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Original article

Results of PONDx, a prospective multicenter study of the Oncotype DX® breast cancer assay: Real-life utilization and decision impact in French clinical practice

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ABSTRACT

Adjuvant chemotherapy shows clear benefits in HER2-positive and triple-negative breast cancer (BC). Its benefits are less universal in BCs expressing hormone receptors. The 21-gene Oncotype DX® Breast Recurrence Score test was designed for HR+, HER2− early-stage BC before decision on adjuvant chemotherapy. Its validity and utility was demonstrated prospectively across multiple studies.

The observational study PONDx characterized the use of Oncotype DX® Breast in routine practice in France and evaluated its decision impact. Of 882 ER-positive BC patients (67% postmenopausal), most (79%) had N0/Nmic node involvement, grade 2 tumors (68%), tumor size 1–5 cm (88%), and ductal histology (78%). BCs with histopathologically elevated recurrence risk included grade 3: 18%; N1: 21%; Ki67 > 20%: 31%.

Recurrence Score results by prognostic category were: <18: 54%, 18–30: 36%; >30: 10%. Compared to recommendations before individual availability of the score, results prompted net absolute reductions in chemotherapy recommendations of 36% (total population), and 29% (grade 3 and/or Ki67 > 20% histologies). Decisions reflected prognostic implications: in the Recurrence Score <18 category, 95% of patients received recommendations of hormonal therapy only, in the >30 category, 97.5% were recommended additional chemotherapy; 95% followed the final recommendations of their physicians.

The Recurrence Score provides independent predictive and prognostic information in ER + N0/N1 early BC, including high-risk subgroups. PONDx further characterizes the population where the test is beneficial in real-life use and fits current clinical needs.

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Oncotype DX® Breast enables relevant net reductions in chemotherapy use, sparing patients from serious toxicities. Its therapeutic implications are highly accepted by physicians and patients.

Abbreviations

AGO	Arbeitsgemeinschaft Gynäkologische Onkologie (German Working Group for Gynecological Oncology)
ASCO	American Society of Clinical Oncology
CT	chemotherapy
ER	estrogen receptor
ESMO	European Society of Medical Oncology
HER2	human epidermal growth factor receptor 2
HT	hormonal therapy
N	lymph node
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
PR	progesterone receptor

1. Background

Breast cancer is the main cause of female cancer deaths in France. The disease incidence is high, with 54.000 new cases newly diagnosed in 2015 [1]. A vast majority of patients do not show detectable distant metastasis on diagnosis. In these cases, surgical tumor resection with conditional lymph node dissection is the primary treatment of choice. Adjuvant systemic treatments including hormonal therapy and chemotherapy aim at the reduction of the distant recurrence rate and improvement of breast-cancer specific survival. The decision on the individual choice of adjuvant therapeutic modalities is made according to several prognostic and/or predictive factors including patient age, tumor size, histological type and grade, lymph node involvement and expression on the tumor cell-surface of hormone receptors for estrogen (ER) progesterone (PR), and the human epidermal growth factor receptor 2 (HER2) as well as the percentage of tumor cells expressing the proliferation marker Ki67 [2].

While post-surgical adjuvant chemotherapy is universally accepted [3] and shows clear benefits in patients with HER2-positive and triple negative (ER−, PR−, and HER2−) tumors (together comprising roughly 30% of all cases), its benefits are far less universal in the more common breast cancers expressing hormone receptors (HR) (60–70% of cases). In ER + HER2−cancers, adjuvant chemotherapy is estimated to reduce the overall 10-year recurrence rate by an absolute margin of less than 10% [3]. This implies that an important proportion of patients does not experience any benefit from this treatment modality. Nonetheless, a large proportion of patients with these tumors not only receive hormonal therapy (HT) but also chemotherapy (CT) as a means of precaution, exposing them to a range of significant toxicities.

In the hormone receptor positive tumors, the conventional clinical, biological and histopathological do not reliably identify patients who are likely to derive a significant chemotherapy benefit in terms of cancer recurrence reduction that justifies the induced toxicities. Current treatment guidelines point out challenges in defining criteria for adding adjuvant chemotherapy to hormonal therapy when treating patients with ER-positive, HER2-negative early stage breast cancer. These guidelines also underscore an important role for the tumor profiling with multi-gene expression assays in decision-making and avoidance of overtreatment. Therefore, this approach increasingly advocated to predict the benefit of adjuvant chemotherapy and thus aid treatment decisions in patients with hormone-receptor positive breast cancers.

