

# Initial experience with the *Oncotype* DX assay in decision-making for adjuvant therapy of early oestrogen receptor–positive breast cancer in Hong Kong

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## ABSTRACT

**Objective:** To examine the impact of the 21-gene *Oncotype* DX Breast Cancer Assay on the adjuvant treatment decision-making process for early-stage breast cancer in Hong Kong.

**Design:** Retrospective study.

**Setting:** Private hospital, Hong Kong.

**Patients:** Study included cases of early-stage breast cancer (T1-2N0-1M0, oestrogen receptor–positive, human epidermal growth factor receptor 2–negative) that were presented at a multidisciplinary breast meeting at a single site. Cases were selected for *Oncotype* DX testing with the assistance of Adjuvant! Online. The recommendations for adjuvant therapy before and after obtaining the *Oncotype* DX Recurrence Score results were analysed.

**Results:** A total of 154 cases that met the inclusion criteria were discussed at our multidisciplinary breast meeting. Of these, 64 cases with no clear recommendation by the Meeting Panel were selected for this study and reviewed. The distribution of Recurrence Score results was similar to that reported by others, with a somewhat higher proportion of low Recurrence Scores. Treatment recommendation was changed for 20 (31%) patients after the *Oncotype* DX result was received. Of the changes in treatment decisions, 16 (80%) were changes to lower-intensity regimens (either equipoise or hormonal therapy).

The number of cases receiving an equipoise recommendation decreased by nine (82%), based on the additional information provided by the *Oncotype* DX test.

**Conclusion:** The *Oncotype* DX Recurrence Score information impacts the decision-making process for adjuvant therapy for early-stage breast cancer in the multidisciplinary care setting in Hong Kong. A larger-scale study is required to gain more experience, evaluate its impact more thoroughly, and assess its cost-effectiveness.

Hong Kong Med J 2014;20:401–6

DOI: 10.12809/hkmj134140

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This article was published on 20 Jun 2014 at www.hkmj.org.

## New knowledge added by this study

- Application of the *Oncotype* DX Breast Cancer Assay reduces adjuvant chemotherapy recommendations for early-stage breast cancer in a multidisciplinary clinic environment in the Chinese population.
- Application of the *Oncotype* DX Breast Cancer Assay to early-stage breast cancer cases reduces the proportion of equipoise chemotherapy recommendations.

## Implications for clinical practice or policy

- The *Oncotype* DX Breast Cancer Assay can assist in making definitive treatment recommendations.

## Introduction

Breast cancer is the most common cancer among women in Hong Kong, with an incidence of 54.8 per 100 000 population in 2010.<sup>1</sup> Over the past two decades, breast cancer incidence in Hong Kong has been trending upward, from a lifetime risk of 1 in 27 women in 2000 to a lifetime risk of 1 in 19

women in 2010. As a result, Hong Kong now has an intermediate-to-high breast cancer incidence compared with other Asian countries. The median age of diagnosis of breast cancer is 53 years. Early-stage breast cancer (ESBC; defined as stages 0 to II) is most common at diagnosis, accounting for 81.3% of cases.<sup>2</sup> The most common stage at diagnosis is

## Oncotype DX 測試對香港早期ER+乳腺癌輔助療法的決策過程的初步經驗

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目的：探討21-基因Oncotype DX乳腺癌分析對香港早期乳腺癌輔助治療決策程序的影響。

設計：回顧研究。

安排：香港一所私家醫院。

患者：在一個研究站點的多科會診中提交的早期乳腺癌（T1-2N0-1M0、ER+、HER2-）病例中，挑選部分接受Oncotype DX測試及Adjuvant! Online輔助治療的病例。對在收到Oncotype DX復發指數結果前和後的輔助療法建議進行分析。

結果：共154份符合入選標準的病例，其中沒有明確會診建議的64份病例入選本研究並接受審查。復發指數結果的分佈與其他機構公佈的結果相似，惟低復發指數所佔比例略高。在收到Oncotype DX結果後，對20名患者（31%）的治療建議作出修改。在被修改的治療決策中，有16例（80%）改為低強度方案（不明確或激素治療）。基於Oncotype DX測試提供的額外資料，接受不明確建議的病例數量減少9人（82%）。

