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# Radiotherapy Benefit in High-Risk Patients Classified by an 18-Gene Panel

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## Abstract

**Purpose:** An 18-gene classifier (18-GC) was developed to identify breast cancer patients of low- and high-risk in any recurrence. However, the benefit of adjuvant radiotherapy for high-risk patients identified by the 18-GC is still unclear. This study was therefore performed to explore if these high-risk patient would benefit from adjuvant radiotherapy.

**Methods:** Two hundred and thirteen patients with operable breast cancer were enrolled in the study. Propensity score analysis was conducted with ratio of 2:1 to match patients with (n=142) or without (n=71) adjuvant radiotherapy by age, T stage, N stage, tumor grade and ER status. We use pre-defined 18-gene scoring algorithm to define scores ≥ 21 and ≥ 44 as the high-risk group of Distant Recurrence (DR) and Local/Regional Recurrence (LRR), respectively. The primary outcome is 5-years Relapse Free Survival (RFS) rate.

**Results:** Forty two of the 213 patients had an 18-GC risk score lower than 21 (low DR risk) whereas the remaining 171 had a score greater or equal to 21 (high DR risk). The low- and high-risk group had an RFS at 96.8% and 77.4%, respectively. The radiotherapy treatment and the high DR risk score was found to have a statistically significant interaction (P=0.0122). The 114 and 57 patients treated and untreated with radiotherapy had a 5-yr RFS at 85.7% and 61.3%, respectively (P=0.0008).

**Conclusion:** The 18-GC can predict both the extent of radiotherapy benefit and the risk of recurrence of breast cancer.

**Keywords: Breast cancer; Recurrence, Prognosis; Microarray gene-expression profiling; Radiotherapy benefit**

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## Introduction

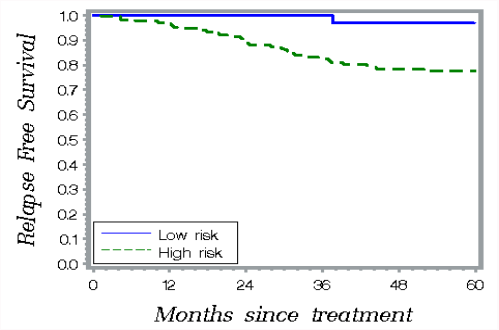
The benefit of Post-Mastectomy Radiotherapy (PMRT) is not only to reduce Local/Regional Recurrence (LRR) but also any recurrence (both LRR and distant recurrence, DR), which lead to better long-term survival [1]. In this background, PMRT for breast cancer has gradually been accepted to the extent that it has had a systemic effect on preventing distant recurrence and in reducing breast cancer mortality [2]. However, the lack of biological markers to determine adjuvant radiotherapy leads to excessive treatment of low-risk patients and a neglect of the truly high-risk patients. Genomic tools such as gene-expression profiling assays like Oncotype DX have been used to predict the DR risk of breast cancer [3]. By identifying both low- and high-recurrence risk patients, such tools can overcome the issues of chemotherapy overtreatment, especially for those with early-stage breast cancer [4,5]. On the contrary, there are still lacks of biomarkers that can be applied to guide the benefit of PMRT in early stage breast cancer. For example, NCCN guidelines have strongly recommended N1 patients should consider having PMRT; In fact, the majority of them would be over treated [6]. In light of this, we have developed an 18-gene classifier (18-GC) that is capable of identifying low-risk and high-risk LRR patients after mastectomy [7]. Moreover, both DR and LRR risk in breast cancer patients could be predicted by this 18-GC [8]. But the interaction between the 18-GC and the benefit of radiotherapy is still not clear. We thus conducted this study to elucidate whether patients classified by the 18-GC as high risk could benefit from adjuvant radiotherapy.

