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Impact of the 21-gene recurrence score assay in adjuvant chemotherapy selection for node-negative, hormone receptor-positive breast cancer in the Chinese population

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The 21-Gene Recurrence Score Assay has been intensively studied and recommended by major guidelines for treatment decision in early breast cancer. Its impact in adjuvant chemotherapy selection for Chinese population has not been revealed.

The prospective part of this study enrolled consecutive node-negative, hormone receptor-positive patients who underwent 21-gene RS testing at Breast Surgery Department of PUMCH (n=134) between May 2012 and August 2013(21-gene RS group). Risk categories were assigned based on the RS and on standard clinicopathologic criteria according to St. Gallen and Adjuvant! Online. The chemotherapy selection and the oncologists' confidence in decision-making before and after RS testing were recorded. The retrospective part of this study compared the chemotherapy decision in the 21-gene RS group and a control group without RS testing (diagnosed between Jan 2011 and Apr 2012,n=170).

A total of 304 patients were included in the analysis (134 21-gene RS group, 170 controls). Based on RS, 97 patients were classified as low risk, 29 patients as intermediate risk, and 8 patients as high risk. Tumor grade (P=0.002), PR expression (P<0.001) and Ki-67 index (P<0.001) were significantly different between the 3 risk cohorts.Comparing the St. Gallen guidelines and RS, there was a 41% concordance between risk groups. By using Adjuvant! Online, the correlation between the predicted BCSM and RS was nominal (r=0.10). A total of 29% 21-gene RS group patients changed their treatment decisions after RS testing (P<0.001, 95% CI, 0.18 to 0.49) with 6% (8/134) patients changing to receive chemotherapy besides endocrine therapy and 23% (31/134) changing to reject chemotherapy. After RS testing, more than one half of the oncologists increased their confidence level in treatment recommendation. In the control group, 67.6% (115/170) patients chose chemotherapy plus endocrine therapy. The chemotherapy percentage was much higher than that of 21-gene RS group (30/134, 22%).

This is the first study to demonstrate a reduction in the use of adjuvant chemotherapy in Chinese woman with node-negative hormone receptor-positive breast cancer, based on use of the RS. The RS had an impact on the physicians' treatment decision-making.

Key words: 21-Gene, recurrence score, adjuvant chemotherapy, breast cancer

Breast cancer is one of the most common malignancies in women worldwide and is the leading cancer-related cause of death in women. The incidence of breast cancer in China continues to rise in the past decades [1]. Increased awareness and screening have resulted in increased detection of node-negative, small breast cancers. More than half of the early breast cancers (EBC) are hormone receptor (HR)-positive [2]. For hormone receptor-positive lymph node-negative EBC, the risk of recurrence and the potential benefit of chemotherapy have to be assessed to select the proper patients who may benefit from the addition of chemotherapy to endocrine therapy.

During the past years, gene expression profiles have been shown to provide prognostic and predictive information beyond traditional parameters in EBC. Several commercially available multigene assays have been validated in node-negative breast cancer patients especially 21-gene recurrence score® [RS], oncotype DX [3].

The National Comprehensive Cancer Network (NCCN) Guidelines have considered 21-gene RT-PCR assay as "an option for patients with node-negative tumors that are HR-positive, HER-2 negative and >0.5cm to guide risk stratification and chemotherapy benefit" since 2011 [4].

The use of the Recurrence Score® to guide clinical treatment decisions has been recommended not only by ASCO [5] and NCCN, but also by ESMO [6] and the St. Gallen Consensus Guidelines [7].

Early evaluation of 21-gene RS in the National Surgical Adjuvant Breast and Bowel Projects (NSABP) Study B-14 trial demonstrated that RS provided significant predictive power of outcome independent of age and tumor size [8]. And the use of RS in NSABP B-20(tamoxifen versus tamoxifen plus chemotherapy) showed its predictive power of chemotherapy benefit; that is, patients with a low RS (<18) did not benefit from the addition of chemotherapy to tamoxifen, whereas a clinically and statistically significant benefit was observed in patients with a high RS (>30). Benefit from chemotherapy in patients with an intermediate RS was still uncertain, and this question is currently under investigation in the TAILORx trial [9].