結論：Oncotype DX 復發指數資料對香港多科團隊進行輔助療法決策的過程產生了影響。需要進行更大範圍的研究及積累更多經驗，以更全面評估Oncotype DX乳腺癌分析的影響力及其成本效益。

stage II (39.7%).<sup>2</sup>

Among those diagnosed with ESBC in Hong Kong, 98% undergo surgery, 62% receive adjuvant chemotherapy, and 66% receive hormonal therapy (HT). Adjuvant therapy has been shown to increase survival,<sup>3</sup> which includes HT, chemotherapy, or both. The decision to administer adjuvant therapy depends on clinical, pathological, and histochemical features of the tumour, which influence the risk of recurrence.<sup>4,5</sup> At our institution, it has been the practice since 2003 to discuss all breast cancer cases at the multidisciplinary breast meeting (MDM) prior to making adjuvant treatment recommendations. In this model, cases are submitted for weekly review by a group of health care professionals including surgeons, oncologists, pathologists, and experts from other disciplines who can add value to optimising the treatment plan for each patient.

The Oncotype DX Breast Cancer Assay (Oncotype DX; Genomic Health, Inc, Redwood City [CA], US) has been validated to measure the risk of recurrence in patients with oestrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), and lymph node negative tumours. The Oncotype DX test analysed 21 genes and generated a Recurrence Score which is used to quantify the likelihood of distant disease

recurrence at 10 years post-treatment. For prognostic use, the Recurrence Score value is categorised into low- (<18), intermediate- (18-30), and high-risk (>30) groups. Typically, patients receiving a low Recurrence Score result will receive HT in the absence of other factors that increase the risk of recurrence. Patients receiving high scores have a higher risk of recurrence and are more likely to respond to chemotherapy; therefore, these patients often receive a combination of chemotherapy followed by HT. The appropriate therapy for patients with an intermediate score is the subject of ongoing clinical trials. Several prospective studies have validated its prognostic and predictive significance using data from the NSABP-B14, NSABP-20, and SWOG 8814 trials.<sup>6,7</sup> Oncotype DX has now been incorporated into the National Comprehensive Cancer Network and the St Gallen guidelines for use.<sup>4,5</sup>

Significant toxicity and cost can accrue to patients undergoing adjuvant chemotherapy, but only a small proportion experience survival benefits. The Recurrence Score result can be used to assess the 10-year risk of recurrence and the potential benefit from adjuvant chemotherapy and, thereby, assist in development of a treatment plan that makes optimal use of resources for the patient's benefit.

The aim of this study was to examine the impact of the additional information provided by the Oncotype DX test on the clinical treatment decisions for patients diagnosed with ESBC. The study compared treatment regimens proposed by a multidisciplinary breast cancer team before and after receipt of the Oncotype DX results.

## Methods

### Study design

This single-centre study was conducted at the Hong Kong Sanatorium and Hospital, a private institution in Hong Kong. This study was a retrospective review of patients with breast cancer who had surgery between 2008 and 2011, whose cases had been reviewed by the MDM, and who had received Oncotype DX assay testing to obtain additional information on recurrence risk. Recurrence risk was assessed by the MDM using clinical factors (including age, tumour size, number of positive lymph nodes, and grade) and Adjuvant! Online,<sup>8</sup> and a provisional treatment recommendation was made. The Oncotype DX test was ordered after the MDM to obtain additional recurrence risk information when there was a difference of opinion on interpretation of available information. The test was not ordered when a consensus of opinion on treatment recommendation was reached. Cost of testing was borne by insurance or the patient. For each case, the MDM made final treatment recommendations after consideration of the Recurrence Score results; the

actual treatment received took into account patient preference, and might have differed from that recommended by the MDM. Eligible patients had ESBC (T1-2N0-1M0 tumours) that was determined to be ER+, HER2-, and with at most one positive lymph node. In addition, the patient profile was consistent with that prescribed by international guidelines for application of this assessment.<sup>4,5</sup> The Recurrence Score result was discussed for all patients and a recommendation was made by simple majority of opinion. Therapy recommendations before Recurrence Score result were categorised as chemohormonal therapy (CHT), equipoise where a clear recommendation for either CHT or HT was not possible, or HT. Changes in intensity of therapy were categorised as increased intensity from HT to equipoise or CHT and equipoise to CHT; changes were categorised as decreased intensity for changes from CHT to equipoise or HT and equipoise to HT.

### Statistical analysis

Data were summarised by using descriptive statistics. For cases considered in this study, the distribution of parameter values in the sample was described by calculating the mean, median, and range where appropriate.

