ANTICANCER RESEARCH *39*: 297-303 (2019)
doi:10.21873/anticanres.13111

Gene-expression Profiling – A Decision Impact Analysis: Decision Dependency on Oncotype DX® as a Function of Oncological Work Experience in 117 Cases

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Abstract. *Background: Estimating distant recurrence risk in women with estrogen receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer is still challenging. Oncotype DX® is a gene expression-based test predicting the likelihood of recurrent disease. This study analyzed the difference in oncological decision making with and without the knowledge of gene-expression tests based on oncological work experience. Materials and Methods: This was a retrospective analysis including n=113 patients diagnosed with hormone receptor-positive, HER2-negative breast cancer between 2011 and 2015 at the Municipal Breast Cancer Center Cologne, Germany. All 113 patients underwent evaluation by OncotypeDX®. An oncological Tumor Board with knowledge of these results served as baseline (control group). This baseline was compared to the treatment decision for adjuvant chemotherapy reached by oncologists with different experience levels (less than 5 years, between 5 and 15 years and more than 15 years) who were not provided the OncotypeDX® results. Results: Inexperience led to a significant increase in recommendations for chemotherapy, with those made by the Tumor Board being least frequent (41.6% vs. <5 years=55.6%, 5-15 years=50.4%, and >15 years=42.5%; p<0.05). An exploratory subgroup analysis showed the Tumor Board was significantly less likely to recommend chemotherapy for patients with Ki67 >14%, pN1 and postmenopausal status than were oncologists with up to 15 years experience, with a strong trend for those with tumor size larger than pT2. Conclusion: With a maximum reduction of 14.2% for those with the lowest level of oncological experience, the likelihood of recommending chemotherapy was found to decrease with increasing oncological work experience. A subgroup analysis showed that differences in decision making were most likely in patients with a Ki67 >14%, tumor sizes larger than pT2, pN1 and postmenopausal patients. It is the opinion of this study group that gene-expression testing is especially pertinent for these subgroups.*

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Key Words: gene-expression analysis, adjuvant chemotherapy, Oncotype DX®.

Estimating distant recurrence risk in women with estrogen receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer is still challenging. Oncotype DX® (Genomic Health, USA) is a 21-gene essay designed to predict the likelihood of recurrent disease (1, 2). While a plethora of prognostic factors estimating the likelihood of tumor recurrence and predictive factors estimating the likelihood of tumor response to a particular therapy are available, the decision for or against a chemotherapy is often a difficult one. Current prognostic factors such as tumor size and nodal status, as well as hormone receptor status, in short tumor morphology, are still critical for oncological decision-making. The same is true for HER2 overexpression. Some parameters are both predictive and prognostic in nature such as HER2 overexpression and hormone receptor status.

The Oncotype DX® is also a prognostic, as well as a predictive tool. This has been established in a variety of trials. The prognostic value of the Oncotype test has been established from archived material from the NSABP-B14 (3, 4), NSABP-B28 (5), transATAC (6), as well as in prospective trials such as TAILORX (7-9) and PlanB (10, 11). Several register trials also showed prognostic value *i.e.* the Clalit (12, 13) and the Surveillance, Epidemiology and End Results (SEER) (4, 14) databases. Within all these trials Oncotype DX® was established as a predictive and prognostic tool for node-negative and node-positive (N0 and

N1) breast cancer regarding the risk of recurrence after 10 years. Currently, the Oncotype DX® is the only assay that has been retrospectively and prospectively analyzed for the prediction of chemotherapy efficacy in patients with N0 and N1 disease. This is especially true for anthracycline-and taxane-based chemotherapy cohorts.

Today, it is well-established that the use of this test may lead to a significant reduction of chemotherapy application/ recommendation. A multitude of publications are available on this topic, leading to several reviews and meta-analysis of decision impact in this area (15-18). This investigator-driven study asked the question whether this is true across all levels of oncological work experience, the hypothesis being that with increasing oncological experience, physicians may be better able to judge the necessity of administering chemotherapy. We therefore evaluated the difference in oncological decision making with and without the knowledge of gene-expression tests as a function of oncological work experience, resulting in the following questions: Is there an influence of oncological work experience on favoring chemotherapy? Is there a difference between recommendations of chemotherapy with and without the knowledge of the Oncotype DX® results? Which subgroups are most influenced by the absence of Oncotype DX® testing?