The 21-gene RS assay is now widely used for treatment decision-making in the United States and some European countries. A recent meta-analysis [10] showed that the results are very consistent for Node-negative ER-positive disease in countries with different therapeutic tradition. The RS led to approximately 37% change in treatment decision. But there are limited data available on the treatment impact of RS for Asian population especially for Chinese patients. Given the increasing incidence of EBC in China, it is worth to know how the RS influence the chemotherapy decision and predict the recurrence and chemotherapy benefit for the population.

The current study was designed to evaluate the impact of the RS results on treatment decisions in node-negative ER-positive BC patients.

Patients and methods

The study was approved by the institutional review boards of Peking Union Medical College Hospital (PUMCH). All patients in the prospective part of this study provided their signed informed consent.

Patients. The prospective part of this study enrolled consecutive node-negative, hormone receptor-positive patients who underwent 21-gene RS testing (Surexam®, Guangzhou, China) at Breast Surgery Department of PUMCH (n=134) between May 2012 and August 2013(21-gene RS group). The retrospective part of this study compared the chemotherapy decision in the 21-gene RS group and a control group. The control group was identified by reviewing all node-negative, hormone receptor-positive patients treated in the same department and including patients (diagnosed between Jan 2011 and Apr 2012, n=170) for whom treatment decisions were based on clinicopathologic parameters alone and whose baseline characteristics were similar to those in the 21-gene RS group. All patients were recommended to receive endocrine therapy.

Information was obtained on age, tumor size, grade, estrogen receptorr (ER) and progesterone receptor (PR) status (% staining by immunohistochemistry, IHC), HER2/neu status (IHC staining score [0, 1+, 2+, 3+] and when available FISH ratio), Ki-67 and RS (only in 21-gene RS group). In addition, following treatment information were collected: type of locoregional therapy, type of adjuvant hormonal therapy and whether adjuvant chemotherapy was used.

Patient inclusion criteria were age ≥18 years, good performance status (ECOG 0–1) and no contraindication for receiving systemic chemotherapy and endocrine therapy. Patients were excluded from this study if they had been treated with neoadjuvant chemotherapy and/or endocrine therapy.

Treatment recommendation. In the prospective part of the study, each patient was seen by her oncologist to discuss adjuvant therapy as soon as the post-surgical histopathology results were available. A written recommendation for or against chemotherapy was made by the oncologist on standard clinicopathologic characteristics according to guidelines from St. Gallen, and Adjuvant! Online. The oncologist's confidence level in chemotherapy recommendation was recorded at the same time. Confidence was rated on a semi-quantitative scale as minimum, low, intermediate, high or absolute. The 21-gene RS test was requested and the patient was scheduled to see her oncologist for the second time once the result was available. The RS information was added to the clinical data already available and a final decision for or against chemotherapy recorded. The oncologist's confidence level was recorded again after the chemotherapy final decision-making.

The patients were assigned into risk categories based on the RS and on standard clinical pathologic characteristics according to guidelines from St. Gallen, and Adjuvant! Online. Patients with an RS of <18 were classified as low risk, 18–30 as intermediate risk, and >30 as high risk. Patients were stratified into risk groups based on the St. Gallen consensus recommendations published in 2007. Only the low- and intermediate-risk groups were used, as our study population was limited to node-negative patients. The low-risk group included patients with tumor size ≤2 cm, tumor grade 1, positive ER and/or PR expression, and age ≥35 years; lymphovascular invasion was assumed to be negative. Patients were stratified into the intermediate risk group if they possessed at least one of the following features: tumor size>2 cm, tumor grade 2 or 3, ER and PR negative, HER2/neu overexpression, or age<35 years. The 10-year breast cancer-specific mortality (BCSM) was calculated for each patient using the Adjuvant! software standard version 8.0 (http://www.adjuvantonline.com);.

