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Breast Cancer

Prospective Clinical Utility Study of the Use of the 21-Gene Assay in Adjuvant Clinical Decision Making in Women With Estrogen Receptor-Positive Early Invasive Breast Cancer: Results From the SWITCH Study

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Key Words. Adjuvant • Chemotherapy • Early breast cancer • Estrogen receptor-positive

Abstract

Background. The 21-gene Onco*type* DX Recurrence Score assay is a validated assay to help decide the appropriate treatment for estrogen receptor-positive (ER+), early-stage breast cancer (EBC) in the adjuvant setting. The choice of adjuvant treatments might vary considerably in different countries according to various treatment guidelines. This prospective multicenter study is the first to assess the impact of the Onco*type* DX assay in the French clinical setting.

Methods. A total of 100 patients with ER+, human epidermal growth factor receptor 2-negative EBC, and node-negative (pN0) disease or micrometastases in up to 3 lymph nodes (pN1mi) were enrolled. Treatment recommendations, physicians' confidence before and after knowing the Recurrence Score value, and physicians' perception of the assay were recorded.

Results. Of the 100 patients, 95 were evaluable (83 pN0, 12 pN1mi). Treatment recommendations changed in 37% of patients, predominantly from chemoendocrine to endocrine treatment alone. The proportion of patients recommended chemotherapy decreased from 52% pretest to 25% post-test. Of patients originally recommended chemotherapy, 61% were recommended endocrine treatment alone after receiving the Recurrence Score result. For both pN0 and pN1mi patients, post-test recommendations appeared to follow the Recurrence Score result for low and high values. Physicians' confidence improved significantly.

Conclusion. These are the first prospective data on the impact of the Onco*type* DX assay on adjuvant treatment decisions in France. Using the assay was associated with a significant change in treatment decisions and an overall reduction in chemotherapy use. These data are consistent with those presented from European and non-European studies. ***The Oncologist*** 2015; 20:873–879

Implications for Practice: This study shows that in estrogen receptor-positive, human epidermal growth factor receptor 2-negative early breast cancer (either node-negative or with micrometastases in up to 3 lymph nodes), Onco*type* DX testing is associated with a treatment recommendation change in more than a third of patients (primarily from chemoendocrine treatment to endocrine treatment alone but also in the opposite direction) and an overall reduction in chemotherapy use. These results are consistent with those from other decision impact studies worldwide and further emphasize the role of Onco*type* DX testing in management of early breast cancer, as reflected in international treatment guidelines.

Introduction

Only a small proportion of patients with hormone receptor-positive (HR+) invasive early breast cancer (EBC) benefit from chemotherapy [1, 2]. However, a relatively high proportion of women are recommended chemotherapy in France [3].

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A key challenge in making treatment decisions for patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2 (HER2)-negative EBC is that the traditional markers used are mainly prognostic and not predictive of chemotherapy benefit. A relatively high proportion of patients is also classified as intermediate risk by most classical markers.

The Onco*type* DX Recurrence Score assay is a real-time reverse transcriptase-polymerase chain reaction-based assay specifically developed and optimized for use in archival formalin-fixed, paraffin-embedded tumor tissue [4, 5]. It determines the expression of 5 reference genes and 16 cancer-related genes selected based on the correlation of gene expression and the risk of distant recurrence [6–8]. The Onco*type* DX breast cancer assay has been validated as a prognostic marker in both node-negative and node-positive HR+ disease [2, 9–11]. The Recurrence Score has also been validated as a predictive marker for the magnitude of adjuvant chemotherapy benefit [2, 11] with a significant benefit in patients with high Recurrence Score values (28% absolute benefit in 10-year risk of distant recurrence) and minimal, if any, benefit from chemotherapy in patients with low values. In patients with intermediate values (Recurrence Scores of 18–30), the available data cannot rule out that some patients may benefit from chemotherapy [2, 11].

The use of this assay to guide clinical treatment decisions has been addressed within clinical guidelines [12–15]. The 2013 St. Gallen Consensus acknowledges the assay not only as a prognostic test but also as a marker predictive of chemotherapy responsiveness for patients with luminal disease [15].