Materials and Methods

This was a single-center, retrospective, anonymized patient data analysis of 113 breast cancer cases. Patient data recruitment occurred from the years 2015 to 2017 in the breast-cancer center of the municipal Hospital of Cologne, Holweide. All patients were female. The median age of patients was 54 (range=31-76) years. Overall, 49.6% of the patients were postmenopausal (n=56). Most patients (78.8%, n=89) had a non-specific tumor type (NST) and the majority (64.6%, n=73) of tumors were pT2 tumors or less. None of the patients had distant metastases. All breast tumors were hormone receptor-positive and 85.7% (n=96) of the tumors displayed a G2 grading. Only 8.8% (n=10) of the patients displayed a Ki67 staining of 25% or more. Fluorescence *in situ* hybridization or chromogenic *in situ* hybridization analysis was performed in cases of unclear HER2 status *i.e.* HER2 2+, but in this study were all negative. Tumors were equally distributed between left and right breast, although 5.3% of the patients (n=6) had bilateral breast cancer. In cases of differing cancer biology, the more aggressive tumor was submitted to Oncotype DX® testing. Patient cases were anonymized.

Oncotype DX®. This 21-gene assay results in a Recurrence Score (RS) and was developed and tested prospectively and retrospectively. The test involves assessing tumor RNA levels by reverse transcriptase polymerase chain reaction, followed by a central review of the specimens through Genomic Health resulting in said RS. The RS in turn offers a measure of recurrence risk (19).

Tumor board. The control group of this trial is represented by a Tumor Board decision with knowledge of Oncotype DX® test results. The primary endpoint was recommendation or not of chemotherapy. The Tumor Board consisted of several gynecological/ surgical oncologists, internal medicine oncologists, radiologists, radiation therapists as well as psycho-oncologists and breast care nurses. A decision for or against chemotherapy was unanimous for all 113 cases. The experience level of this Tumor Board varied across all tested subgroups. All decisions were made after previous sentinel node biopsy, thus nodal status was known. Patients with low-risk Oncotype DX® recurrence scores were not recommended chemotherapy, high-risk Oncotype DX® recurrence scores always yield a recommendation for chemotherapy. Intermediate-risk Oncotypes were again discussed in the Tumor Board although a tendency towards chemotherapy recommendation was common for these types of situations. When Oncotype DX® testing initiation deviated from the recommended procedure, for example G3 cancer and N+ and age <35 years, the test was performed at the patient's insistence. Table I shows an overview of patient characteristics.

Table I. *Overview of patient and tumor characteristics (113 females).*

Characteristic	Value
Age, years	
Median (range)	54 (31-76)
Menopause status, n (%)	
Premenopausal	57 (50.4)
Histology, n (%)	
NST	89 (78.8)
invasive lobular	14 (12.4)
Other	10 (8.8)
Other, n (%)	
Lymph node status pN0	61 (54.0)
Lymphangiosis L0	69 (63.3)
Ki67 (%)	
≤14	66 (58.4)
>14	37 (32.7)
≥25	10 (8.8)
Grading, n (%)	
1	7 (6.19)
2	96 (84.96)
3	9 (7.96)
NA	1 (0.88)
Median IRS (range)	
ER	12 (0-12)
PR	9 (0-12)
HER2/neu expression, n (%)	
0	44 (38.9)
1+	55 (48.7)
2+	14 (12.4)
Side, n (%)	
Left	54 (47.8)
Right	53 (46.9)
Bilateral	6 (5.3)
Size, n (%)	
pT1a	3 (2.7)
pT1b	9 (8.0)
pT1c	62 (54.9)
pT2	37 (32.7)
pT3	57 (50.4)

NST: No specified type, IRS: immunoreactive score, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2.

