The Impact of EndoPredict Clinical Score on Chemotherapy Recommendations in Women with Invasive ER⁺/HER2⁻ Breast Cancer Stratified as Having Moderate or Poor Prognosis by Nottingham Prognostic Index

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Abstract. *Background:* The Nottingham Prognostic Index (NPI) was developed using tumour pathological features to guide decisions regarding adjuvant therapy in breast cancer. Recent breakthroughs in molecular biology aided development of genomic assays such as EndoPredict, which have been shown to provide excellent prognostic information. *The current study investigated the impact of EndoPredict Clinical (EPclin), a composite of clinicopathological data and EndoPredict score, on chemotherapy recommendations based on NPI. Patients and Methods:* A total of 120 patients with oestrogen receptor-positive (ER⁺)/human epidermal growth factor receptor 2-negative (HER2⁻) breast cancer who were candidates for post-operative adjuvant chemotherapy at a single tertiary centre were included. Both NPI and EPclin were applied to all patients. NPI differentiated patients into groups with excellent/good prognosis (N=41; NPI≤3.4) or moderate/poor prognosis (N=79; NPI>3.4). The latter were considered for adjuvant chemotherapy. *Results:* There was discordance in results of 31% of cases; 35% of the patients/candidates for adjuvant chemotherapy according to NPI were reclassified as being at low risk of recurrence by EPclin. *Conclusion:* Genomic profiling using EPclin reduces the potential need for adjuvant chemotherapy in women with ER⁺/HER2⁻ breast cancer who are candidates for chemotherapy according to the NPI.

The use of adjuvant therapy in conjunction with surgical resection in the treatment of breast cancer has since long

been an essential intervention in reducing the rate of recurrence. However, the morbidity associated with chemotherapy and radiotherapy has also been an important consideration in questions pertaining to the treatment of breast cancer (1). Several tools have been developed to aid in decisions regarding adjuvant therapy. These include specialist guidelines, such as the St. Gallen consensus (2). In addition, cancer registries were created and form the basis of online prognostic tools, such as NHS PREDICT and Adjuvant Online! (AO) (3, 4).

Various predictive tools have been developed for breast cancer including pathology-based scoring systems, such as the Nottingham Prognostic Index (NPI), which uses tumour pathological features to guide decisions regarding adjuvant systemic therapy (5). The NPI was developed in 1982 after a multivariate analysis identified a limited set of variables which were predictive of disease recurrence. The NPI divided patients into three subsets based on their predicted prognosis (6). This index is currently in use in the UK but is yet to gain currency in other medical systems.

Recent breakthroughs in molecular biology have aided development of genomic assays (e.g. MammaPrint, Oncotype DX[®], and EndoPredict). These genomic assays have been demonstrated to provide excellent prognostic information and guide decision making in patients with oestrogen receptor-positive (ER⁺)/human epidermal growth factor receptor 2 negative (HER2⁻) breast cancer (7). EndoPredict Clinical (EPclin) is a further refinement of EndoPredict. It is composite tool in which the results of 12-gene molecular score, of EndoPredict are combined with tumour size, and nodal status to determine the risk of recurrence. Studies have shown that it provides superior clinical information (8, 9).

This current study compared and contrasted the results of EPclin compared to NPI in selecting appropriate patients for adjuvant chemotherapy.

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Key Words: Genomic assays, prognosis, adjuvant therapy, breast cancer.

Patients and Methods

The study was conducted at the London Breast Institute and patients were recruited between December 2015 and December 2016. The inclusion criteria were female patients with newly diagnosed ER⁺/HER2⁻, node-positive or -negative primary breast cancer who underwent breast-conserving surgery or mastectomy (with or without reconstruction) and sentinel lymph node biopsy with/without axillary lymph node clearance. Exclusion criteria were patients with inoperable disease.

Pathological analysis was conducted at the Pathology Department of the London Breast Institute. EndoPredict was performed on paraffin-embedded tumour samples, and the EPclin score was calculated by combining the EndoPredict score derived from a 12-molecule array with the nodal status and tumour size. The patients were stratified into low (EPclin ≤3.3) and high-risk groups (EPclin >3.3) (9). The patients recruited were also assessed using NPI. The formula used was as follows:

$$NPI=(0.2S)+N+G$$

Calculation of NPI required the nodal status (N=0 for no nodal involvement, N=2 if 1-3 nodes were involved, and N=3 if more were involved), the size of the lesion in centimetres (S), and tumour grade (G) (5).