The Oncotype DX® Breast test is a 21-gene assay designed for use in HR+, HER2− early-stage breast cancer patients before the decision on the option of adjuvant chemotherapy. It measures the transcriptional activity of 21 genes (16 cancer-associated genes and 5 housekeeping genes) and uses the expression pattern to calculate a recurrence score between 0 and 100: the higher the score, the greater the risk of recurrence of an invasive breast cancer. The score results are interpreted in three categories (low risk: Recurrence Score results <18; intermediate risk: Recurrence Score results = 18–30; high risk: Recurrence Score results ≥31). These categories are based on comprehensive prospective studies on the correlation of Recurrence Score results and recurrence-free rates in patients receiving adjuvant HT or HT + CT [4]. The Recurrence Score result provides two types of information on tumor biology: (i) an estimate of the individual risk of distant cancer recurrence within 10 years, (ii) an estimate of the likelihood of a benefit from chemotherapy.

The clinical validity and utility of Oncotype DX Breast Recurrence Score® test has been demonstrated prospectively across multiple studies in more than 96,000 breast cancer patients worldwide including multiple validation studies (4000 patients [5–9]) as well as long-term prospective studies (TAILORx [10], WSG Plan B [11,12]), a prospective cohort study (Clalit [13,14]) and analyses from a prospective epidemiological database (SEER [15]). Its clinical impact and pharmacoeconomic benefit in routine care has been show in 20 decision-impact studies. The Oncotype DX® test is based on level Ia evidence and has been incorporated in leading internationally-accepted clinical guidelines on the treatement of early breast cancer (St. Gallen [16], ESMO [17], NCCN [18], ASCO [19], NICE [20] and AGO [21]).

The market access program PONDx (Prospective multicenter study of the ONcotype Dx test) was initiated in 2015 to provide access to the Oncotype DX Breast Recurrence Score® assay in France prior to the inclusion of the test in reimbursement schemes. PONDx collected real-life data regarding the test utilization in French routine clinical practice. PONDx allowed to collect data on the use of the test while the RiHN innovation funding (Référentiel des Actes Innovants hors Nomenclature) was in place (between January 2016 and until July 2016) which represent more than 94% (836/882) of all PONDx data.

2. Methods

2.1. Patients and ethical approval

PONDx was an observational multicenter prospective study collecting data on the real-life use of Oncotype DX Breast Recurrence Score® test by physicians in routine clinical practice settings throughout France. Each treating physician had the responsibility to inform and obtain consent of patients to participate to this observational study. Pseudonymized patient data were acquired via

a dedicated internet platform. Only aggregated data (at least 10 cases per center) were used for the analyses performed in this study. Data were hosted and managed by an external provider certified according to ISO 27001 and ISO 27799:2008.

Patient eligibility criteria for this analysis correspond to the population for which the Oncotype DX Breast Recurrence Score® test is validated, i.e. adult patients with a recent first diagnosis of a single non-metastatic invasive breast tumor with ER positive (ER+) and HER2 negative (HER2−) status, plus available documentation of lymph node involvement as either N0 (node negative), Nmic (micrometastatic) or N1 (1–3 positive nodes).

The following data items were documented: patient age and sex, menopausal status, conventional clinical and pathological disease characteristics including histologic type, tumor size and grade, nodal status, receptor status including ER, PR, and HER2 receptors, and the Ki67 proliferation marker. The hormonal receptor status (ER and PR) was considered positive according to standardized European guidelines using a cut-off of ≥10% stained tumor cell nuclei. The Oncotype DX Breast Recurrence Score® results and the type of treatment (hormonal therapy plus/minus chemotherapy, or other modalities) recommended by the treating physician for the individual patient both before (pre-Recurrence Score results) and after (post Recurrence Score results) availability of the test results as well as patient acceptance of the recommendations were documented.

2.2. Objectives and statistical analyses

The primary aim of PONDx study was to evaluate the impact on treatment decisions of the use of the Oncotype DX Breast Recurrence Score® assay in routine clinical practice in France. Secondary objectives included (i) the description of the patient population in which the test is performed; (ii) the analysis of the subgroup of patients with “high-risk” tumor according to clinicopathological features.

Analyses were performed for the full population and for subpopulations of “high-risk” tumor patients defined as having a grade 3 tumor and/or a Ki67 positivity rate of >20%.