Table II. *Recommendations for chemotherapy by the Tumor Board compared to oncologists of different experience according to patient and tumor characteristics.*

		Tumor Board	<5 Years of experience		5-15 Years of experience		>15 Years of experience	
	N (%)	N (%)	N (%)	*p*-Value	N (%)	*p*-Value	N (%)	*p*-Value
Factor								
Total	113 (%)	47 (41.6)	63 (55.8)	0.0333	57 (50.4)	0.182	48 (42.5)	0.888
Age								
<40 Years	4 (3.5)	1 (25.0)	2 (50.0)	N/A	2 (50.0)	N/A	2 (50.0)	N/A
40-70 Years	99 (87.6)	42 (42.4)	54 (54.5)	0.088	50 (50.5)	0.254	42 (42.4)	>0.99
>70 Years	10 (8.9)	4 (40.0)	7 (70.0)	0.177	5 (50.0)	0.655	4 (40.0)	>0.99
Size								
≤ pT2	73 (64.6)	26 (35.6)	35 (47.9)	0.131	33 (45.2)	0.238	24 (32.9)	0.729
> pT2	40 (35.4)	21 (52.5)	28 (70.0)	0.108	24 (60.0)	0.498	24 (60.0)	0.498
Nodal status								
pN0	61 (54)	23 (37.7)	21 (34.4)	0.708	22 (36.1)	0.842	16 (26.2)	0.174
pN1	52 (46)	24 (46.2)	42 (80.0)	0.0002	35 (67.3)	0.030	32 (61.5)	0.115
Ki67								
≤14%	66 (58.4)	25 (37.9)	26 (39.4)	0.863	22 (33.3)	0.584	23 (34.8)	0.718
>14%	37 (32.7)	17 (45.9)	27 (73.0)	0.018	25 (67.6)	0.061	17 (45.9)	>0.99
≥25%	10 (8.9)	5 (50.0)	10 (100.0)	0.01	10 (100.0)	0.01	8 (80.0)	0.159
Menopause								
Pre	57 (50.4)	23 (40.4)	27 (47.4)	0.45	28 (49.1)	0.346	23 (40.4)	>0.99
Post	56 (49.6)	24 (42.9)	36 (64.3)	0.023	29 (51.8)	0.343	25 (44.6)	0.842
Histology								
NST	89 (78.8)	38 (42.7)	53 (59.6)	0.025	50 (56.2)	0.072	39 (43.8)	0.888
Invasive lobular	14 (12.1)	5 (35.7)	5 (35.7)	>0.99	4 (28.6)	0.689	5 (35.7)	>0.99
Other	10 (8.9)	4 (40.0)	5 (50.0)	0.658	3 (30.0)	0.639	4 (40.0)	>0.99

NST: No specified type.

Test groups. Treatment decisions (adjuvant chemotherapy or not) reached by gynecological oncologists with different experience levels were compared to that of the Tumor Board. Oncologists were divided according to low, moderate and extensive experience, namely less than 5 years, between 5 and 15 years, and more than 15 years, and were not provided the Oncotype DX® recurrence scores. All clinicians had access to clinical and histopathological data. A single test person was tested in each category (one per experience class) requiring each of them to evaluate all 113 cases. The goal was to obtain a recommendation for or against chemotherapy. Results were then compared to those of the Tumor Board. The primary endpoint was the likelihood of chemotherapy being administered as a function of oncological work experience. A subgroup analysis followed, evaluating these differences by tumor size, nodal status, Ki67, menopausal status and tumor histology (See Table II).

Statistics. Statistical analysis was performed using the VassarStats® (Vassar College, Poughkeepsie, NY, USA) statistics program. Student's *t*- and chi-squared tests were used in order to evaluate significances when appropriate. All reported *p*-values are two-sided and values of $p<0.05$ were considered statistically significant.

