC) setting. In this model, cases are reviewed by health care professionals from several disciplines, including surgery, oncology, and pathology, in an effort to optimize the treatment plan for each patient. An initial retrospective, single-center assessment of the influence of genomic technologies, such as the Onco*type* DX Breast Cancer Assay, on the decision to administer adjuvant therapy in a Chinese population recently suggested the assay would help inform patient treatment decisions.[19] The purpose of this study was to extend those findings through prospective evaluation of the influence of the assay on MDC adjuvant treatment decisions at multiple centers in Hong Kong and to characterize the nature of that influence.

Methods

Study Design

This single-arm prospective study was conducted at 6 institutions in Hong Kong: Hong Kong Sanatorium and Hospital, Kwong Wah Hospital Breast Center, United Christian Hospital Kowloon East Cluster Breast Center, Pamela Youde Nether Sole Eastern Hospital, St. Paul's Hospital, and Northern District Hospital - New Territories Cluster Breast Center. Eligible physicians included oncologists and surgeons who represent the MDC in interactions with patients with breast cancer (treating physicians). Eligible patients included women between 18 and 69 years of age who have ESBC (T1-2 N0 including N0(+i); T1pN1mic) that is ER^+ and does not overexpress HER2. Additional patient eligibility requirements include Eastern Cooperative Oncology Group performance score of 0 or 1, and tumor sample adequate for Onco*type* DX testing as determined by central review at Genomic Health, Inc.

Following surgery and pathology assessment, participation was offered to consecutive eligible patients at the first post-surgery visit. Consenting patients discussed their treatment plan with the treating physician, and the cases were then presented at the MDC. The MDC consensus treatment recommendations were used to complete the pre-Onco*type* DX treatment recommendation, then the physician completed the remaining questionnaire items and the test was ordered. Upon receipt of the test result, the case was reviewed again by the MDC, and a second treatment recommendation was made. At the second study visit, the treating physician reviewed the post-assay treatment recommendation from the MDC with the patient. The treating physician then completed the post-Onco*type* DX questionnaire, recording the revised MDC recommendation and their responses to the additional questionnaire items.

The primary objective of this study was to characterize the effect of the Onco*type* DX Recurrence Score result on physicians' treatment recommendations, as informed by the MDC, by measuring changes in these recommendations from before testing to after testing. In addition, the changes in confidence of the treating physician in their treatment recommendation from before to after testing were assessed.

Ethics Committees at each institution approved the study protocol. All subjects signed informed consent prior to enrollment in the study.

Physician Questionnaires

The pre-assay questionnaire was answered by the treating physician after the first study visit. The questionnaire assessed the pre-assay treatment recommendation from the MDC, as well as the physician's confidence in the treatment decision. The intensity of the CT regimen recommended (as defined on the Adjuvant! Online website[20]) was recorded. Examples of low-intensity regimens included cyclophosphamide, methotrexate, and fluorouracil (CMF), doxorubicin and cyclophosphamide (AC), taxotere and cyclophosphamide (TC), or comparable regimens; examples of intermediate intensity regimens included 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC)/5-fluorouracil, epirubicin, and cyclophosphamide (FEC) × 6, AC × 4, and paclitaxel × 4 in 3 weekly cycles, or comparable regimens; examples of high-intensity regimens included dose-dense AC then paclitaxel; docetaxel, doxorubicin, and cyclophosphamide (TAC) or FEC/FAC × 3 then docetaxel × 3 or comparable regimens. The post-assay questionnaire was completed by the treating physician following a second MDC meeting and second study visit. The revised treatment recommendation, the physician's confidence in that recommendation after receiving Onco*type* DX information, and the influence of Onco*type* DX information on the treatment decision were assessed.

Statistical Analyses

The study was designed with a planned enrollment of 150 patients. The sample was described with descriptive statistics using the mean, median, range, and 95% confidence intervals (CIs) where appropriate. The McNemar test was used to compare the proportion of patients

receiving a combined chemotherapy and hormone therapy (CHT) recommendation pre-Oncotype DX versus post-Oncotype DX. Physicians used a 5-category Likert scale to rate their level of agreement or disagreement with pre- and post-assay statements for each patient. The distribution of ratings (ie, proportions of patients with each rating) were calculated for each statement. Pre- to post-assay changes in levels of agreement/disagreement were analyzed.

