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Impact of MammaPrint on Clinical Decision-Making in South African Patients with Early-Stage Breast Cancer

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■ **Abstract:** The aim of the study was to evaluate the impact of MammaPrint on treatment decision-making in patients with breast cancer. Clinicopathologic information of all breast cancer patients referred for MammaPrint testing in South Africa was collected from 2007 until 2014. A total of 107 patients (109 tumors) with estrogen receptor/progesterone receptor positive and human epidermal growth factor receptor-2 negative tumors were selected with tumors ≥10 mm, or when 1–3 nodes were involved without extra-nodal extension. None of the clinical indicators correlated significantly with the MammaPrint risk classification, which changed the decision for adjuvant chemotherapy in 52% of patients. Of 60 patients who were clinically high risk, 62% had a low-risk MammaPrint result and of the 47 clinically low -risk patients 40% had a high-risk MammaPrint result. This study indicates that MammaPrint could reduce the need for adjuvant chemotherapy by 17% using the selection criteria stipulated. The significant impact on treatment decisions confirmed the clinical utility of MammaPrint independent of standard clinicopathologic risk factors as supported by long-term clinical outcome studies. ■

Key Words: adjuvant chemotherapy, breast cancer, genomic profiling, impact, Mammaprint

Adjuvant chemotherapy in breast cancer improves the 10-year survival by 15–20%, which implies that most patients gain no additional benefit while being exposed to significant treatment related morbidity. Current treatment guidelines including the use of online applications such as Adjuvant Online to provide more objective decision-making, attempt to identify patients who might benefit from adjuvant chemotherapy (1). These methods use clinical, morphological and histologic parameters as surrogates for tumor biology and metastatic potential. However, they correlate poorly with the tumor genetics as the true driver of biologic behavior.

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Several genes with prognostic significance have been identified over the past 25-years allowing the development of gene expression signatures for treatment selection. Currently only MammaPrint and Oncotype Dx are available in South Africa with considerable discordance (20–30%) reported between these two assays, previously compared among others for their added value over and above standard parameters (2). While several studies questioned the added benefit of the 21-gene assay (3), the ability to provide estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) mRNA expression (TargetPrint) independent of the 70-gene profile as well as molecular subtyping (BluePrint) has increased the clinical utility of the versatile MammaPrint platform in South Africa (4) and elsewhere.

MammaPrint was introduced in South Africa in 2007 after FDA approval as supported by significant

prognostic and predictive value in both the adjuvant and neo-adjuvant settings. In conjunction with several health care funders, a MammaPrint Pre-screen Algorithm (MPA) was formulated in 2009 to ensure cost-effective use in South Africa (5). The aim was to identify patients who would be least likely to gain any benefit from chemotherapy limiting the test to untreated ER and/or PR positive, HER2 negative tumors ≤4 cm with <4 lymph nodes involved. After publication of prospective data from the RASTER trial reporting excellent 5-year survival in MammaPrint low-risk patients (6), the initial South African MPA was adapted to include tumors larger than 4 cm.

In this study we investigated the impact of MammaPrint on clinical decision-making by evaluating the clinicopathologic profile, MammaPrint result and proposed treatment plan of 107 consecutive Southern African patients.

METHODS

All patients with early-stage breast cancer referred for MammaPrint testing between 2007 and 2014 were considered for inclusion in this study. MammaPrint risk scoring and ER, PR and HER2 receptor status were determined as previously described (4,5). Patients with incomplete clinical data, those without the option of endocrine therapy (ER/PR negative) or with HER2-positive tumors or ≥4 nodes involved were excluded. Node-negative tumors less than 10 mm or the presence of extra-nodal tumor extension were also excluded. A selected patient group, least likely to gain benefit from adjuvant chemotherapy, was therefore analyzed that conformed to the following criteria: (i) tumor size ≥10 mm without nodal involvement or ≤3 positive lymph nodes, (ii) ER and/or PR positivity, (iii) HER2 negativity, and (iv) no prior neo-adjuvant treatment received.

Anonymized demographic and clinical information (age, medical comorbidities), pathologic data (tumor size, grade, and hormone receptor status) and MammaPrint results were extracted from a central data base. Relevant information was entered into Adjuvant! Online (AOL) and the predicted 10-year mortality documented. Patients were classified as high-risk versus low-risk, with the following criteria used to select clinically high-risk patients: (i) Predicted 10-year mortality (AOL) ≥10%, (ii) or macro-metastases in 1–3 lymph nodes, or (iii) tumor size >20 mm with at least grade II differentiation in post-menopausal patients, or (iv) tumor size >15 mm with grade III differentiation, or (v) any tumor >20 mm in size in pre-menopausal patients (<50 years of age). These selection criteria are fairly conservative and reflect local South African protocols for use of adjuvant chemotherapy. In order to avoid inter-observer variation in clinical risk classification a computer based algorithm was employed to stratify patients.

The different MammaPrint result groups were compared with logistic regression models in terms of clinical risk factors. When comparing tumor properties the models were adjusted for the correlation between pairs of tumors in the same patients. Functions from R, available from www.r-project.org were used for statistical analysis.