Ethics Committee approval. This study was conducted in accordance with Institutional Review Board standard operating procedures. An Ethics Committee vote was deemed unnecessary by the Ethikkommission der Aerztekammer Nordrhein as per the use of completely anonymized patient data.

Results

Overall a total of 113 sets of patient data were evaluated. The Tumor Board reached a recommendation for a chemotherapy in 41.6% of all patients (n=47). Without knowledge of the Oncotype DX®, the oncologist with extensive experience recommended chemotherapy in 42.5% of all cases (n=48), with moderate experience in 50.4% of all cases (n=57) and the least experienced recommended chemotherapy in 55.8% cases (n=63), the latter differing significantly from the Tumor Board decision ($p=0.033$). Use of Oncotype DX® yielded an overall chemotherapy reduction of between 0.9% and 14.2%. The decrease of 14.2% compared to those with the least experience level was statistically significant. An exploratory subgroup analysis stratified these differences by age, tumor size, nodal status, Ki67, menopausal status and tumor histology.

Within the patient age subgroup, three cohorts were evaluated. Ninety-nine patients (87.7%) were between the age

of 40 and 70 years. This being the largest cohort, there was no significant difference in the likelihood of chemotherapy recommendation between the Tumor Board and experienced physicians (>15 years of experience): Both recommended adjuvant chemotherapy in 42.2% of all cases for this age group; the oncologist with moderate experience recommended adjuvant chemotherapy in 50.5% and with the least in 54.5% (p=0.088). For those aged below 40 years, recommendation for chemotherapy was more likely across all experience levels without the use of an Oncotype DX®, although significantly different due to small sample size. Similar results were shown for patients older than 70 years of age.

Tumor size subgroup analysis showed 64.6% (n=73) of all patients to have pT2 tumor or less. For patients with tumors ≤pT2 in size, chemotherapy was recommended in 35.6% by the Tumor Board. No significant difference was seen in comparison with the most experienced oncologist (32.9%). A slight non significant increase in chemotherapy recommendation was again shown with decreasing experience (moderate: 45.2% and low: 47.9%). A similar trend was shown for those with tumors above pT2, although for this subset recommendation for chemotherapy by all experience levels was higher (Tumor Board: 52.5% *vs*. 60%, 60% and 70%, respectively), without statistical significance.

Nodal status also showed a trend towards increasing likelihood of chemotherapy administration with decreasing oncological experience. Sixty-one (54%) patients had node-negative disease. The Tumor Board recommended chemotherapy in 37.7% of these cases, while the most experienced oncologist recommended chemotherapy in 26.2% (p=0.174). Recommendation for chemotherapy was similarly lower by those with moderate and least experience (36.1% and 34.4% respectively (p=0.842, p=0.708)). However, a stark difference was seen in the nodal-positive subgroup. While chemotherapy recommendations were made least frequently by the Tumor Board (46.5%), they were made significantly more frequently by the most (64.5%) and moderately experienced (67.3%), and statistically significantly increased for the most inexperienced (80.0%, p=0.0002). The Discussion section will address the problem of perceived higher oncological aggressiveness due to nodal positivity.

Ki67 subgroup analysis placed most patients had Ki67 ≤14% (58.1%) and 8.8% had Ki67 ≥25%. For the low-risk group (Ki67 ≤14%), the Tumor Board recommended chemotherapy in 37.9% of the cases. This was mirrored by all three experience levels. The moderate-risk group of (Ki67=14-25%) again yielded increasing chemotherapy recommendations with decreasing experience. While the Tumor Board and the most experienced did not differ, both recommending chemotherapy in 45.9% of all cases, the recommendation rate increased 21.7% for the moderately experienced oncologist (p=0.061). This trend reached significance however for the least experienced, where chemotherapy was recommended in 73% of cases (p=0.018). A drastic increase in recommendation for chemotherapy without the knowledge of Oncotype DX® recurrence scores was shown for patients with Ki67 ≥25%. With only 10 patients in this subset, the Tumor Board recommended chemotherapy for half. Across all experience levels, chemotherapy recommendation was significantly increased (extensive experience: 80%, p=0.022; moderate and low experience: 100%; p<0.001).