Results

One hundred fifty consecutive eligible patients at 6 centers were enrolled. Of these, 4 patients were not evaluable: 2 had bilateral tumors, 1 was estrogen receptor-negative by immunohistochemistry, and 1 was not recommended any adjuvant therapy. The 146 evaluable patients included 68 (46.6%) patients who were premenopausal (Table 1). There were 123 patients (84.2%) who were node-negative and 23 patients (15.8%) with micrometastatic disease. The patients had predominantly T1 tumors (100/146; 68.5%); 45 (30.8%) had T2 stage tumors. There was a single T3 stage tumor. Thirty-seven patients (25.3%) had low-grade tumors, 69 (47.3%) had intermediate-grade tumors, and 36 (24.7%) had high-grade tumors; grade was not available for 4 patients (2.7%). All 146 patients (100.0%) had ER^+ tumors (Allred score of 3 or higher).

Just over half (74/146; 50.7%) of patients had low Recurrence Score results (Table 1), while 51 patients (34.9%) had intermediate Recurrence Score results, and 21 patients (14.4%) had results in the high range. These results are similar to other published distributions of Recurrence Score results.[21-24]

Any change in treatment recommendation, including changes in the intensity of CT regimen, was examined in this study. We observed an overall change in therapy recommendation in 34 of 146 patients (23.3%; 95% CI, 16.7%-31.0%; see Table 2), while a change in CT intensity was observed in 7 of 146 patients (4.8%). This represents a decrease in treatment intensity for 28 patients (19.2%; 95% CI, 13.1%-26.5%) and an increase for 6 patients (4.1%; 95% CI, 1.5%-8.7%). Changes in therapy recommendation in which CT was either added or removed entirely after receiving the Oncotype DX test results are shown in Table 3. Prior to receiving the Oncotype DX result, 70 patients (47.9%) in this cohort received an initial recommendation for HT alone, and 76 patients (52.1%) received a recommendation that included CT. Following receipt of the assay results, 3 of the 70 patients (4.2%) with a pre-assay recommendation for HT were recommended CHT and 24 of the 76 patients (31.6%) with a pre-assay recommendation for CHT were recommended HT. Therefore, adjuvant CT recommendations were changed for 27 of 146 patients (18.5%; 95% CI, 12.6%-28.5%), and the proportion of patients receiving a recommendation that included any kind of CT decreased from 52.1% pre-assay to 37.7% post-assay, for a net change of 14.4% ($P < .001$; McNemar test) and a relative net change of 27.6%.

The impact of Recurrence Score results on the therapy recommendation was also examined by Recurrence Score group (Table 2). In the low Recurrence Score group, 21 (28.4%) patients had a change in their therapy recommendation after receipt of the Recurrence Score result. All changes were either to no CT (18 patients) or to lower intensity CT regimens (3 patients). Similarly, in the intermediate Recurrence Score group, 7 (13.7%) patients received a changed treatment recommendation: 6 patients for no CT and 1 patient for lower intensity CT. In contrast, 6 (28.6%) patients in the High Recurrence Score group received changed treatment recommendations; 3 to add CT to HT and 3 to higher intensity CT regimens.

Table 1 Patient and Tumor Characteristics

Characteristic	n (%)
Number of Patients	146
Age	
<40 years	11 (7.5)
40-49 years	47 (32.2)
50-59 years	51 (34.9)
≥60 years	37 (25.3)
Menopausal status	
Pre	68 (46.6)
Post	78 (53.4)
Tumor size (cm)	
≤1	23 (15.8)
1.1-2.0	77 (52.7)
2.1-4.0	44 (30.1)
>4.0	2 (1.4)
Tumor grade	
1	37 (25.3)
2	69 (47.3)
3	36 (24.7)
N/A	4 (2.7)
T stage	
1	30 (20.5)
1a	1 (0.7)
1b	19 (13.0)
1c	50 (34.2)
2	45 (30.8)
3	1 (0.7)
Nodal status	
N0	123 (84.2)
ITC	10 (6.8)
N1(mi)	13 (8.9)
Estrogen receptor status[a]	
Positive	146 (100.0)
Negative	0 (0)
HER2[b]	
Negative	72 (49.3)
Equivocal	74 (50.7)
Positive	0 (0)
Recurrence score	
Low (<18)	74 (50.7)
Intermediate (18-30)	51 (34.9)
High (≥31)	21 (14.4)