RESULTS

Records of 144 tumors in 141 female patients were available. Of these, 107 patients representing 109 tumors (two patients had more than one tumor) conformed to the inclusion criteria. The baseline characteristics of the study group are summarized in Table 1. All the tumors ($n = 109$) were ER and/or PR-positive and HER2-negative. A total of 80 patients (75%) were classified as node-negative, with micrometastases noted for eight (7.5%) patients.

Figure 1 shows the distribution of nodal status between MammaPrint high-risk and low-risk patients.

Table 1. Description of the Clinical Characteristics of the Study Population in Relation to the MammaPrint Test Result

	Mammaprint result	
Characteristics	Low risk	High risk
Number of patients, $n = 107$	65	42
Number of tumors, $n = 109$	67	42
Age, years, mean ± SD	53.1 ± 10.8	51.4 ± 11.9
Patient clinical risk, count (% of risk)		
High	37 (61.7)	23 (38.3)
Low	28 (59.6)	19 (40.4)
Tumor size (mm), median (range)	18 (8–55)	16 (11–33)
Nodal involvement, count (% of involvement)		
Negative	48 (58.5)	34 (41.5)
Micromets	5 (62.5)	3 (37.5)
Positive	14 (73.7%)	5 (26.3)
Tumor type, count (% of type)		
Lobular	14 (77.8)	4 (22.2)
Ductal Ca all grades	53 (58.2)	38 (41.8)
Grade 1	19 (61.3)	12 (38.7)
Grade 2	29 (62.2)	17 (37.8)
Grade 3	5 (35.7)	9 (64.3)

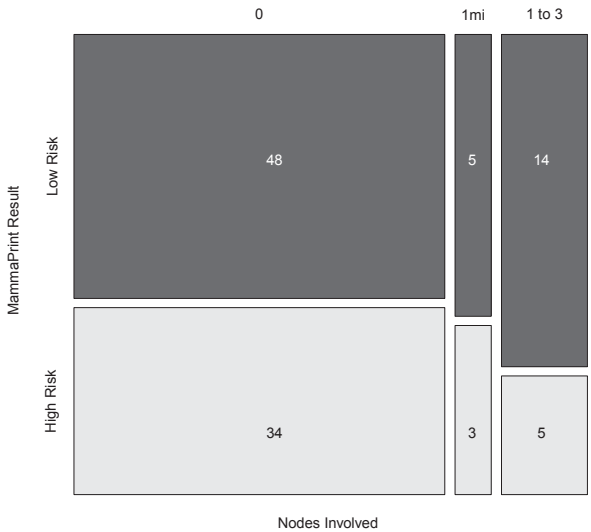

Figure 1. Mosaic plot of the number of tumors classified by nodes according to MammaPrint risk stratification. There is no significant association between the MammaPrint test result and node involvement (p = 0.458).

Figure 2 shows the distribution of tumor grade and type between MammaPrint high-risk and low-risk patients. Only two node-positive tumors <10 mm were included. The majority of tumors were grade 1 ($n = 31$) and 2 ($n = 46$) invasive ductal carcinomas (IDC), of which 29 (37.6%) exhibited a high-risk MammaPrint profile. A limited number of tumors were classified as grade 3 IDC ($n = 14$) with the majority (64%) classified as MammaPrint high-risk. Among 18 lobular carcinomas, 14 (78%) exhibited a low-risk profile.

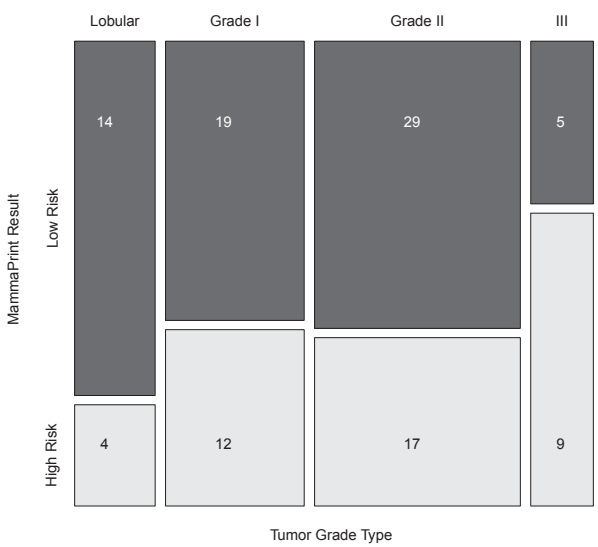

Figure 2. Mosaic plot of observed number of tumors, according to tumor type / grade and Mammaprint result. Grade I–III tumors are all ductal carcinoma and no significant association was found between the MammaPrint test result and tumor type / grade (p = 0.138).