The therapeutic recommendations derived from the risk stratification from both tests were compared for concordance and discordance.

Results

A total of 120 patients underwent mastectomy or breast-conserving surgery for ER⁺/HER2⁻ breast cancer at a single centre, the London Breast Institute at The Princess Grace Hospital. The mean age was 55 years (median age=54 years, range=31-77 years). The EndoPredict and the EPclin scores were determined in 120 tumours from these 120 patients. Based on the classification described by Filipit *et al.* (9), patients were divided into two recurrence risk groups: Low risk (EPclin ≤3.3) and high risk (EPclin >3.3). Sixty (50%) out of 120 patients were classified as having high risk and 60 (50%) as having low risk (range=1.9-5.7) (Figure 1). The median EPclin score for the low-risk group was 2.7 and for the high-risk group was 3.8 (Table I).

The NPI differentiated the patients into groups with excellent/good prognosis (n=41; NPI ≤3.4) or moderate/poor prognosis (n=79; NPI >3.4). The latter group (65.8% of the cohort) were considered potential candidates for adjuvant chemotherapy (Table II).

Twenty-eight out (35%) of the 79 patients considered candidates for adjuvant chemotherapy according to the NPI score were reclassified as being at low risk of recurrence by EPclin (<3.3), potentially leading to a 32% reduction in chemotherapy prescriptions. Similarly, nine (22%) out of the 41 patients in the group with excellent/good prognosis by NPI were classified as being at high risk of recurrence by EPclin and were offered adjuvant chemotherapy.

Table I. Summary of EndoPredict Clinical (EPclin) results.

EpClin risk category	No. of patients (%)	Median score	Range
High	60 (50%)	3.8	3.32-5.7
Low	60 (50%)	2.7	1.9-3.27

A total of 37 cases out of 120 (31%) were discordant. In total, EPclin potentially reduced the number of patients requiring adjuvant chemotherapy to 60 (a reduction of 24%) (Figure 1).

Discussion

Breast cancer continues to be the second most commonly diagnosed cancer in female second only to skin cancer. It also is the second leading cause of cancer death in women after lung cancer (10-11). In the past, breast cancer required radical surgery incurring severe morbidity and poor outcomes. Fortunately, survival has greatly improved over the years, despite a general move to less radical and less morbid surgical resections (10-12). This trend has been enabled by a series of breakthroughs, including advances in adjuvant and neoadjuvant chemo- and radiotherapy, endocrine therapy, prognostic tools and guidelines based on prospective trials and cancer trials, and, more recently, genomic assays harnessing recent developments in molecular biology (7, 13-15).

At the heart of this most recent development in the management of breast cancer is the recognition of breast cancer as a highly heterogenous cluster of distinct neoplastic diseases identifiable by distinct molecular signatures. At the time of writing, seven such molecular types had been identified (16, 17). This new insight has made it feasible to tailor patient treatment according to more accurate risk stratification by genomic assays. These assays have been demonstrated to be robust and reliable, and have been included in various clinical guidelines, including those published by NICE (18). EPclin, being a composite of the results of a genomic assay and clinical parameters, could potentially be an even more robust tool which could guide clinical decision-making regarding adjuvant therapy (19).

The NPI is a pathology-based index which stratifies patients into low-, medium- and high-risk groups. It has gained currency especially in the UK and was found to be comparable to the cancer registry-based online tools which were developed in subsequent years (4). It has been argued that there is still role for the NPI in relatively resource-deprived areas, where deploying genomic assays may be a significantly capital-intensive endeavour. If non-inferiority of NPI to EPclin is proven, it would raise interesting prospects for healthcare delivery in such settings (20).

Figure 1. Flowchart showing risk stratification of patients according to EndoPredict Clinical (EPCLin) and Nottingham Prognostic Index (NPI).

However, the results of our study demonstrate a significant discordance between the results of EPCLin and NPI. In light of our results, it is likely that genomic profiling using EPCLin reduces the potential need for adjuvant chemotherapy by 32% in women with ER⁺/HER2⁻ breast cancer who are considered potential candidates for chemotherapy according to the widely used NPI. Such a large proportion of patients being spared adjuvant chemotherapy translates into less morbidity, improved quality of life, and less expenditure of clinical resources.