Menopausal status did not seem to impact decision making. Overall, 50.4% of the patients were premenopausal. Chemotherapy recommendation by the Tumor Board for this group was 40.4%, and recommendation decreased with increasing experience, although no significant difference was reached. However, a trend was apparent for the postmenopausal cohort where a steady increase in recommendation for chemotherapy reached significance (64.3% by the least experienced oncologist, p=0.036).

Histological subtype showed 78.8% of all tumors to be NST breast cancer. Within the NST cohort, the were premenopausal. The Tumor Board recommended chemotherapy in 42.7% of all cases, similarly to the most experienced oncologist (43.8%). However, a strong trend towards increased likelihood of chemotherapy was shown for decisions by the moderately experienced (56.2%, p=0.072) and a significant increase was shown for decisions by the least experienced (59.6%, p=0.025). No significant difference or trend was shown for lobular or other breast cancer subgroups.

Discussion

Primarily, this work agrees with the available meta-analyses for Oncotype DX® use. A significant overall reduction in chemotherapy recommendation was shown for several subgroups across different experience levels. Most importantly, this work profoundly demonstrates the impact of oncological work experience on clinical decision making. In everyday practice, Tumor Boards usually include experienced oncologists with extensive experience, thus minimizing the impact of Oncotype DX®. However, it must be kept in mind that oncologists of all three experience levels are allowed to administer and decide on chemotherapy. In situations where oncologists with a high level of experience are not available, Oncotype DX® use should thus be considered more frequently.

The subgroup analyses showed several interesting facts. As reported in previous work, we found that the use of an Oncotype DX® assay generally reduced the frequency of recommendation for adjuvant chemotherapy (1, 2). This was either shown as a trend or a significant difference in all subgroups.

The experienced oncologist (>15 years). There was no significant difference between Tumor Board recommendation and decisions made by an experienced oncologist for any of the

subgroups. However, trends were observed. Decisions for chemotherapy without the knowledge of Oncotype DX® recurrence scores seemed to increase with increasing tumor size >pT2 (60% *vs*. 52.5% Tumor Board, p=0.48). The same was true for nodal positivity. Although no significance was reached here, very likely due to low patient numbers, there was a strong trend towards a more careful oncological approach, *i.e*. chemotherapy for the nodal positive subgroup. The Tumor Board recommended 46.2% of those with pN1 cancer to receive chemotherapy while the experienced oncologist recommended 61.5% of these patients to have chemotherapy. At a p-value of 0.115, significance was not reached, however. this trend immediately became significant when lowering the experience level, with an increase of chemotherapy recommendation peaking with 80% for the pN1 group by the oncologist with least experience. This behavior mirrors a typical tendency within the oncological community to associate nodal involvement with high tumor aggressiveness, thus recommending chemotherapy. The inverse seems to be true for nodal negativity, pN0 (Tumor Board: 37.7%, most experienced: 26.2%, p=0.174). This may be problematic since underestimation of tumor aggressiveness leads to dangerously inadequate therapy regimens. While for patients with pN0 disease there was no difference for the moderately and least experienced oncologists, the experienced oncologist seemed to underestimate tumor aggressiveness as shown in a reduction of 10.5% in chemotherapy recommendation when no Oncotype DX® was used. This trend was not significant and warrants further investigation.

The only other obvious deviation from Tumor Board recommendation by the most experienced oncologist was a 30% increase in chemotherapy recommendation for patients with Ki67 values above 25% (p=0.159). This cohort was low in number (n=10); this difference would surely reach significance with a larger cohort. Due to this trend, it is important to impress upon the reader the significance of the fact that evaluation of Ki67 is known to have a large inter-pathologist variability (20, 21). Nonetheless, oncologists, even those with great experience, seem to overestimate its value.

In summary, for the highly experienced oncologist, tumor size, nodal positivity and high Ki67 tend to lead to an increase in chemotherapy recommendation when Oncotype DX® is not used.