## Results

During the study period from 1 August 2008 to 30 June 2011, a total of 620 breast cancer patients with T1-2N0-1M0 tumours underwent surgery. Among them, 154 were ER+ HER2- cases. A total of 66 cases for which there was no unanimity in the MDM were reviewed, of which 64 fulfilled the inclusion criteria for this study; two cases were excluded because HER2 status was determined to be overexpressed by immunohistochemistry. The tumours were predominantly grade II (63%) and similar proportions were stage IA (42%) and stage IIA (48%), with small number of stage IIB cases (9%) [Table 1]. Nine patients with positive lymph nodes (N1 or N1a) were included in the study based on clinical and pathological assessments suggesting less-aggressive disease.

The Recurrence Score values were categorised as low- (<18), intermediate- (18-30), and high-risk (>30) according to the *OncoType* DX assay recommendation which gave an estimated distant recurrence rate after the use of HT alone. The panel discussed the possible benefit of adding chemotherapy to the treatment regimen for each patient to reach a consensus recommendation specific for the patient. In this study, the majority of patients had a low-risk Recurrence Score (64%) whilst patients with intermediate- and high-risk Recurrence Score values were less frequent (30% and 6%, respectively). The distribution of Recurrence Score results by tumour stage is shown in Table 2.

TABLE 1. Patient and tumour characteristics (n=64)

Characteristic	No. (%) of cases*
Patient age (years)	
Mean	48
Range	24-67
Tumour size (cm)	
Mean	2.28
Median	2.05
Range	0.60-7.20
Tumour grade	
Grade I	18 (28)
Grade II	40 (63)
Grade III	6 (9)
Tumour stage†	
IA	27 (42)
IIA	31 (48)
IIB	6 (9)

\* Or as otherwise stated

† % may not total 100 because of rounding

TABLE 2. Distribution of Recurrence Score by stage

Stage	No. (%)			
	Low	Intermediate	High	Total
IA	17 (63)	7 (26)	3 (11)	27 (100)
IIA	21 (68)	9 (29)	1 (3)	31 (100)
IIB	3 (50)	3 (50)	0 (0)	6 (100)
<b>Total</b>	<b>41 (64)</b>	<b>19 (30)</b>	<b>4 (6)</b>	<b>64 (100)</b>

In this cohort, the distribution of Recurrence Score results by stage was similar to the overall distribution of the Recurrence Score results. Stage IA tumours were comprised of 63% low and 26% intermediate Recurrence Score results, while stage IIA tumours were comprised of 68% low and 29% intermediate Recurrence Score results. Stage IIB tumours were evenly split between low and intermediate scores.

The specific changes in treatment recommendations for all patients in the study are shown in Table 3. Overall, the treatment recommendations for 20 (31%) of the 64 patients changed intensity when the Recurrence Score result was considered. The changes in treatment decisions were predominantly to HT (14/20; 70% of changed treatment recommendations) for the entire cohort. Other changes included two recommendations (10% of changed recommendations) that were changed from CHT to equipoise and four (20%) which resulted in a higher-intensity CHT recommendation over HT or equipoise. Interestingly, five of six stage

IIB cases received CHT recommendations both pre- and post-Recurrence Score result. In the sixth stage IIB case, a patient with lobular carcinoma staged as T3N0M0 with a Recurrence Score result of 8, the treatment recommendation was changed from CHT to HT upon receipt of the score.

The distribution of treatment recommendations by stage before and after *Oncotype DX* testing is shown in Table 3. For stage I patients, recommendations were changed in eight (30%) of 27 patients, while for stage II patients recommendations were changed in 12 (32%) of 37 patients. As for the entire cohort, the changes in treatment decisions were predominantly to HT for both stage I (5/8, 63%) and stage II (9/12, 75%) patients. In the stage I tumours, all four equipoise recommendations (15% of recommendations prior to *Oncotype DX* testing) were changed after testing. The proportion of CHT recommendations remained the same at 13 (48%) and HT recommendations increased from 10 (37%) to 14 (52%) after receipt of the Recurrence Score result. In stage II tumours, the proportion receiving recommendations for equipoise decreased from 7 (19%) to 2 (5%). The CHT recommendations decreased somewhat from 26 (70%) to 22 (59%), while the proportion receiving a HT recommendation increased from 4 (11%) to 13 (35%).