These findings are similar to those of our study comparing EPCLin and NHS PREDICT, a cancer registry-based online prognostic tool. We found a discordance of 41.66% (21). Taken together, the results of the present study show that the gulf between genomic assays and tests based on older modalities is significant, and it may not be possible to bridge this gap by improvements in these tools which are limited to

their current underlying technology and datasets. In addition, it underlines the place of genomic assays in the current management of breast cancer. Tools such as NPI and NHS PREDICT cannot be advocated as alternatives to genomic assays, even in resource-poor settings.

Conclusion

The discrepancy between the results given by the NPI and EPCLin examined in this study cannot be ignored and may have profound implications for patient morbidity and quality of life. Furthermore, it would be worth conducting a study into the potential for cost-saving in terms of resources, clinical sessions and patient recovery time when using genomic assays, and to what degree they would offset the capital investment required in health systems in the developing world.

Table II. Collation of Nottingham Prognostic Index (NPI) and EndoPredict Clinical (EPclin) results.

Patient number	Age, years	Tumour grade	Tumour size (mm)	Number of involved lymph nodes	NPI score	NPI risk group	EPclin score	EPclin risk group
1	49	2	25	1	4.5	Moderate	3.7	High
2	59	2	25	1	4.5	Moderate	4.6	High
3	45	2	55	1	5.1	Moderate	3.6	High
4	46	2	10	0	3.2	Good	1.9	Low
5	49	3	23	0	4.46	Moderate	3.2	Low
6	54	2	20	0	3.4	Good	3.6	High
7	47	2	38	0	3.76	Moderate	3	Low
8	45	2	15	1	4.3	Moderate	3.7	High
9	46	1	19	0	2.38	Excellent	2.7	Low
10	68	2	14	0	3.28	Good	3.2	Low
11	54	1	15	1	3.3	Good	2.7	Low
12	44	2	22	1	4.44	Moderate	2.9	Low
13	49	1	15	0	2.3	Excellent	2.1	Low
14	74	2	25	2	4.5	Moderate	3.7	High
15	58	3	40	2	5.8	Poor	4.8	High
16	54	3	16	0	4.32	Moderate	2.7	Low
17	70	2	13	0	3.26	Good	2.9	Low
18	59	2	17	1	4.26	Moderate	3.68	High
19	66	2	12	0	3.24	Good	3.8	High
20	50	2	46	3	4.92	Moderate	4	High
21	46	2	20	0	3.4	Good	2.9	Low
22	49	2	13	0	3.26	Good	2.6	Low
23	65	2	15	0	3.3	Good	2	Low
24	71	3	65	6	7.3	Poor	4.9	High
25	49	2	20	0	3.4	Good	3	Low
26	70	2	10	2	4.2	Moderate	2.7	Low
27	46	2	15	0	3.3	Good	3.1	Low
28	61	3	30	0	4.6	Moderate	4.6	High
29	54	2	8	0	3.16	Good	2	Low
30	68	2	7	0	3.14	Good	4	High
31	43	3	20	1	5.4	Moderate	4.2	High
32	44	2	28	1	4.56	Moderate	4.3	High
33	50	1	17	0	2.34	Excellent	2.8	Low
34	52	2	45	0	3.9	Moderate	3	Low
35	58	2	16	1	4.32	Moderate	4.7	High
36	40	2	15	1	4.3	Moderate	3.5	High
37	63	2	18	0	3.36	Good	2.7	Low
38	65	3	8	2	5.16	Moderate	4.4	High
39	53	2	15	1	4.3	Moderate	3.4	High
40	56	2	30	0	3.6	Moderate	3.2	Low
41	42	3	20	0	4.4	Moderate	3.8	High
42	58	3	20	0	4.4	Moderate	3.9	High
43	63	2	17	0	3.34	Good	2.6	Low
44	54	2	15	0	3.3	Good	2.9	Low
45	59	2	7	0	3.14	Good	2.1	Low
46	54	3	10	0	4.2	Moderate	4.1	High
47	46	2	53	0	4.06	Moderate	2.1	Low
48	75	2	50	0	4	Moderate	4	High
49	62	2	26	0	3.52	Moderate	2.9	Low
50	56	2	19	0	3.38	Good	2.7	Low
51	59	2	25	0	3.5	Moderate	4.3	High
52	46	3	20	0	4.4	Moderate	4.3	High
53	49	3	46	0	4.92	Moderate	3.26	Low
54	33	2	30	0	3.6	Moderate	2.8	Low
55	63	2	43	0	3.86	Moderate	3.27	Low
56	49	2	33	0	3.66	Moderate	2.2	Low
57	48	2	44	0	3.88	Moderate	2.4	Low
58	70	3	11	0	4.22	Moderate	3.2	Low
59	69	2	42	0	3.84	Moderate	2.7	Low