Several prospective studies showed that knowledge of the Recurrence Score result affects management of patients [16–22]. Results are very consistent across different health care systems, with treatment recommendations changing in approximately one third of patients. Use of the assay has been found to be cost-effective or even cost-saving in different national health care systems [22–32]. This study was performed as a prospective clinical study to evaluate the impact of the Onco*type* DX breast cancer assay on adjuvant decision making in French clinical practice for patients with ER+ EBC.

Materials and Methods

The SWITCH study was a prospective study involving seven French centers (ClinicalTrials.gov identifier NCT01446185). It was approved by the national ethics committee and the local research committees of all participating institutions. All patients provided written informed consent.

Study Objectives

The primary objective was to assess the impact on adjuvant treatment decisions when using the Recurrence Score result in patients with ER+, HER2-negative EBC with node-negative disease (pN0) or with micrometastasis in up to 3 lymph nodes (pN1mi). The secondary objectives were to assess (a) the participating physicians' level of confidence in their treatment decision before (pretest) and after (post-test) receiving the Recurrence Score result and (b) their perceptions regarding the utility of the assay.

Patients

Enrollment was offered consecutively to eligible women who had operable invasive EBC, ER+ (defined by >10% of cells stained [33]), HER2-negative pN0 or histological proof of micrometastasis in regional lymph nodes (pN1mi). Other inclusion criteria were: potential candidate for systemic chemotherapy, good performance status, age of ≥18 years, and signed informed consent for the study.

Adjuvant Treatment Recommendations

Investigators had to document their treatment recommendations before and after knowing the Recurrence Score result. Each case was discussed twice within the respective institution's multidisciplinary tumor board. In the first board meeting, adjuvant treatment was recommended according to the valid French guidelines [3] based on clinical and histopathological information. An improvement in disease-free survival of >5% was usually regarded as a cutoff for recommending chemotherapy. Each case was rediscussed in a second meeting, and treatment was recommended considering the Recurrence Score result.

Physician's Questionnaires

A baseline questionnaire captured physicians' initial treatment recommendations and answers to queries regarding their confidence in their treatment recommendations before the assay had been performed. A follow-up questionnaire recorded treatment recommendations, as well as physicians' confidence in their recommendations and their perceptions of the assay post-test. Answers could be chosen from a Likert scale with the following options: strongly disagree, disagree, neither disagree nor agree, agree, strongly agree, and do not know.

Statistics

Sample size was determined based on the assumption of an overall treatment recommendation change rate (from an initial recommendation for chemoendocrine to endocrine treatment and vice versa) of 18%. A sample size of 100 patients allowed determination of this switch rate with a 95% confidence interval (CI) of 11.0%–26.9% (i.e., with a CI width of 15.9%).

Descriptive statistics were used to summarize patient and tumor characteristics. The proportion of patients for whom treatment recommendations changed from before to after knowledge of the assay result was calculated for all patients by nodal status and by Recurrence Score group (low indicates Recurrence Score results of <18, intermediate indicates Recurrence Score results between 18 and 30, and high indicates Recurrence Score results of ≥31). The chemotherapy alone and chemoendocrine therapy options were combined, as were the observation and endocrine therapy options. Change rates were reported with 95% CI calculated using the Clopper-Pearson method. McNemar's test was used to assess whether the proportion of patients recommended chemotherapy changed from pretest to post-test.

The physicians' level of confidence in the adjuvant treatment recommendation was measured both pretest and post-test in the response to the question: "I am confident in my treatment recommendation." The physicians' post-test perceptions of the utility of the assay were assessed by the answers to the question: "The Oncotype DX assay results provided additional information." Answers were assigned numeric values from 1 to 5, respectively. Evolution of the level of confidence pretest to post-test was derived by subtracting the pretest value from the post-test value (resulting negative values were reported as decreases in confidence, and resulting positive values were reported as increases in confidence) and assessed using the signed rank test.

Results

Patient and Tumor Characteristics

In total, 100 patients were enrolled between January 2011 and December 2011. Of those 100 patients, 5 were excluded from the analysis (2 inadequate tissue sample, 2 had a treatment decision before receiving the test result, and 1 had no post-test recommendation available) leaving 95 evaluable patients. Complete patient and tumor characteristics and the distribution of the Recurrence Score values are listed in Table 1. Overall, 52 (54%) patients were in the low, 38 (40%) in the intermediate, and 5 (5%) in the high Recurrence Score groups.