Statistical analysis. The primary end-point of this study was treatment recommendations before and after RS testing. Secondary end-points included oncologist's confidence level in treatment recommendation before and after RS testing and treatment recommendations in the control group without RS information. The sample-size estimate for the prospective study was based on an expected proportion of 20% from recommending chemotherapy to no chemotherapy and an expected proportion of 5% from no chemotherapy to chemotherapy after 21-gene RS testing. To detect this with a two-sided 5% level and 90% power, a total of 113 patients

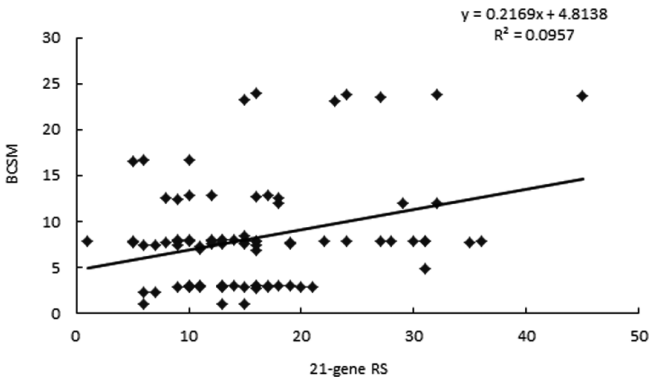

Figure 1. Correlation between recurrence score and BCSM calculated by Adjuvant! Online

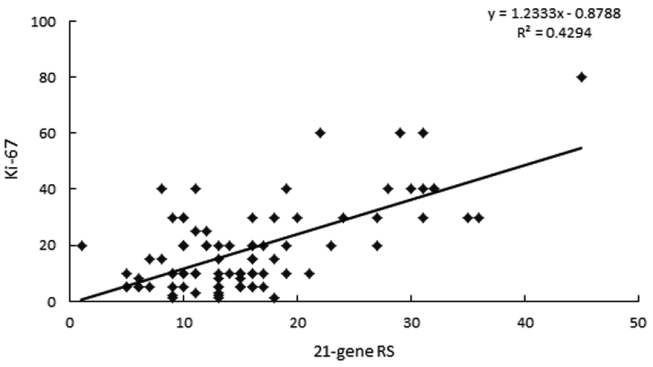

Figure 2. Correlation between recurrence score and Ki-67 expression

were required by using the online calculator (http://www.statstodo.com/SSizMcNemar_Pgm.php).

We compared the distribution of our patient population among the different risk groups based on each method of risk assessment in the 21-gene RS group. We compared clinical characteristics in patients receiving and not receiving adjuvant chemotherapy in 21-gene RS group and control group in retrospective part of the study.

Descriptive statistics were used for analysis because of the small numbers in some subgroups. The chi-square test was used for categorical variables. The Spearman correlation coefficient (r) was used to determine the correlation between continuous variables. $P<0.05$ was considered to indicate a significant result, and all significance test were reported as two-sided. Statistical analyses were performed using SPSS (version 19.0).

Table 1. Baseline patient and tumor characteristics

	21-gene RS group (N =134)	Control group (N =170)	P value
Age			
Median(range), years	48 (29-69)	49(26-77)	
Age category, N (%)			0.441
≤50 years	80 (59.7)	94 (55.3)	
>50 years	54 (40.3)	76 (44.7)	
Histology, N (%)			0.762
IDC	117 (87.3)	153 (90.0)	
ILC	14 (10.4)	14 (8.2)	
IDC+ILC	3 (2.2)	3 (1.8)	
Tumor size, N (%)			0.064
≤2cm	114 (85.0)	134 (78.8)	
>2cm	17 (12.7)	36 (21.2)	
Not applicable	3 (2.2)	0	
Tumorgrade, N (%)			0.124
Grade 1	30 (22.4)	23 (13.5)	
Grade 2	78 (58.2)	89 (52.4)	
Grade 3	17 (12.7)	30 (17.6)	
Not applicable	9 (6.7)	28 (16.5)	
Ki-67 category, N (%)			0.579
≤20%	96 (71.6)	106 (62.4)	
>20%	36 (26.9)	46 (27.1)	
Not applicable	2 (1.5)	18 (10.6)	

Results

A total of 304 patients were included in the analysis (134 21-gene RS group, 170 controls; Table 1). The 21-gene group patients were diagnosed from May 2012 to August 2013, whereas the controls were diagnosed from January 2011 to April 2012 in PUMCH. These two groups were not absolutely balanced with respect to age, tumor size, and tumor grade, with the clinicopathological characteristics of the control group associated with more chemotherapy use compared with those of 21-gene RS group (i.e., larger tumors, higher proportion of grade 3, but with no statistical difference).