The distribution of Recurrence Score categories by therapy recommendation before and after receipt of *Oncotype DX* results is shown in the Figure. The number of low Recurrence Score cases in the CHT group decreased from 20 before Recurrence Score information to 13 after the Recurrence Score result was obtained, while the number of low Recurrence Score cases in the group that did not require chemotherapy increased from 21 to 28 once the Recurrence Score information was available. While two patients in the high Recurrence Score group did not receive a recommendation for CHT pre-*Oncotype DX*, all the cases with high Recurrence Scores received a recommendation for CHT post-*Oncotype DX*.

### Discussion

This first analysis of the impact of the *Oncotype DX* Breast Cancer Assay on adjuvant treatment for early-breast cancer in Hong Kong revealed similarities with studies in other populations worldwide with regard to the distribution of Recurrence Score results, proportion of treatment recommendations that changed upon consideration of *Oncotype DX* information, and shift in proportions of chemotherapy recommendations compared with other treatment recommendations.<sup>9-13</sup>

The Recurrence Score distribution observed in this retrospectively selected cohort of breast cancer patients is similar to that observed in other studies of ESBC, with predominance of lower Recurrence Score values. These results are also comparable to the Asia-Pacific region's Recurrence Score distribution reported by Genomic Health: low risk=51%, intermediate risk=33%, and high risk=16%.<sup>14</sup> The distribution observed in this study differed from other studies<sup>9,12,13</sup> in that the proportion

TABLE 3. Changes in treatment recommendation

Pre-Recurrence Score	Post-Recurrence Score recommendation, No. (%)			Row total, No. (%)
	CHT	Equipoise	HT	
<b>Stage I</b>				
CHT	10 (77)	0	3 (23)	13 (48)
Equipoise	2 (50)	0	2 (50)	4 (15)
HT	1 (10)	0	9 (90)	10 (37)
Subtotal	13 (48)	0	14 (52)	27 (100)
<b>Stage II</b>				
CHT	21 (81)	2 (8)	3 (12)	26 (70)
Equipoise	1 (14)	0	6 (86)	7 (19)
HT	0	0	4 (100)	4 (11)
Subtotal	22 (59)	2 (5)	13 (35)	37 (100)
<b>Overall</b>				
CHT	31 (79)	2 (5)	6 (15)	39 (61)
Equipoise	3 (27)	0	8 (73)	11 (17)
HT	1 (7)	0	13 (93)	14 (22)
<b>Total</b>	<b>35 (55)</b>	<b>2 (3)</b>	<b>27 (42)</b>	<b>64 (100)</b>

Abbreviations: CHT = chemohormonal therapy; HT = hormonal therapy

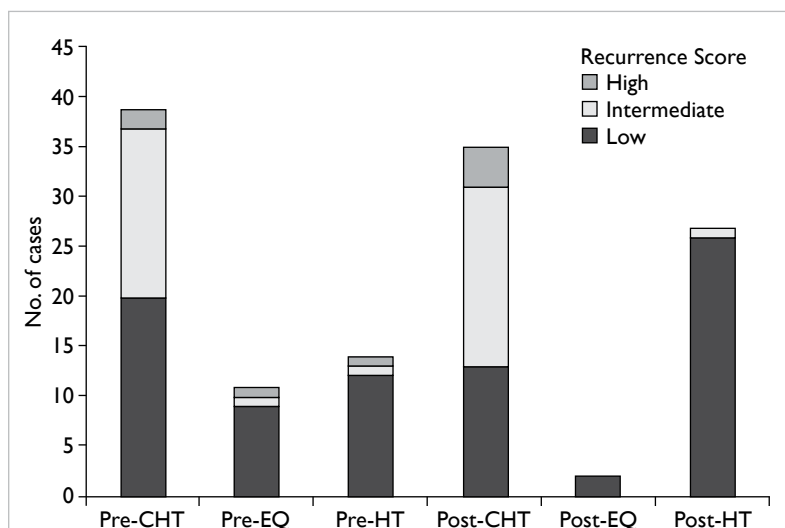


FIG. Distribution of Recurrence Score groups by treatment recommendation pre- and post-*Oncotype DX* test  
 The cases were categorised by therapy recommendation pre-*Oncotype DX* testing (pre-HT, pre-EQ, pre-CHT) and the same cases were re-categorised by therapy recommendation post-*Oncotype DX* testing (post-HT, post-EQ, post-CHT)  
 Abbreviations: CHT = chemohormonal therapy; EQ = equipoise; HT = hormonal therapy