Table II. Continued

Table II. *Continued*

Patient number	Age, years	Tumour grade	Tumour size (mm)	Number of involved lymph nodes	NPI score	NPI risk group	EPclin score	EPclin risk group
60	40	3	20	0	4.4	Moderate	3.9	High
61	45	2	14	0	3.28	Good	2	Low
62	48	3	26	0	4.52	Moderate	3.8	High
63	58	2	30	0	3.6	Moderate	4.1	High
64	47	2	23	0	3.46	Moderate	3	Low
65	64	2	27	0	3.54	Moderate	3.1	Low
66	54	3	18	0	4.36	Moderate	3	Low
67	50	2	17	0	3.34	Good	2.2	Low
68	66	3	8	2	5.16	Moderate	4.4	High
69	59	2	40	0	3.8	Moderate	3	Low
70	64	2	24	0	3.48	Moderate	3.5	High
71	43	2	15	2	4.3	Moderate	4.6	High
72	57	2	9	1	4.18	Moderate	2.2	Low
73	52	3	22	0	4.44	Moderate	3.4	High
74	73	2	30	0	3.6	Moderate	3.6	High
75	60	2	16	0	3.32	Good	3.2	Low
76	48	2	4	0	3.08	Good	2.3	Low
77	55	2	21	0	3.42	Moderate	3.6	High
78	55	2	43	1	4.86	Moderate	4.1	High
79	48	2	23	1	4.46	Moderate	3.8	High
80	52	2	17	0	3.34	Good	3.5	High
81	49	1	20	0	2.4	Excellent	2.6	Low
82	50	2	13	1	4.26	Moderate	3.6	High
83	58	2	16	4	5.32	Moderate	4.9	High
84	76	2	25	0	3.5	Moderate	2.2	Low
85	68	3	34	0	4.68	Moderate	3.5	High
86	54	2	60	0	4.2	Moderate	3.5	High
87	67	2	15	0	3.3	Good	3.1	Low
88	64	2	20	1	4.4	Moderate	3.7	High
89	55	1	41	0	2.82	Good	3.5	High
90	54	2	17	0	3.34	Good	2.8	Low
91	65	2	12	0	3.24	Good	2.6	Low
92	47	2	30	0	3.6	Moderate	3.32	High
93	48	2	8	0	3.16	Good	2.3	Low
94	68	2	15	0	3.3	Good	2.4	Low
95	70	2	30	0	3.6	Moderate	2.7	Low
96	66	2	48	1	4.96	Moderate	5.3	High
97	47	2	9	0	3.18	Good	2	Low
98	65	3	20	0	4.4	Moderate	3.5	High
99	48	3	17	0	4.34	Moderate	4.2	High
100	77	2	22	0	3.44	Moderate	3.8	High
101	36	3	52	0	5.04	Moderate	3.6	High
102	56	3	12	0	4.24	Moderate	4.2	High
103	60	2	12	0	3.24	Good	2.5	Low
104	60	3	30	0	4.6	Moderate	4.4	High
105	46	2	12	0	3.24	Good	2.8	Low
106	31	2	6	0	3.12	Good	3.8	High
107	67	3	6	0	4.12	Moderate	3	Low
108	61	2	25	1	4.5	Moderate	3.9	High
109	65	2	10	0	3.2	Good	2.6	Low
110	43	3	20	0	4.4	Moderate	3.8	High
111	46	2	51	1	5.02	Moderate	4.3	High
112	50	2	70	8	6.4	Poor	5.7	High
113	42	2	55	0	4.1	Moderate	3.5	High
114	49	2	20	0	3.4	Good	2.6	Low
115	64	2	26	0	3.52	Moderate	3.4	High
116	59	2	14	0	3.28	Good	3.5	High
117	61	2	23	1	4.46	Moderate	3.7	High
118	55	2	33	0	3.66	Moderate	3.2	Low
119	49	2	27	0	3.54	Moderate	2.3	Low
120	42	2	6.6	0	3.13	Good	2.7	Low

Conflicts of Interest

The Authors have no conflicts of interest to report pertaining to this study. The Author Kefah Mokbel provides medical advisory and consultancy to Myriad Genetics.

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Received May 25, 2018

Revised June 11, 2018

Accepted June 14, 2018