Changes in treatment recommendation and impact on chemotherapy use were calculated by comparing the percentage of patients having a recommendation of HT or HT + CT before versus after availability of the test results. Descriptive statistics were used to summarize clinicopathological characteristics. Variables were described by the size and percentage rate.

3. Results

3.1. Characteristics of the patient population

Complete datasets from 882 breast cancer patients who underwent Oncotype DX Breast Recurrence Score® testing were provided by 53 private practices and public treatment centers (public hospitals, university hospitals, comprehensive cancer centers). The patients included were almost exclusively female (n = 878), predominantly postmenopausal (67%), and showed a wide age distribution (27% < 50 years, and 14% > 70 years).

The predominant tumor characteristics were N0 or Nmic (79%), grade 2 (68%), tumor size pT1c (1–2 cm) (57%) and ductal histology

Table 1
Patient and disease characteristics in the total population of HER2 negative patients and in predefined risk groups.

Characteristic		Total population		Patients with grade 3 tumors		Patients with Ki67 > 20%	
		Number of patients [n]	Percentage [%]	Number of patients [n]	Percentage [%]	Number of patients [n]	Percentage [%]
Sex	Female	862	99.5	157	100	261	99
	Male	4	0.5	0	0	2	1
Age, years	<35	12	1	1	1	5	2
	35–50	221	26	27	17	57	22
	51–70	510	59	98	62	150	57
	>70	123	14	31	20	51	19
Menopausal status	Pre	203	23	24	15	53	20
	Peri	80	9	11	7	21	8
	Post	579	67	122	78	187	71
	NA	4	0	0	0	2	1
Nodal involvement	N0	613	71	127	81	203	77
	Nmic	72	8	7	4	18	7
	N1	181	21	23	15	42	16
Histological type	Ductal	676	78	126	80	211	80
	Lobular	124	14	12	8	33	13
	Other	66	8	19	12	19	7
Tumor grade	G1	120	14	0	0	16	6
	G2	589	68	0	0	160	61
	G3	157	18	157	100	87	33
Tumor size	<1 cm	79	9	14	9	21	8
	1–2 cm	491	57	92	59	156	59
	2.1–5 cm	270	31	50	32	80	30
	>5 cm	26	3	2	1	6	2
ER status*	positive	864	100	157	100	262	100
	negative	2	0	0	0	1	0
PR status*	positive	744	86	128	82	217	83
	negative	122	14	29	18	46	17
HER status	positive	0	0	0	0	0	0
	dubious	6	1	2	1	5	2
	negative	860	99	155	99	258	98
Ki67 positive cells	<10%	158	18	5	3		0
	10–20%	331	38	24	15		0
	21–30%	162	19	39	25	101	38
	>30%	101	12	48	31	162	62
	NA	114	13	41	26		0

Table 2
Recurrence score distribution by patient and tumor characteristics.

Characteristics		n =	Percentage [%] of patients with Recurrence Score results by category		
			<18	18–30	>30
Total population		866	54%	36%	10%
Preselected risk factors	Grade 3	157	29%	44%	27%
	Ki 67 > 20%	263	39%	41%	19%
Age	<35	12	42%	50%	8%
	35–50	221	57%	36%	7%
	51–70	510	55%	36%	9%
	>70	123	52%	36%	12%
Tumor grade	1	120	72%	26%	3%
	2	589	58%	36%	6%
	3	157	30%	45%	25%
Tumor size	<1 cm	79	53%	41%	6%
	1–2 cm	491	53%	38%	9%
	2.1–5 cm	270	57%	34%	9%
	>5 cm	26	69%	19%	12%
Nodal status	N0	613	54%	37%	9%
	Nmic	72	57%	35%	8%
	N1 (1–3 nodes)	181	56%	36%	8%
Ki67 positive cells	<10%	158	68%	30%	3%
	10–20%	331	61%	35%	4%
	21–30%	162	42%	46%	12%
	>30%	101	38%	34%	29%
	NA	114	51%	39%	11%

(78%). A sizeable fraction of patients had a high recurrence risk as defined by tumor grade and nodal status (grade 3: 18%; N1: 21%). All patients had ER positive tumors. Two percent (n = 16) patients initially identify by centers as HER2-were finally HER2-positive by Oncotype DX, confirmed locally and excluded from decision impact analysis. Table 1 shows the patient and disease characteristics of the total population. The Recurrence Score values were <18 in 55% (n = 474), 18–30 in 36% (n = 314) and >30 in 9% (n = 78) of the patients. Table 2 shows the distribution of Recurrence Score results according to tumor grade and size, patient age, Ki67 positivity categories and nodal status.