of low Recurrence Score results was higher and the proportion of high Recurrence Score results was lower than previously observed. Since these cases were estimated to derive borderline benefit based on their initial assessment using Adjuvant! Online and clinical parameters, it might be expected that Recurrence Score distribution in this cohort would be skewed at the lower end as well. When examined by stage, the Recurrence Score distribution did not change substantially. In fact, all six stage IIB tumours had low or intermediate Recurrence Scores, including the single T3 tumour in this study. This observation is consistent with that in other studies<sup>9,15,16</sup> showing that the Recurrence Score assay provides information not inherent to traditional clinicopathological assessments of the tumour.

Inclusion of *Oncotype DX* information led to a change in 20 (31%) of 64 treatment plans. These results correspond with similar decision impact studies from the US,<sup>12,13,17</sup> European Union,<sup>9,10</sup> and the Middle East<sup>11</sup> that assessed the impact of Recurrence Score information on choice of adjuvant therapy in ESBC. The proportion of treatment plans that changed in these studies ranged from 25% to 40%, so the 30% observed in this study is typical.

The proportion of changes to CHT or in the other direction to HT as a result of *Oncotype DX* testing in breast cancer is also similar to that in other studies, with the proportion of CHT recommendations decreasing and the proportion of HT recommendations increasing.<sup>9-13</sup> Changes were largely to lower-intensity treatments, with 80% of the 20 changed recommendations shifting from CHT or equipoise to a lower-intensity regimen. Most of these transitions to lower-intensity treatment recommendations resulted from movement of the equipoise cases to HT (40% of changes). An additional 30% of the changes were shifts from CHT to HT recommendations. This effect was seen with the only T3 tumour in the study, classified as T3N0M0, a case which transitioned from a CHT recommendation to HT after receiving a low-risk Recurrence Score of 8. Recurrence Score information resulted in increases in treatment intensity as well. The two cases with a high score that were not originally given a CHT recommendation were switched to CHT after consideration of the Recurrence Score.

Adjuvant treatment for ESBC is an important, yet complex area faced by oncologists. To patients, this is a life-changing decision, the outcome of which will drastically impact their lives. The decision whether to give chemotherapy as part of adjuvant therapy to cancer patients can be difficult with traditional prognostic indicators as, often, they have been insufficient to identify patients who will benefit from those who may not benefit. A number of prognostic tools have been developed, including *Oncotype DX* and Adjuvant!

Online that can aid the multidisciplinary team in making decisions on adjuvant treatment. The additional information provided by the *Oncotype DX* Recurrence Score result provides the physician with unique information in the assessment of risk of recurrence. In this study, cases were selected that were deemed to have intermediate risk using clinical factors and Adjuvant! Online, and for which there was no unanimous agreement. This was exemplified by inclusion of nine lymph node-positive cases. Their disease was considered less aggressive based on assessment of the tumour biology, creating uncertainty about the necessity of chemotherapy for these patients. Thus, the *Oncotype DX* test was recommended so that the multidisciplinary team would have additional information on which they could base their adjuvant treatment decisions. Given the high proportion of ESBC cases in Hong Kong, such cases may be frequent and there is an evident need for *Oncotype DX* testing to assist in making treatment recommendations. The additional information gained can help physicians and patients avoid expensive and toxic chemotherapy.

Limitations of the study were its retrospective nature. In addition, selection of patients was non-uniform; cases were selected based on their intermediate-risk assessment in MDMs; and the selected cases were the ones for which the physicians had difficulty in making treatment recommendations.

## Conclusion

This study demonstrated that the distribution of *Oncotype DX* Recurrence Score results in the population of women with ESBC in Hong Kong is similar to that reported in other geographical regions in the world. The impact of the Recurrence Score information on adjuvant treatment decisions in Hong Kong was also similar to that reported by others, with the main effect being a shift in treatment recommendations to lower-intensity regimens. Finally, the proportion of equipoise chemotherapy recommendations was greatly reduced, suggesting that the Recurrence Score can assist in making definitive treatment recommendations in cases for which physicians are ambivalent about using chemotherapy.

## Acknowledgements

The authors wish to thank The Hong Kong Sanatorium and Hospital for supporting and facilitating the weekly multidisciplinary breast meeting and the members of the Multidisciplinary Breast Team for their active participation.

## Declaration

No conflicts of interest were declared by authors.

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