[a]Estrogen receptor status determined by immunohistochemistry.
[b]HER2 status determined by immunohistochemistry; if equivocal (score of 2+) patient retested by fluorescence in situ hybridization, with HER2/CEP17 ratio of 2.2 or greater indicating positive.

Table 2 Changes in Treatment Recommendations

	Recurrence Score Groups			
	Low (<18) n (% of Group)	Intermediate (18-30) n (% of Group)	High (≥31) n (% of Group)	Total n (% of Group)
Any change	21 (28.4)	7 (13.7)	6 (28.6)	34 (23.3)
CHT to HT	18 (24.3)	6 (11.8)	0 (0)	24
Decrease intensity of CHT	3 (4.1)	1 (2.0)	0 (0)	4
HT to CHT	0 (0)	0 (0)	3 (14.3)	3
Increase intensity of CHT	0 (0)	0 (0)	3 (14.3)	3
Total	74	51	21	146

Abbreviations: CHT = combined chemotherapy and hormone therapy; CT = chemotherapy; HT = hormone therapy.

Physicians were queried about confidence in their treatment decisions before and after receipt of Oncotype DX information and asked whether the test influenced their clinical decision. Before receipt of the test results, 97 (66%) responded "agree" and 43 (29%) "strongly agree" to the statement, "I am confident in my treatment recommendation prior to ordering Oncotype DX" (Figure 1). After the test results were known, 74 (51%) responded "agree" and 58 (40%) "strongly agree" with the statement, "I am confident in my treatment recommendation after ordering the Oncotype DX assay." Responses regarding whether the Oncotype DX assay result had influenced their treatment recommendation were distributed similarly to the changes in treatment recommendations: in 30% of the cases, physicians answered either "strongly agree" or "agree" that the assay influenced their decision. Of the remaining 70% of the cases, 57% responded "disagree" or "strongly disagree," and 13% indicated "neither disagree nor agree" that the test had influenced their decision. (Figure 2).

Table 3 Change in Chemotherapy Utilization

	Post-Assay				
	HT Alone	HT + First-Generation CT	HT + Second-Generation CT	HT + Third-Generation CT	All
Pre-assay					
HT Alone	67	3	0	0	70
HT + first-generation CT[a]	20	28	3	0	51
HT + second-generation CT[b]	4	4	15	0	23
HT + third-generation CT[c]	0	0	0	2	2
All	91	35	18	2	146

Abbreviations: CT = chemotherapy; HT = hormone therapy.
[a]First-generation chemotherapy regimens included cyclophosphamide, methotrexate, and fluorouracil (CMF), doxorubicin and cyclophosphamide (AC), taxotere and cyclophosphamide (TC) or comparable regimens.
[b]Second-generation chemotherapy regimens included 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC)/5-fluorouracil, epirubicin, and cyclophosphamide (FEC) × 6, AC × 4 and paclitaxel × 4 in 3 weekly cycles, or comparable regimens.
[c]Third generation chemotherapy regimens included dose-dense AC then paclitaxel; docetaxel, doxorubicin, and cyclophosphamide (TAC) or FEC/FAC × 3 then docetaxel × 3, or comparable regimens.