3.2. Decision impact

Prior to the availability of the Recurrence Score results (pre RS results), physicians recommended a regimen of hormonal plus chemotherapy (HT + CT) in 66% (n = 499) of the patients, while 34% (n = 262) were to receive hormonal treatment (HT) only (Fig. 1a).

After the Recurrence Score results became available (post RS), the physicians changed their treatment recommendation in 44% of patients: 61% of HT + CT recommendations were changed to HT alone, while 13% of HT alone recommendations were changed to HT + CT. Now, 30% of the patients were to receive HT + CT (n = 228) and 70% HT alone (n = 533), corresponding to a reduction of 36% in recommendations for chemotherapy.

Physician's decisions reflected the prognostic and predictive implications of the Recurrence Score categories: among the patients in the Recurrence Score <18 category, 95% received a recommendation of HT alone while in the Recurrence Score >30 category, 97.5% were recommended to undergo CT + HT. The great majority of the patients (95%) followed the final recommendation of their physicians.

3.3. Patients with tumor size <1 cm

Seventy-nine HER2 negative patients (9%) had a tumor size less than 1 cm. Of these, 28 (35%) had grade 1 tumors, 37 (47%) grade 2 and 14 (18%) grade 3. Sixty-one patients (77%) had N0 nodal status and 18 were Nmic or N1 (23%). The pre RS treatment recommendation was available for 74 patients: it was HT-CT for 40 (54%) and HT alone for 34 (46%). After availability of the RS results, 24 patients (60%) were switched from HT-CT to HT alone. All of them had a RS result <26 and for 18 of them the RS result was below 18. For six patients (17%), the treatment recommendation was modified from HT to HT-CT; 5 of these patients had a RS result >26.

3.4. Patients with tumor size 1–2 cm

Five hundred patients (65%) had a tumor size between 1 and 2 cm. Of these, 58 (12%) were grade 1, 347 (69%) grade 2 and 95 (19%) grade 3. Nodal status was: 367 patients (74%) N0, 46 (9%) Nmic and 87 (17%) N1. Ki67 was <10% for 76 patients (15%), 10–20% for 197 patients (40%), 21–30% for 101 patients (20%), >30% for 61 patients (12%) and unknown for 65 patients (13%). Data for pre and post test information were available for 449 patients (90%), pre-test recommendation was HT-CT for 286 patients (64%) and HT for 163 patients (36%). Post-test, 162 patients (57%) were switched from HT-CT to HT alone while 22 (13%) were switched from HT to HT-CT, all of the latter group had an intermediate RS. (RS 18–30: n = 10; RS > 30: n = 11; unknown: 1).

3.5. Younger patients (age ≤50 years)

Eighty-three (26%) of 314 patients had an age ≤50 (data were collected in categories of age <35, 35–50, 51–70 and > 70 years), pre and post treatment recommendations were available for 72 patients in this subpopulation. Sixty-two patients (86%) had an initial recommendation HT + CT, which was changed to HT alone for 17 patients (24%) after testing. For these patients, the RS result was in the range of 18–24. In this population initial HT alone treatment was recommended for 17 patients, it was changed to HT-CT after testing for 3 of them (RS results were 19, 27 and 29).