**Table 1:** Baseline characteristics of the 213 patients.

| Variables | Adjuvant RT | | p-value |
|---|---|---|---|
| | No | Yes | |
| Age | | | 0.7937 |
| <= 40 | 11 (15.5%) | 24 (16.9%) | |
| >40 | 60 (84.5) | 118 (83.1%) | |
| Stage | | | 0.0706 |
| I | 2 (2.8%) | 17 (12.0%) | |
| II | 67 (94.4%) | 119 (83.8%) | |
| III | 2 (2.8%) | 6 (4.2%) | |
| T stage | | | 0.6883 |
| 1 | 25 (35.2%) | 54 (38.0%) | |
| 2 | 46 (64.8%) | 88 (62.0%) | |
| N stage | | | 0.9113 |
| 0 | 23 (32.4%) | 48 (33.8%) | |
| 1 | 47 (66.2%) | 91 (64.1%) | |
| 2 | 1 (1.4%) | 3 (2.1%) | |
| LVI | | | 0.5883 |
| Absent/Focal | 53 (74.6%) | 101 (71.1%) | |
| Prominent | 18 (25.4%) | 41 (28.9%) | |
| ER | | | 0.6033 |
| Negative | 21 (29.6%) | 47 (33.1%) | |
| Positive | 50 (70.4% | 95 (66.9%) | |
| PR | | | 0.435 |
| Negative | 34 (47.9%) | 60 (42.2%) | |
| Positive | 37 (52.1%) | 82 (57.8%) | |
| Surgery | | | 0.7339 |
| Mastectomy | 64 (90.1%) | 130 (91.5%) | |
| BCT | 7 (9.9%) | 12 (8.5%) | |

**Table 2:** LRR model cutoff and DR model cutoff by 18-gene classifier.

| LRR | | | |
|---|---|---|---|
| 18-GC score | Locoregional Relapse | | |
| | No | Yes | Total |
| <44 | 162 | 7 | 169 |
| | 95.90% | 4.10% | |
| ≥ 44 | 30 | 14 | 44 |
| | 68.20% | 31.80% | |
| Total | 192 | 21 | 213 |
| Fisher's Exact Test p<0.0001 | | | |
| DR | | | |
| 18-GC score | Distant Metastasis | | |
| | No | Yes | Total |
| <21 | 42 | 0 | 42 |
| | 100% | 0% | |
| ≥ 21 | 143 | 28 | 171 |
| | 83.60% | 16.40% | |
| Total | 185 | 28 | 213 |
| Chi-Square | | | 0.0049 |




| 18-gene score | Relapse | | | |
|---|---|---|---|---|
| | No | Yes | Total | 5-yr RFS |
| <21 | 40 | 2 | 42 | 96.80% |
| | 95.24 | 4.76% | | |
| ≥21 | 136 | 35 | 171 | 77.40% |
| | 79.53% | 20.47% | | |
| Total | 176 | 37 | 213 | P = 0.0161 |

**Figure 1:** Relapse-free survival in patients with score of <21 and 21.

# Results

## Patient characteristics

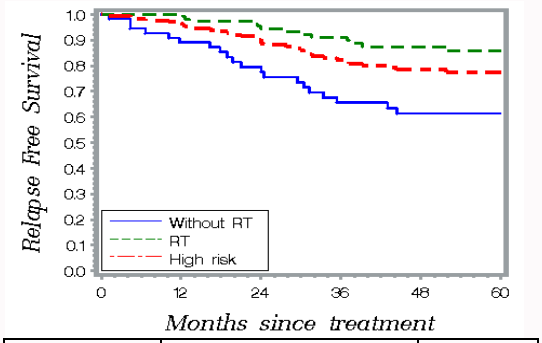
Baseline characteristics of the 213 patients were as shown in Table 1. The median follow-up interval for patients without metastasis was 56.5 months (ranging from 0 to 112.3 months). A patient at 40 years old or younger at diagnosis was 16.4% (35/213). The majority of patients were at stage II (87.3%; 186/213). The primary tumor size was usually >2 cm but ≤ 5 cm (62.9%; 134/213) and N1 disease was the most common (64.9%; 138/213). Most patients were ER positive (68.1%; 145/213) or PR positive (55.9%; 119/213). Prominent Lymph Vascular Invasion (LVI) was present in 27.7% of the patients (59/213).

## Recurrence risk classification by the 18-GC

By using the LRR model of the 18-GC (cutoff score of 44), 169 and 44 of the 213 patients were classified as low- and high-risk in LRR, respectively (Table 2). The LRR rate in patients with score <44 was 4.1% and patients with score ≥ 44 31.8% (p<0.0001). By using the DR model of the 18-GC (cutff score of 21), 42 and 171 of the 213 patients were classified as low- and high-risk in DR, respectively. Whereas none of the 42 patients with score <21 had any distant relapse, 28 of the 171 (16.4%) patients with score ≥ 21 developed a distant relapse (Table 2). The NPV and PPV of the 18-GC DR score were thus 100% and 16.4%, respectively. Since preventing any recurrence becomes the primary endpoint for the effect of adjuvant radiotherapy [9], the cutoff of radiotherapy benefit in this study used score of 21 instead of 44 to explore the benefit of radiotherapy. When any (locoregional and distant) relapse events were included, whereas two of the 42 low DR-risk patients had any relapse, 35 of the 171 high DR-risk patients developed a relapse event (Figure 1). The NPV and PPV of the 18-GC DR model were thus 95.2% and 20.5%, respectively. The Kaplan-Meier plot of the low- and high-risk patients is shown in Figure 1, with a five-year Relapse-Free Survival (RFS) at 96.8% and 77.4%, respectively, P=0.0161.