Shift in Treatment Recommendations

Treatment recommendations before and after the assay are listed in Table 2. Overall, the shift in treatment recommendations was predominantly from chemotherapy to no chemotherapy. Of the 95 patients, 35 (37% [95% CI: 27%–47%]) had a change in adjuvant treatment recommendation, with 30 (32%) omitting chemotherapy and 5 (5%) adding chemotherapy. Of 49 patients initially recommended chemotherapy, 30 (61%) were not recommended chemotherapy after receiving the Recurrence Score result (Fig. 1). Of 46 patients initially recommended no chemotherapy, 5 (11%) were recommended chemotherapy post-test. The proportion of patients recommended chemotherapy decreased from 52% pretest to 25% post-test ($p < .001$; McNemar's test).

Changes in recommendations by Recurrence Score group are shown in Table 3. Post-test treatment decisions seemed to follow the Recurrence Score result for low and high values. In the low Recurrence Score group, 21 of 24 patients (88%) initially recommended chemotherapy had chemotherapy omitted in their post-test treatment recommendation. All of the 5 patients in the high Recurrence Score group had a post-test recommendation for chemotherapy.

Changes in recommendations by nodal status are shown in Table 4. A statistically significant reduction in recommendations for chemotherapy was observed in pN0 patients ($p < .001$). Of the 42 patients who had no pretest recommendation for chemotherapy, 5 were shifted to chemotherapy post-test. Of the 41 patients with a prior recommendation for chemotherapy, 25 were shifted to no chemotherapy. This corresponded to 6% and 30% of all pN0 patients, respectively. The reduction in chemotherapy recommendations in the 12 pN1mi patients was of borderline statistical significance ($p = .063$), which may be the consequence of the small number of patients. No patient changed from no chemotherapy pretest to chemotherapy post-test, whereas 5 of 8 patients with a pretest chemotherapy recommendation changed to no chemotherapy post-test, corresponding to 42% of all pN1mi patients.

Table 1. Patient characteristics

Characteristic	*n* (%)
Patient age	
30–39 years	2 (2)
40–49 years	24 (25)
50–59 years	30 (32)
60–69 years	28 (29)
70–79 years	11 (12)
Menopausal status	
Premenopausal	29 (31)
Perimenopausal	12 (13)
Postmenopausal	54 (57)
Tumor size	
≤2 cm	76 (80)
>2 cm	18 (19)
Not recorded	1 (1)
Tumor grade	
G1	9 (9)
G2	76 (79)
G3	11 (12)
Number of positive nodes	
0	83 (87)
1	9 (9)
2	2 (2)
3	1 (1)
Histology	
Invasive ductal carcinoma	72 (75)
Invasive lobular carcinoma	22 (23)
Mucinous carcinoma	1 (1)
other	1 (1)
Recurrence score values	
Low (<18)	52 (55)
Intermediate (18–30)	38 (40)
High (≥31)	5 (5)

The total number of patients (*n*) was 95.

Table 2. Treatment recommendations before and after Oncotype DX testing

	Post-Oncotype DX, *n* (%)		
Pre-Oncotype DX chemotherapy	No	Yes	Total
No	41 (43)	5 (5)	46 (48)
Yes	30 (32)	19 (20)	49 (52)
Total	71 (75)	24 (25)	95 (100)