3.6. Patients with intermediate RS results

Based on the RS cutoff of the recent publication of TAILORx, 314

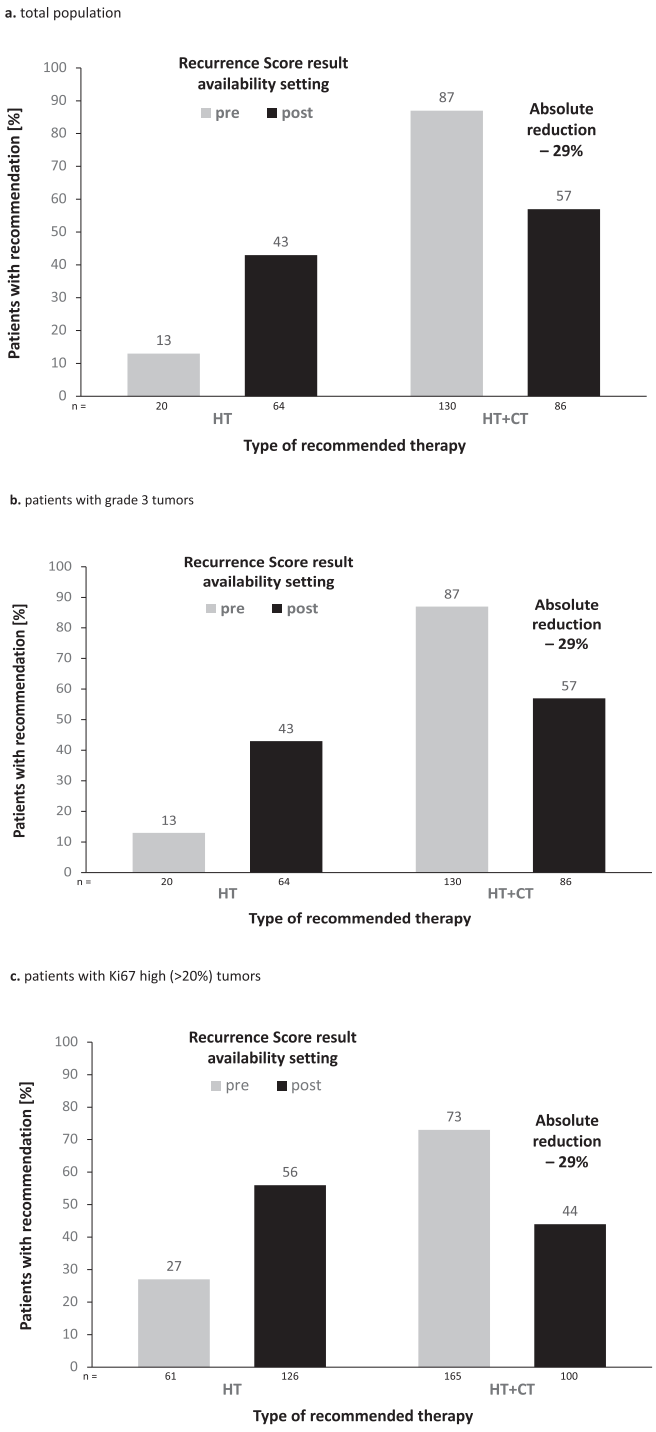

Fig. 1. Decision impact of the Oncotype DX Breast Recurrence Score® results on adjuvant therapies in breast cancer patients. Change of physician's treatment recommendations before (pre Recurrence Score) and after (post Recurrence Score) availability of the Recurrences Score result. Patients who received recommendations other than HT or HT + CT before and/or after availability of test results were excluded from this analysis. **a.** total population, **b.** patients with grade 3 tumors, **c.** patients with Ki67 high (>20%) tumors.

HER2− patients had a RS in the category 18−30, the exact results of 5 patients were missing. For 195 (63%) pre-test treatment recommendation was HT + CT, it was switched to HT alone for 76 patients (39%) when the RS result became available.

3.7. Analysis of patients with tumors considered high-risk by histopathological criteria

Among the 157 HER2− patients with grade 3 tumors, 87% (n = 130) had a pre-Recurrence Score recommendation of HT + CT (Fig. 1b). This proportion was reduced to 57% (n = 86) after the Recurrence Score result became available (post Recurrence Score results), i.e. 38% (50/130) of the HT + CT recommendations were changed to HT alone, while 30% (n = 6/20) of the HT alone recommendations were changed to HT + CT. This resulted in a net reduction of 29% in chemotherapy recommendations for patients with G3 tumors.

Likewise, among the patients HER2− with high Ki67 (>20%) status, 73% (n = 165) received a pre-Recurrence Score recommendation of HT + CT (Fig. 1c). This proportion was reduced to 44% (n = 100) after the Recurrence Score result became available (post Recurrence Score results), i.e. 47% (n = 78) of the HT + CT recommendations were changed to HT alone, while 21% (n = 13) of the HT alone recommendations were changed to HT + CT. This resulted in a net reduction of 29% in chemotherapy recommendations for patients with high Ki67 status.

In agreement with the results in the total population, physician's final decision reflected the Recurrence Score categories in high-risk patients with G3 and high Ki67 tumors, respectively: 84% and 83% recommendations for HT alone in patients with Recurrence Score results <18; 93% and 96% recommendations for CT-HT among patients with Recurrence Score results >30.

In these subpopulations, 94% and 97% of the patients, respectively, followed the final recommendations of their physicians whether or not it had been changed after the availability of their individual Recurrence Score.