## Benefit of radiotherapy for high-risk patients classified by the 18-GC

Of the 213 patients, 42 were grouped as low-risk and were not further analyzed for radiotherapy benefit due to a high RFS at 96.8%. In contrast, the remaining 171 patients with score ≥ 21 were further analyzed for evaluating the benefit of radiotherapy. Among the 171




| Adjuvant R/T | Relapse | | | |
|---|---|---|---|---|
| | No | Yes | Total | 5-yr RFS |
| No | 37 | 20 | 57 | 61.30% |
| | 64.91% | 35.09% | | |
| Yes | 99 | 15 | 114 | 85.70% |
| | 86.84% | 13.16% | | |
| Total | 136 | 35 | 171 | p = 0.0008 |

**Figure 2:** Comparison between adjuvant radiotherapy categories and RFS.

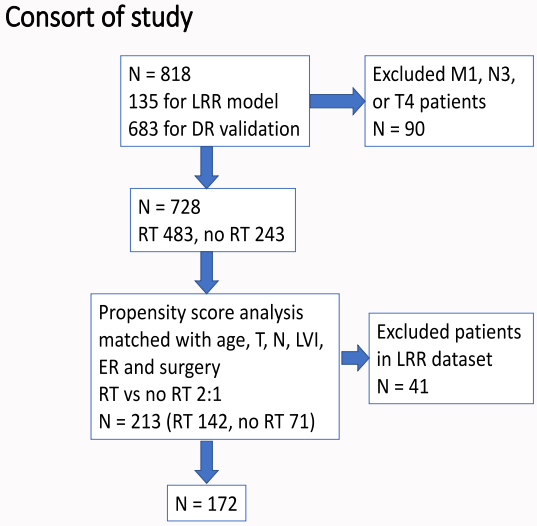


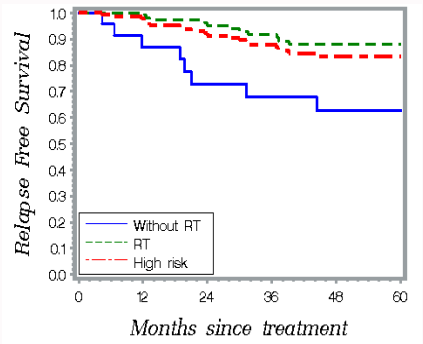

**Figure 3:** Study consort.

patients, 114 and 57 were treated with and without radiotherapy, respectively. For the patients treated with no radiotherapy, 20 out of 57 (35.1%) had relapse whereas for those treated with radiotherapy, only 15 out of 114 (13.2%) developed a relapse event. The Kaplan-Meier plot of the relapse-free patients for the two treatment groups is shown in Figure 2. The five-year Kaplan-Meier estimate for RFS was improved from 61.3% to 85.7% by including adjuvant radiotherapy for treatment (P=0.0009). The absolute benefits of radiotherapy for the 18-GC high-risk patients group is thus around 24.4%.

Excluding patients whose data had been used for the 18-GC development (Figure 3), 36 patients were low risk (score <21) and 136 patients were high risk (score ≥ 21). Among the high-risk patients, the 5-year RFS was improved by adjuvant radiotherapy from 62.5% to 88.0% (Figure 4, p=0.0122).

## Discussion

The absolute benefit of adjuvant radiotherapy in high-risk breast cancer identified by the 18-GC was 24.4% in the current study. Majority of these patients (87.3%) were stage II (T2 or N1). PMRT,




| Score ≥ 21 | Relapse | | Total | 5-yr RFS | p-value |
|---|---|---|---|---|---|
| | No | Yes | | | |
| Adj RT | | | | | 0.0122 |
| No | 17 | 8 | 25 | 62.60% | |
| | -68% | -32% | | | |
| Yes | 99 | 12 | 111 | 88.00% | |
| | -89.20% | (10.8%) | | | |

**Figure 4:** Comparison between adjuvant radiotherapy categories and RFS (excluding patients whose data had been used for 18-gene classifier development).