A total of 60 patients (56.1%) were clinically high-risk and 47 patients (43.9%) clinically low-risk. In contrast, 65 patients (60.8%) had a MammaPrint low-risk tumor and 42 patients (39.2%) at least one MammaPrint high-risk tumor. Figure 3 provides an illustrative comparison of risk stratification based on clinical classification criteria as opposed to gene expression profiling using the 70-gene MammaPrint assay. This indicates that 56 patients (52%) had a change in their treatment plan based on gene profiling. This resulted in only 42 patients being offered chemotherapy instead of the 60 deemed to be high-risk based on clinical criteria, a reduction of 18 patients (17%). There was no correlation between the clinical risk assessment and the MammaPrint result with Cohen's kappa coefficient of 0.00 (95% CI: −0.18 to 0.17, p = 0.96).

DISCUSSION

Due to a change in the treatment plan in 52% of early-stage breast cancer patients based on MammaPrint results, 37 clinically high-risk patients (61.7%) could be spared unnecessary chemotherapy and 19 clinically low-risk patients (40.4%) who would not have been offered chemotherapy could expect a 25% improvement in recurrence-free survival (6) by the addition of adjuvant chemotherapy. This implies a large cost saving which would counter the initial cost of the test. Furthermore, if selected borderline HER2 positive patients (4) are included into the MPA the offset of the reduced cost of anti-HER2 agents could be even greater.

The cost-effectiveness of any test is determined by the testing algorithm. The use of MammaPrint could have negative cost implications if only low-risk patients are referred as reflected in the large percentage (82.6%) of node negative and N1mi patients included in this study. With 20–30% of patients expected to present with nodal involvement and local reports of nodal involvement in 20% of sentinel node biopsies for early-stage breast cancer (7), the number of node-positive patients in this study were lower than expected. Node-positivity is considered a strong indication for chemotherapy and such patients might benefit most from tumor profiling. Similarly, we found that 38 (34.9%) of the tumors were less than

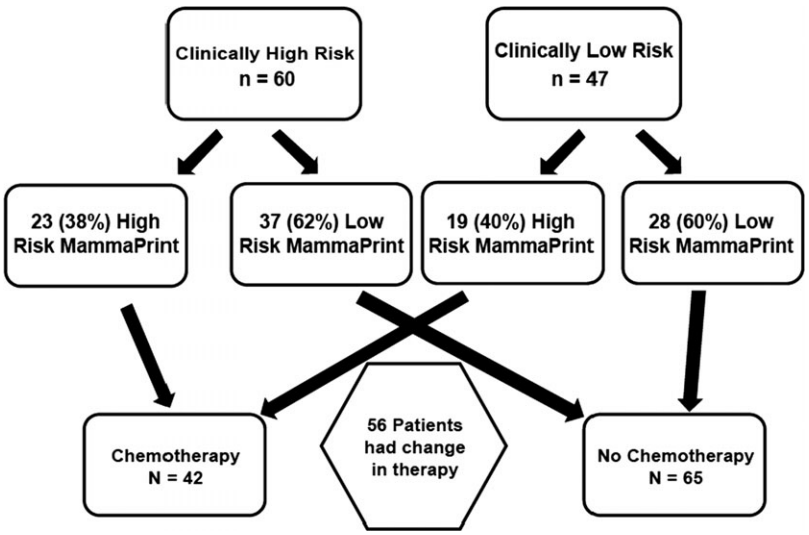

Figure 3. Diagram illustrating the impact of MammaPrint on final treatment. There was no significant association between the MammaPrint test result and clinical risk ($p = 0.826$).

15 mm in size and with a mean size of 18 mm only 6 (5.5%) tumors ≥40 mm. This indicates a possible reluctance by clinicians to request MammaPrint in patients with established clinical indications for chemotherapy.

Several studies have reported a correlation between the Oncotype DX Recurrence Score and age, tumor grade and tumor, while we found no significant correlation between these clinical indicators and the MammaPrint result. Saghatchian et al. (8) reported that patients with 4–9 positive nodes have a 60% chance of having poor prognostic gene profiles. This group as well as the patients with extra-nodal spread in any number of nodes were excluded from our selection criteria due to insufficient evidence. We also excluded node-negative tumors less than 10 mm in size because the predictive value of gene profiling is still lacking despite validation of the prognostic value of MammaPrint in these tumors (9). Patients with HER2-positive, node-negative tumors smaller than 10 mm have a low risk of recurrence, showing a favorable prognosis despite omission of adjuvant chemotherapy [10].

In conclusion, no significant association was found between traditional clinicopathologic factors of relevance used to determine eligibility for adjuvant chemotherapy and the genomic risk profile indicated by MammaPrint. Although some studies have demonstrated more high-risk profiles in grade III infiltrating ductal carcinoma, we could not confirm these findings possibly due to small numbers, but noted this as the only subgroup to have more high than low-risk MammaPrint results. In view of the excellent 5-year outcome of low-risk MammaPrint patients reported in the RASTER trial (6), our findings support extension of the locally developed MPA (5) to include tumors larger than 4 cm for cost-effective application microarray-based gene profiling.

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DISCLOSURE

Prof MJ Kotze is a director and shareholder of Gknowmix (Pty) Ltd., that has developed a database tool for research translation under the auspices of the South African Medical Research Council. The authors have no affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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