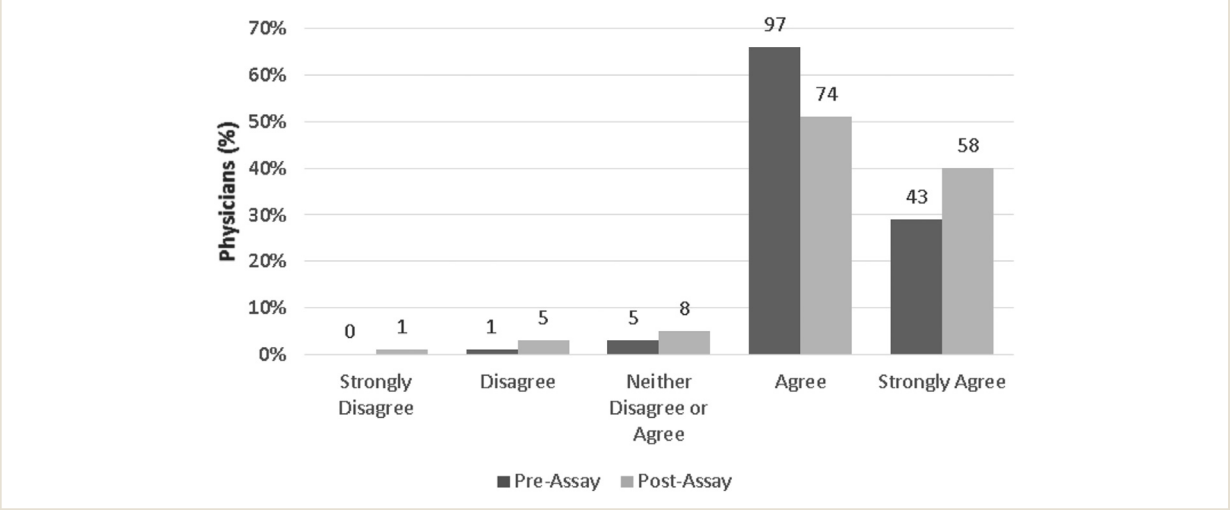
Discussion

Studies conducted in multiple countries support use of the Oncotype DX Breast Cancer Assay as an independent prognostic variable, in conjunction with conventional clinicopathologic parameters in predicting breast cancer recurrences.[21-28] Use of this assay has been incorporated into multiple clinical guidelines, including the National Comprehensive Cancer Network, the American Society of Clinical Onocology, the National Institute for Health and Care Excellence, the European Society for Medical Oncology, and the St Gallen Consensus as part of the adjuvant therapy risk evaluation.[14-18] This is the first prospective study on the impact of the Oncotype DX assay on adjuvant therapy decision-making for Chinese patients and the first to quantitate changes in CT intensity resulting from Recurrence Score information.

We designed the study to evaluate the effect of the Recurrence Score on the change in adjuvant therapy including changes in intensity of chemotherapy, in addition to CT use or not. This was included in order to gain insight into the real-world utility of the assay. The decision to recommend adjuvant therapy for patients with limited risk is a complex one that incorporates decisions not only on whether to advise adjuvant therapy, but also the type of agent(s). Increasing CT intensity (as defined by the Adjuvant! Online clinical risk calculator) confers greater risk reduction for recurrence of breast cancer. Therefore, examining changes in CT intensity in relation to Recurrence Score result may provide more granular insight into how physicians integrate recurrence risk information into their CT regimen decisions. The proportion of patients with a change in treatment recommendation, including change in CT intensity, was 23%. Of these, 1 in 5 was a change in CT intensity, suggesting that physicians found Recurrence Score information useful for finer levels of risk discrimination. The individual Recurrence Score results for the down changes in CT intensity were 16, 16, 17, and 18, and the scores for the increase in intensity were 43, 48, and 62. The down-shifting of CT intensity occurred in patients with scores that fell within the randomized group for the Trial Assigning IndividuaLized Options for Treatment (TAILORx) trial. This may reflect a degree of reservation to withhold CT completely in this group of patients at present, pending the full results from the TAILORx trial. Although there is no direct data showing that patients with very high scores benefit from increased intensity of CT, practitioners in this study seemed to have adopted this view.