4. Discussion

PONDx documented the real-world, utility and value of the Oncotype DX Breast Recurrence Score® test in a large cohort of patients in France, complementing a range of multiple decision impact studies that utilized consistent methodology involving >2500 patients in Germany, France, UK, Spain [22] and Australia [23] and other countries. The routine use of the Oncotype DX Breast Recurrence Score® test impacts French physician decisions and allows a decrease in the prescription of adjuvant chemotherapy by 35% in the PONDx patients in France and in similar patient cohorts from countries around the world [24–39].

The patient populations and the rates of changes in treatment recommendations from this study are similarto previously reported decision impact studies and suggests that treating physicians are consistently and appropriately incorporating the Recurrence Score results into their clinical practice.

Modification of treatment decision in PONDx was consistently more pronounced in direction of chemotherapy de-escalation and concordant across different subpopulations analyzed. No increase of chemotherapy decisions was observed in any of these subpopulations. PONDx was designed prior to the availability of the TAILORx results. New cutoff values derived from this landmark study will probably lead to an additional reduction of chemotherapy recommendations in routine clinical practice in patients with RS < 25. These results will also favor systemic adjuvant chemotherapy in all patients with RS > 25. The high rate of patients following the secondary treatment recommendation of their physicians supports the acceptance of genomic testing results among French physicians and patients.

The use of chemotherapeutic regimens in adjuvant therapy of early breast cancer is clearly associated with acute adverse effects and long-term sequelae including fatigue, cardiotoxicity, secondary

leukaemia, cognitive deterioration [40] and peripheral neuropathy [41], depending on the regimen used. Moreover, quality of life and work capacity may be deteriorated [42]. Assessing the benefit-risk balance of adjuvant chemotherapy in patients with ER + HER2− primary breast cancer remains a challenge. The use of the Oncotype DX Breast Recurrence Score® test in these patients may thus contribute significantly to a reduction of the side effects burden and long-term sequelae of these toxic therapies while preserving adjuvant treatment outcomes in terms of tumor recurrence and cancer-related survival.

While most treatment changes involved the omission of CT, a smaller fraction of patients were switched from HT alone to HT + CT. This means that restricting the use of the Recurrence Score result to patients with initial HT + CT recommendations would miss the chance to identify patients who might benefit from CT as indicated by a high Recurrence Score result despite having presumably low-risk tumor according to clinical-histopathological features.

Limitations of the current study include the lack of information on factors influencing the selection of patients for testing, while may be assumed that is based on physician's experience and his perspective on the potential benefit of molecular testing for the individual patient.

In addition, data on the potential economic impact and cost-efficacy of the Oncotype DX Breast Recurrence Score® test were not acquired. However, the economic impact could be extrapolated based on the net reduction of chemotherapy use, given the well-studied cost of chemotherapies in France.

Adjuvant chemotherapy decisions in ER+/HER2-early breast cancer in France are based on classical prognosis (node status, histologic grade, size, Ki67%, age) and predictive factors (hormonal receptor status, HER2 status) [43].

Some centers use their own local or regional recommendations (examples: Remagus [44] or Référentiel APHP [45], and others use various international guidelines (ESMO [7], St. Gallen [16], ASCO [19] or NCCN [8]). For this study, none of participaring centers used chemotherapy decision algorithms (for example AOL or Predict). It must be noted that locoregional guidelines mostly derive from international recommendations. However, a French survey assessed the factors impacting the decision for adjuvant chemotherapy and showed a heterogeneity of decision in borderline cases with in one case 52% of physicians opting for adjuvant chemotherapy versus 48% for endocrine therapy alone [46].

5. Conclusions

The results of PONDx confirm that the Oncotype DX Breast Recurrence Score® test provides independent clinical utility beyond standard clinical and pathological parameters in the ER + N0/N1 early breast cancer population and in subgroups of patients deemed at high risk by conventional factors. The study results help to further define the patient population in which the test is performed and fits current clinical practice needs.

The Recurrence Score result changes and/or supports final treatment decisions with a significant impact on treatment decisions. i.e. a reduction of chemotherapy use, in particular. The therapeutic implications of the Recurrence Score results are highly accepted by physicians and patients.

Importantly, the use of the Oncotype DX Breast Recurrence Score® leads to a relevant net reduction in chemotherapy use, sparing acute and long-term toxicities in a significant proportion of patients, and identifying a smaller number of patients with a potential added benefit of chemotherapy who are not captured by conventional criteria.

Conflicts of interest

None of the authors have conflicts of interest regarding this work.

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