The oncologist with a medium experience level (5-15 years). Since only three levels of experience were evaluated, it was not possible to determine the exact turning point at which the difference in decision making reaches significance. For this level of experience, overall trends and differences were generally placed between low and high levels of experience, as would be expected. Without the knowledge of Oncotype DX® results, recommendations towards chemotherapy was generally higher than that of an experienced oncologist, although not as high as that of an inexperienced oncologist.

The inexperienced oncologist (<5 years). As physicians, we commonly prepare for the worst-case scenario, being pleased, however, whenever this does not become the case. Given this state of mind, we must then allow for the assumption that not all oncological decisions are made by the most experienced oncologists, thus requiring an analysis of the worst-case scenario *i.e*. an inexperienced oncologist with less than 5 years of experience. For this scenario, a significant increase in chemotherapy recommendation of 14.2% (p=0.033) was shown compared with when Oncotype DX® was used.

This overall discrepancy was found across every analyzed subgroup. All patient age groups showed an increased likelihood for chemotherapy administration without Oncotype DX® knowledge, with maximum increase of 30% (p=0.177) for the group aged >70 years, and borderline for those aged 40-70 years (p=0.088). Large tumor size (>pT2) also seemed to affect decision making as an increase of 17.5% (p=0.108) in favor of chemotherapy almost reached significance. Nodal involvement (pN1) as well as Ki67 >14% significantly increased chemotherapy recommendations by the least experienced physicians. For patients with pN1, the increase in chemotherapy recommendation was 33.8% (p=0.0002), which was highly significant. This again demonstrates that nodal status represents a subjectively uneven risk factor which seems to immediately be associated with a high risk of relapse, especially to the inexperienced oncologist. The same seemed to be true for patients with Ki67 values above 14% (27.1% increase, p=0.018) and Ki67 above 25% (50% increase, p=0.01). Given the unreliability of Ki67 as a parameter, this subgroup analysis seemed most interesting as one must be careful not to overestimate the importance of Ki67 values.

Although significance was reached within the postmenopausal cohorts (21.4%, increase, p=0.023) as well as the NST subgroup (16.9% increase, p=0.025), we believe that these were merely expression of the general tendency toward a more careful oncological approach in the absence of Oncotype DX® results.

Is there an influence of oncological work experience on favoring chemotherapy? There is a strong indication that experience level is inversely correlated with the recommendation for chemotherapy in the absence of Oncotype DX® results.

Is there a difference between recommendations for chemotherapy with and without the knowledge of the Oncotype DX® results? We found a significant difference in decision making. For the inexperienced oncologist, the likelihood of recommending chemotherapy was increased by 14.2% (p=0.033).

Which subgroups are most influenced by the absence of Oncotype DX® testing? Subgroup analysis showed Oncotype DX® assays to significantly affect decision making, in particular causing a reduction in chemotherapy for postmenopausal patients and those with pN1, Ki67 ≥14% and NST tumors. Strong trends were also shown for those with >pT2 tumors.

Limitations

The Authors are aware of the fact that a larger number of trialists *i.e.* more physicians within each experience subset, would have improved the level of evidence of this work. This study may be seen as a pilot study. We established baseline knowledge of the possible effect of Oncotype DX® testing on oncological decision making by experience level. It should be noted that within a real-life setting it is quite challenging to obtain participants with high levels of experience that are willing to work through 113 breast cancer cases. This is especially true since this work was a researcher-driven study and no funding was available.

Conclusion

Overall, chemotherapy recommendations were less frequent when Oncotype DX® was used. The likelihood of recommending chemotherapy decreases with increasing oncological work experience. A subgroup analysis showed that differences in decision making were most likely for postmenopausal patients, those with Ki67 >14%, tumor sizes larger than pT2 and pN1. It is the opinion of this study group that gene-expression testing is especially pertinent for these subgroups.

Conflicts of Interest

The Authors declare no conflict of interest in regard to this study.

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Received November 4, 2018
Revised December 9, 2018
Accepted December 12, 2018