The decision change in adjuvant therapy looking at binary CT/no CT recommendations from pre-assay to post-assay was 18.5% which is slightly lower than the proportion of changes historically observed.[29] The predominant change observed was from CHT to HT alone (14%). This is similar to the change reported for the N0 population by Eiermann et al (18% switch from CHT to HT). In both of these studies, a high proportion (57% vs. 52% in this study) of N0 patients received CT recommendations initially.[27] The apparently higher percentage of initial CT recommendations is best explained by the perception by the physicians that these patients have a higher risk of recurrence as defined by clinical parameters and, therefore, merit a more conservative initial therapy recommendation in terms of avoiding undertreatment. Factors that might

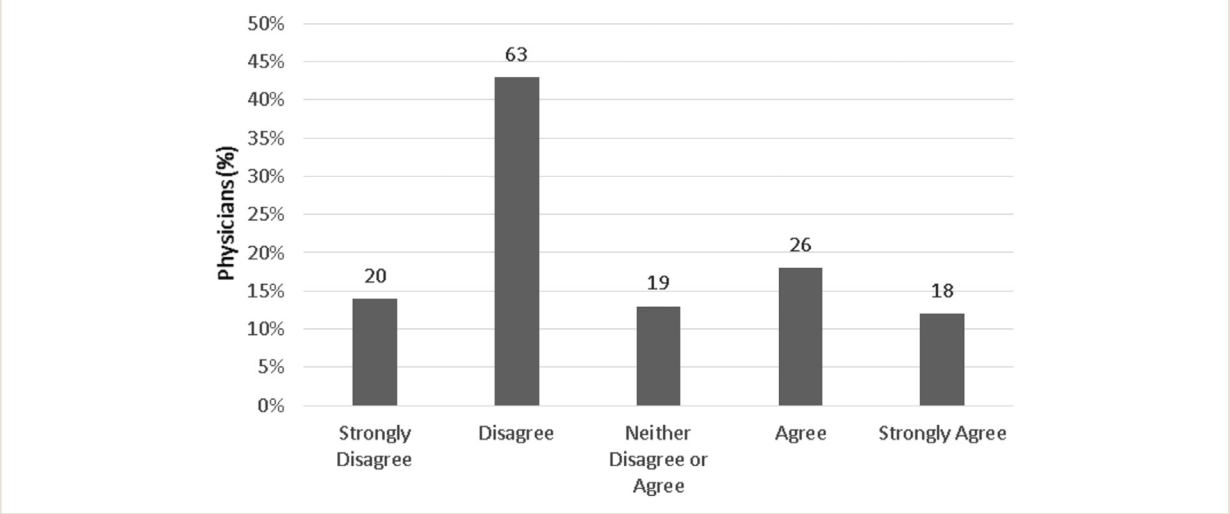
Figure 1 Physician Confidence in Treatment Recommendation. Physicians Were Asked to Respond to the Statement, "I Am Confident in My Treatment Recommendation Prior to Ordering Oncotype DX" by Selecting 1 of the 5 Responses on a 5-Point Likert Scale. Following Receipt of the Recurrence Score Result, Physicians Were Asked to Respond to the Statement, "I Am Confident in My Treatment Recommendation After Ordering the Oncotype DX Assay." The Number of Responses in Each Category Are Shown Above the Bar



drive the opinion that this cohort of patients is at a higher risk of recurrence include the high proportion of premenopausal patients (46.6%) and patients less than 50 years old (39.7%) in this study, both of which are considered risk factors for recurrence. Analysis of the much anticipated TAILORx study results, when they become available, should clarify the use of Recurrence Score results in patients perceived as higher risk, as may be the case here.

This study also illustrates the effect of the Oncotype DX results on the confidence and perceptions of a cohort of physicians who historically had not had access to genomic classifiers. The high confidence in their treatment recommendations may reflect the physicians' comfort with basing recommendations on traditional pathologic factors. Similar high levels of confidence in recommendations have been observed in other studies.[21,25,30] Even with high baseline confidence, following receipt of the assay results, the proportion of physicians who strongly agreed that they are confident in their treatment recommendation further increased. When the perception of influence of the assay results was measured, 30% of

Figure 2 Physician Agreement on Influence of the Oncotype DX Assay on Treatment Recommendations. Physicians Were Asked to Respond to the Statement, "The Results of the Oncotype DX Assay Influenced My Treatment Recommendations." The Number of Responses in Each Category Are Shown Above the Bar



physicians indicated that Oncotype DX had influenced their treatment decision, which is commensurate with the overall rate of decision changes observed. In fact, there was a statistically significant relationship between the answer to the influence question and a change in treatment decision, with an affirmative answer to the influence question associated with a changed treatment recommendation. This suggests that that the influence question was often interpreted as indicating simply that the assay information was used to change a treatment recommendation.