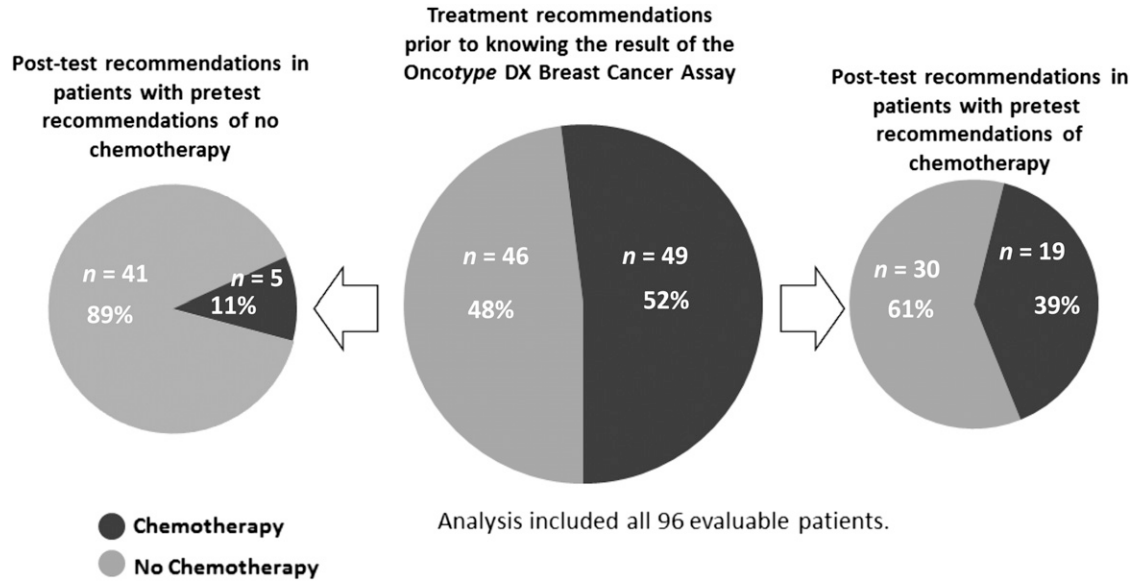

Figure 1. Shift in treatment recommendations by pretest treatment recommendation.

Table 3. Chemotherapy recommendations pre- and post-testing by Recurrence Score group

Group	Pre-Oncotype DX chemotherapy	Post-Oncotype DX, *n* (%)		
		No	Yes	Total
Low Recurrence Score group	No	28 (54)	0 (0)	28 (54)
	Yes	21 (40)	3 (6)	24 (46)
	Total	49 (94)	3 (6)	52 (100)
Intermediate Recurrence Score group	No	13 (34)	5 (13)	18 (47)
	Yes	9 (24)	11 (29)	20 (53)
	Total	22 (58)	16 (42)	38 (100)
High Recurrence Score group	No	0 (0)	0 (0)	0 (0)
	Yes	0 (0)	5 (100)	5 (100)
	Total	0 (0)	5 (100)	5 (100)

Table 4. Chemotherapy recommendations pre- and post-testing by nodal status

Nodal status	Pre-Oncotype DX chemotherapy	Post-Oncotype DX, *n* (%)		
		No	Yes	Total
Node-negative	No	37 (45)	5 (6)	42 (51)
	Yes	25 (30)	16 (19)	41 (49)
	Total	62 (75)	21 (25)	83 (100)
Node-positive	No	4 (33)	0 (0)	4 (33)
	Yes	5 (42)	3 (25)	8 (67)
	Total	9 (75)	3 (25)	12 (100)

Physicians' Confidence in Treatment Recommendation Before and After Oncotype DX Testing

Among 94 cases in which a measure of physicians' confidence was available, there was an overall significant improvement in physicians' confidence ($p < .001$; signed rank test). There were increases by 2 levels in 13 physicians (14%), increases by 1 level in 21 physicians (22%), no change in 47 physicians (50%), and decreases by 1 level in 13 physicians (14%) (Table 5).

Perception of the Clinical Utility of the Test

Physicians agreed or strongly agreed that the Oncotype DX assay results provided additional information in 75 of 94 cases (80% [95% CI: 70%–87%]) in which the physician's response was obtained (Table 6).

Discussion

Here we report the results of the first clinical utility study assessing the impact of integrating the Oncotype DX breast cancer assay into the decision-making process for adjuvant treatment of patients with ER+ EBC in the French clinical setting. Studies with a similar design have been reported from other countries [16–22]. They showed that the initial treatment recommendation is heterogeneous with the initial proportion of patients recommended chemotherapy ranging from 30% to 59%.