including regional node irradiation, is a well-established treatment method to prevent LRR and systemic recurrence [1,10]. Both MA-20 and EORTC 22922 trials questioned whether to give regional nodal irradiation in N1 and high-risk N0 patients after breast-conserving surgery and mastectomy [11,12]. Both trials significantly improved recurrence-free and distant metastasis-free survivals by 3% to 5%. The MA20 study enrolled 1832 patients and showed no significant difference in breast-cancer mortality, with 10-year rates of 10.3% in the nodal-irradiation group and 12.3% in the control group (p=0.11). The EORTC 22922 trial involved 4004 patients and disclosed a marginal effect on overall survival (p=0.06). Both trials included a large number of participating patients to demonstrate a small benefit of overall survival by regional node irradiation. This is very odd in the era of precision medicine: In order to prevent 4 patients from regional recurrence, radiation oncologists ought to also treat the remaining 96 patients [11].

The consequences from radiation treatment are another concern. The relative risk of major coronary artery disease and second lung cancer significantly increases by 7.4% and 8.5% per Gray, respectively [13,14]. These statistics come from large population-based case-control studies. The heart exposure to ionizing radiation increases the rate of ischemic heart disease, which begins within a few years after exposure, and continues for at least 20 years [13]. Similarly, second lung cancer after radiotherapy for early breast cancer is associated with the delivered dose to the lung, which would be inevitable if patient has had regional node irradiation [14].

Therefore, the treatment strategy in the 21$^{th}$ century should shift to personalized medicine, especially in the radiation oncology field [15]. This study aims to provide that genomic information is useful in addition to conventional variables in making the decision for or against PMRT.

The 18-GC has been shown to be an independent predictor for estimation of DR risk [8]. However, it is unclear whether it can also predict the benefit of radiotherapy. To that end, we included in the current study a total of 213 stage I-III breast cancer patients and classified them into low- or high-risk patients in recurrence by using the 18-GC. By comparing the five-year RFS among the 171

high-risk patients treated with or without radiotherapy, it was found that the RFS was improved from 61.3% to 85.7% when radiotherapy was included as a treatment (Figure 2). The absolute benefit of radiotherapy for the 18-GC high-risk patients is thus around 24.4%.

It is noteworthy that our study is limited in that it was a retrospective study and that the patients receiving no adjuvant radiotherapy were limited in numbers. A prospective study with a larger number of patient cases will be needed to comfirm the value in prediction of benefit of radiotherapy in high-risk patients classified by the 18-GC.

In conclusion, in this study we confirmed that the 18-GC is an independent predictor of recurrence risk of breast cancer and demonstrated that the 18-GC is a good tool for predicting benefit of radiotherapy for high risk patients. With the capability of predicting recurrence risk and radiotherapy benefit, the 18-GC may prove to be a good prognosis tool that can provide therapy guidance and alleviate the common over- and under-treatment issues in breast cancer management.

## Materials and Methods

### Patients

Patients' microarray data (n=818) were downloaded from the GEO repository (accession numbers GSE222222). These patients were treated between 2005 and 2014, with the last follow-up date on Oct 30, 2016. Propensity score analysis using age at diagnosis, T stage, N stage, tumor grade, and ER status to match patients with or without radiotherapy by a ratio of 2:1 A total of 213 patients with stage I-III breast cancer were included. Among the 171 18-GC high-risk patients, 114 were treated with radiotherapy and 57 were not. The baseline characteristics are as shown in Table 1. The adjuvant radiotherapy was performed as conventional.

### The 18-GC

The 18-GC contains a panel of genes that are associated with cell cycle and proliferation (DDX39, BUB1B, STIL, TPX2, CCNB1), oncogenic process (BLM, TCF3, PIM1, RCHY1, PTI1), inflammation and immune response (CCR1, NFATC2IP), cell-cell interaction (TRPV6, OBSL1, MMP15), apoptosis (C16ORF7, DTX2) and metabolism (ENSA). The breakpoint value of 21 was used to separate the low- from high-risk category of DR for the 18-GC DR model, whereas the breakpoint value of 44 was used to separate the low- from the high-risk category of LRR for the 18-GC LRR model.

### Statistical analysis

Propensity score analysis was used for matching with age, T stage, N stage, tumor grade, and ER status between patients with and without radiotherapy by a ratio of 2:1 (with *vs.* without radiotherapy = 142:71). The primary end point was RFS. Kaplan-Meier plots were made by plotting time against RFS events for both comparisons of low- *vs.* high-risk and radiotherapy *vs.* no radiotherapy. A P-value less than .05 for the tests was considered significant.

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