Although it is assumed that characteristics of breast cancer are similar around the world, this study adds important information regarding the biology of early breast cancer in women of Chinese descent. There are data emerging from Taiwan that a higher proportion of young, premenopausal patients with breast cancer reflects cancer population demographics that are significantly different from the Western world, which may underlie the perception of higher recurrence risk in this population.[1,31,32] However, in this population of Chinese women, the Recurrence Score distribution is similar to the distributions in studies from other geographic areas. Therefore, additional studies of ESBC patients from China may be needed to evaluate possible differences in biology and any impact on the results of genomic classifiers.

In conclusion, this study demonstrates the value of adding the Onco*type* DX assay to the adjuvant treatment decision making process for ER^+, node-negative ESBC and reduces CT usage in Hong Kong. The impact of the assay on adjuvant therapy decision-making is similar to, although somewhat lower than, other previous international studies. Physician inexperience with the assay and younger patient demographics may underlie this effect, which can be further informed through additional studies.

Clinical Practice Points

- A minority of ESBC patients benefit from adjuvant CT.
- Conventional risk stratification tools do not accurately identify those who can benefit.
- In Western health care systems, the Onco*type* DX assay has been shown to accurately predict recurrence risk and reduce the utilization of adjuvant CT.
- This study demonstrated that the Onco*type* DX assay impacts treatment decisions in an Asian health care system that utilizes the multidisciplinary meeting model for treatment decision making.
- CT usage was reduced by 27%, and a similar proportion of physicians reported that the assay results influenced their adjuvant treatment recommendation.
- The study provides data on distribution of Recurrence Score values in Hong Kong.
- This study is one of the first to evaluate how the assay influences choice of CT intensity.
- Use of the Oncotype DX assay may help reduce the frequency of adjuvant CT usage and thereby reduce both CT-related morbidity and associated costs.

Acknowledgments

The authors wish to thank Amy Chan and May Lee, the research team at Hong Kong Breast Cancer Foundation, for data collection and compilation; Drs Keeng-Wai Chan, Hioe Fei, Arthur K.C. Lee, K.L. Mak, Gary Tse, and Nancy W.F. Yuen in the Pathology Departments of the participating centers for preparing the tissue blocks for Oncotype DX test submission; and all of the physicians who contributed to the discussions in the multidisciplinary breast meetings at the participating centers. This study was supported by funds from Genomic Health, Inc. Editorial and writing support was provided by Eric R. Schuur, PhD.

Disclosure

Calvin Chao and Carl Yoshizawa report employment with Genomic Health, Inc. All other authors state that they have no conflicts of interest.