Based on traditional clinical and histopathological information, 49% of pN0 patients in our study would have received adjuvant chemotherapy according to our guidelines. This compares with 59% of pN0 patients in the Japanese study, 47% in the U.S. and the German studies, 36% in the Spanish study, and 30% in the Australian study [16, 18–21]. Different treatment traditions but also differences in patient population may affect the differences seen in these studies. One limitation of our study should be noted. Our patient population was primarily low and intermediate risk by classical parameters, and the proportion of tumors with lobular histology was also somewhat higher than in other studies. The distribution of the Recurrence Score results also reflected a low- and intermediate-risk patient population with a low proportion of high values compared with many other studies. Despite the consecutive enrollment asked for in the protocol, we could not preclude some degree of selection. This may have been caused by conventionally high-risk patients not consenting to take the

Table 5. Changes in physicians' confidence from pre- to post-Onco*type* DX testing

Pre-Onco*type* DX	Post-Onco*type* DX, *n*					
	Level 1	Level 2	Level 3	Level 4	Level 5	Total
Level 1	0	**0**	**0**	**0**	**0**	0
Level 2	*1*	0	**2**	**3**	**0**	6
Level 3	*0*	*0*	3	**4**	**10**	17
Level 4	*0*	*0*	*2*	28	**15**	45
Level 5	*0*	*0*	*0*	*10*	16	26
Total	1	0	7	45	41	94

Data were evaluable in 94 cases. Bold numbers indicate an increase in confidence, and italic numbers indicate a decrease in confidence. Level 1 indicates strongly disagree; level 2 indicates disagree; level 3 indicates neither disagree nor agree; level 4 indicates agree; and level 5 indicates strongly agree.

Table 6. Perception of the clinical utility of the Onco*type* DX breast cancer assay

Agreement with the statement "The Onco*type* DX assay results provided additional information"	*n* (%)
Strongly disagree	1 (1)
Disagree	5 (5)
Neither disagree nor agree	13 (14)
Agree	40 (43)
Strongly agree	35 (37)

test as a result of their physicians' conviction of the necessity of adjuvant chemotherapy in their respective cases.

Overall, treatment recommendations in our study changed in 37% of pN0 cases when Recurrence Score results were available as additional information. These results are consistent with those obtained in studies conducted in the U.S., Canada, Japan, Germany, and Spain (Table 7) [16, 17, 19–21]. The change rate in an Australian study was slightly lower (25%), but the proportion of patients originally recommended chemotherapy was also lower than in our study [18]. In our study, of the women with a pretest chemotherapy recommendation, 61% were recommended a less intensive treatment without chemotherapy after knowing the test results. This compares with 39% for the German study, 40% for the Australian study, 48% for the U.S. study, 51% for the Japanese study, and 56% for the Spanish study [16, 18–21]. In the U.K. study, the overall shift in treatment recommendations was 27% for a mixed population of pN0 and pN1mi patients, and 46% of patients with a prior recommendation of chemotherapy were recommended only adjuvant endocrine treatment after the test [22]. We also found a 42% change rate in pN1mi patients, which included only a shift from chemotherapy to no chemotherapy. However, the small number of patients with node-positive disease in our study limits the generalizability of this finding. Also, we had restricted enrollment to patients with micrometastasis in the regional lymph nodes as opposed to four other studies that reported results on the impact of the Recurrence Score in patients with ER+ EBC and 1–3 positive nodes. A U.S. web-based physician survey reported a change rate of 51% in 138 patients with a 33% change rate from chemoendocrine to endocrine therapy [34]. The Australian study found a 26% change in treatment recommendations in 50 patients (Table 7): 12 patients changed to endocrine therapy, and 1 changed to chemoendocrine therapy [18]. In the German study, there was a 39% change rate in 122 patients with a predominant change from chemotherapy to no chemotherapy in 28% [21]. The Japanese study reported a 65% shift in treatment recommendations in 20 patients exclusively from chemotherapy to no chemotherapy [19]. A large retrospective study from Israel in 951 patients with node-positive ER+ EBC found that 24.1% of all patients tested with the Onco*type* DX assay ($n = 282$) received chemotherapy compared with 70.1% of patients with similar baseline characteristics who did not ($n = 669$) [35].