References

1. Leong SP, Shen ZZ, Liu TJ, et al. Is breast cancer the same disease in Asian and Western countries? *World J Surg* 2010; 34:2308-24.
2. *Hong Kong Cancer Registry Annual Report*. Hong Kong: Hong Kong Breast Cancer Foundation; 2012.
3. *Breast Cancer Registry Report, No. 5, Vol 2013*. Hong Kong: Hong Kong Breast Cancer Foundation.
4. Early Breast Cancer Trialists Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 352:930-42.
5. Early Breast Cancer Trialists Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365:1687-717.
6. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; 351:2817-26.
7. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006; 24:3726-34.
8. Albain KS, Barlow WE, Shak S, et al. 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; 11:55-65.
9. Dowsett M, Cuzick J, Wale C, 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; 28:1829-34.
10. Mamounas E, Tang G, Paik NS, et al. Prognostic impact of the 21-gene Recurrence Score on disease-free and overall survival of node-positive, ER-positive breast cancer patients treated with adjuvant chemotherapy: results from NSABP B-28. *ASCO Breast Cancer Symposium*. San Francisco, CA; 2012.
11. Penault-Llorca F, Filleron T, Asselain B, et al. Prediction of recurrence with the Oncotype DX recurrence score in node-positive, HR-positive, breast cancer patients treated with adjuvant chemotherapy: results from the PACS01 trial. *ASCO Annual Meeting*. Chicago, IL; 2014.
12. Solin LJ, Gray R, Goldstein LJ, et al. Prognostic value of biologic subtype and the 21-gene recurrence score relative to local recurrence after breast conservation treatment with radiation for early stage breast carcinoma: results from the Eastern Cooperative Oncology Group E2197 study. *Breast Cancer Res Treat* 2012; 134:683-92.
13. Toi M, Iwata H, Yamanaka T, et al. Clinical significance of the 21-gene signature (Oncotype DX) in hormone receptor-positive early stage primary breast cancer in the Japanese population. *Cancer* 2010; 116:3112-8.
14. Carlson RW, ed. *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer*. National Comprehensive Cancer Network; 2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed: April 12, 2016.
15. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 2013; 24:2206-23.
16. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007; 25:5287-312.
17. NICE. Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4, and Mammostrat. Vol 2015:NICE recommendation on Oncotype usage. Available at: http://www.nice.org.uk/guidance/dg10/chapter/1-recommendations. Accessed: March 16, 2015.
18. Senkus E, Kyriakides S, Penault-Llorca F, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol* 2013; 24:vi7-23.
19. Cheung PS, Tong AC, Leung RC, Kwan WH, Yau TC. Initial experience with the Oncotype DX assay in decision-making for adjuvant therapy of early oestrogen receptor-positive breast cancer in Hong Kong. *Hong Kong Med J* 2014; 20:401-6.

20. Adjuvant Inc. Adjuvant! Online. Available at: https://www.adjuvantonline.com/. Accessed: February 17, 2013
21. Albanell J, Gonzalez A, Ruiz-Borrego M, et al. 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. *Ann Oncol* 2012; 23:625-31.
22. Klang SH, Hammerman A, Liebermann N, Efrat N, Doberne J, Hornberger J. Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. *Value Health* 2010; 13:381-7.
23. Lo SS, Mumby PB, Norton J, et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. *J Clin Oncol* 2010; 28:1671-6.
24. Stemmer SM, Klang SH, Ben-Baruch N, et al. The impact of the 21-gene Recurrence Score assay on clinical decision-making in node-positive (up to 3 positive nodes) estrogen receptor-positive breast cancer patients. *Breast Cancer Res Treat* 2013; 140:83-92.
25. Bargallo JE, Lara F, Shaw-Dulin R, et al. A study of the impact of the 21-gene breast cancer assay on the use of adjuvant chemotherapy in women with breast cancer in a Mexican public hospital. *J Surg Oncol* 2015; 111:203-7.
26. de Boer RH, Baker C, Speakman D, Chao C, Carl Y, Mann GB. The impact of a genomic assay (Oncotype DX) on adjuvant treatment recommendations in early breast cancer. *Med J Aust* 2013; 199:205-8.
27. Eiermann W, Rezai M, Kummel S, et al. 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. *Ann Oncol* 2013; 24:618-24.
28. Holt S, Bertelli G, Humphreys I, et al. A decision impact, decision conflict and economic assessment of routine Oncotype DX testing of 146 women with node-negative or pNImi, ER-positive breast cancer in the U.K. *Br J Cancer* 2013; 108: 2250-8.
29. Harbeck N, Sotlar K, Wuerstlein R, Doisneau-Sixou S. Molecular and protein markers for clinical decision making in breast cancer: today and tomorrow. *Cancer Treat Rev* 2014; 40:434-44.
30. Yamauchi H, Nakagawa C, Takei H, et al. Prospective study of the effect of the 21-gene assay on adjuvant clinical decision-making in Japanese women with estrogen receptor-positive, node-negative, and node-positive breast cancer. *Clin Breast Cancer* 2014; 14:191-7.
31. Ghiasvand R, Adami HO, Harirchi I, Akrami R, Zendehdel K. Higher incidence of premenopausal breast cancer in less developed countries; myth or truth? *BMC Cancer* 2014; 14:343.
32. Lin CH, Chen YC, Chiang CJ, et al. The emerging epidemic of estrogen-related cancers in young women in a developing Asian country. *Int J Cancer* 2012; 130: 2629-37.