The predominant and statistically significant change in our study, as in the other studies, was from a pretest recommendation for chemotherapy to a post-test recommendation without chemotherapy, with a decrease from 52% to 25%. Reassuringly, post-test treatment decisions seemed to follow the Recurrence Score result for low and high Recurrence Score values as was shown for the U.S., Spanish, and German studies [16, 20, 21]. As expected, the reduction in recommendations for chemotherapy was highest in the low Recurrence Score group with a net decrease of 40%. All patients with high Recurrence Score results were treated with chemotherapy. Although there was an overall net reduction of chemotherapy recommendations in the intermediate Recurrence Score group, a high proportion (28%) of patients in this group who were originally recommended endocrine therapy only were recommended chemotherapy post-test. There was no clear cutoff for Recurrence Score values within the intermediate risk group for chemotherapy recommendations. However, numbers in the intermediate subgroup were too small to explore this sufficiently.

We found a significant increase in physicians' confidence in their treatment decisions (36% of cases) after having the test results. The increase is relatively modest compared with that observed in studies in other countries: Japan (86%), U.S. (76%), Canada (59%), Spain (60%), and Germany (45%) [16, 17, 19–21]. However, physicians in our study agreed or strongly agreed that the Onco*type* DX assay results provided additional information in 75 of 94 cases (80% [95% CI: 69%–87%]). It should be noted that the assay was not frequently used in France and that the physicians in our study had limited, if any, experience with using it prior to the study. Results reporting physicians' confidence may thus also reflect cultural differences.

Our study did not include a pharmacoeconomic analysis to evaluate whether the net decrease in chemotherapy recommendations actually translated into economic savings. However, a recently presented analysis of the cost-effectiveness of using the Onco*type* DX breast cancer assay in France compared assignment of adjuvant chemotherapy based on the conventional approach in France and a meta-analysis from nine decision impact studies and projected the use of the test to be cost-saving in French clinical practice because of a decrease in overall chemotherapy costs alongside an increase in overall life years [31]. Findings from pharmacoeconomic analyses of using the assay in decision making in ER+ EBC in various health care systems showed that this approach was, at minimum, cost-effective [22–32].

Table 7. Summary of findings from prospective decision impact studies with Oncotype DX

Study [reference]	Country	Patients, *n*	Change after knowing the Recurrence Score result, %: From chemoendocrine therapy to endocrine therapy alone	Change after knowing the Recurrence Score result, %: From endocrine therapy alone to chemoendocrine therapy
Prospective studies: ER+, node-negative				
Lo et al., 2010 [16]	United States	89	23%	3%
Davidson et al., 2013 [17]	Canada	150	20%	10%
Albanell et al., 2012 [20]	Spain	107	21%	11%
Prospective studies: ER+, node-negative, and node-positive				
de Boer et al., 2013 [18]	Australia	101 (N0)	12% (N0)	12% (N0)
		50 (N+)	24% (N+)	2% (N0)
Yamauchi et al., 2013 [19]	Japan	104 (N0)	26% (N0)	7% (N0)
		20 (N+)	65% (N+)	0% (N+)
Eiermann et al., 2013 [21]	Germany	244 (N0)	18% (N0)	12% (N0)
		122 (N+)[a]	28% (N+)	9% (N0)
Holt et al., 2013 [22]	United Kingdom	142 (pNo or pN1mi)	18%	9%

[a]In 2% of patients, there was a change from observation to chemoendocrine therapy/endocrine therapy.
Abbreviations: N0, node-negative; N+, node-positive.

Conclusion

Because it is not possible to extrapolate data from one country to another, we considered generating specific data from French oncology centers to be highly relevant for making more accurate estimates of the health and economic impact of Oncotype DX use in the French health care system. The results from the SWITCH trial are consistent with those found in other European and non-European countries, confirming that the Oncotype DX breast cancer assay does impact adjuvant decision making in ER+ EBC in clinical practice resulting in a significant, meaningful net reduction in adjuvant chemotherapy recommendations.

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Disclosures

Joseph Gligorov: Genomic Health (C/A); **Xavier B. Pivot:** Roche, TEVA, Amgen (C/A), Pierre Fabre, Genomic Health (H); **Jean-Louis Misset:** ABscience (C/A); **Roman Rouzier:** Genomic Health (RF). The other authors indicated no financial relationships.

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