Table 2 showed the patient characteristics of the 21-gene RS group with different RS risk categories. Most of the patients met the criteria of 2012 NCCN guidelines (HR-positive and Her2/neu-negative, 132/134, 98.5%) for considering 21-gene RS testing as an option. Based on RS, 97 patients were classified as low risk, 29 patients as intermediate risk, and 8 patients as high risk. Tumor grade (P=0.002), PR expression (P<0.001) and Ki-67 index (P<0.001) were significantly different between the 3 risk cohorts (Table 2).

Based on the 2007 St. Gallen guidelines, 28 patients were deemed low risk and 106 patients intermediate risk in the 21-gene RS group. Comparing the St. Gallen guidelines and RS, there was a 41% concordance between risk groups, only one of the patients categorized into low risk by St. Gallen (n=28) was upgraded by RS and 28 of 106 patients categorized in intermediate risk by St. Gallen were still in intermediate risk by the RS. Meanwhile, 70 of 106 patients (66%) were downgraded from intermediate risk by St. Gallen to low risk by the RS and 8 of 106 patients (7.5%) were upgraded from intermediate to high risk (Table 3).

The BCSM calculated by Adjuvant! Online was not divided into low or high risk. It was compared to RS directly without

Table 2. Patient characteristics by risk group as determined by RS

Characteristics	RS risk			P value
	Low (n =97)	Intermediate (n=29)	High (n =8)	
Age				0.467
Mean	49.3	46.9	47.6	
Median (range), years	49(29-69)	45(33-67)	47(34-57)	
Menopausal status, N(%)				0.605
Postmenopausal	35 (36%)	8 (28%)	2 (25%)	
Premenopausal	62 (64%)	21 (72%)	6 (75%)	
Histology, N(%)				0.052
IDC	80	29	8	
ILC	14	0	0	
IDC+ILC	3	0	0	
Tumor size(mean, cm)	1.5	1.6	2.0	0.157
Tumor grade, N(%)				**0.002**
Grade 1	29 (30%)	1 (3.4%)	0 (0%)	
Grade 2	52 (54%)	21 (72%)	5 (62.5%)	
Grade 3	8 (8.2%)	6 (21%)	3 (37.5%)	
ER stain by IHC, N (%)	97(100%)	29(100%)	8(100%)	1.000
PR stain by IHC, N (%)	93(96%)	25(86%)	4(50%)	**0.000**
HER2/neu by IHC				0.875
0	16	5	2	
1+	52	15	4	
2+	28	9	2	
3+	1	0	0	
Ki-67 by IHC, median(IQR)	10(5~20)	30(15~35)	40(30~50)	
Ki-67≤20%, N	83	13	0	**0.000**
Ki-67>20%, N	12	16	8	

the categorization of low, intermediate or high risk. By using Adjuvant! Online, the correlation between the predicted BCSM and RS was nominal (r=0.10) (Figure 1). However, the correlation between Ki-67 and RS was moderate (r=0.43) (Figure 2). The median Ki-67 in low, intermediate and high risk RS group was10% (interquartile range, IQR, 5%~20%), 30%(IQR, 15%~35%) and 40%(IQR, 30%~50%).

Treatment recommendations before and after RS testing. All patients enrolled were recommended to receive endocrine therapy only according to clinicopathological characteristics with or without the patients' preferences. Fifty-three patients (53/134, 40%) and 30 patients (30/134, 22%) chose chemotherapy before and after knowledge of RS. Six percent (8/134) 21-gene RS group patients changed to receive chemotherapy besides endocrine therapy after RS testing. Meanwhile, 23% (31/134) patients changed to reject chemotherapy after that (Figure 3). That is, 29% patients changed their treatment decisions (P<0.001, 95% CI, 0.18 to 0.49). The 30 patients receiving chemotherapy included all patients categorized in high RS risk, 16/29 patients in intermediate RS risk and 6/97 patients in low RS risk (Table 4). Among these16 patients in intermediate RS risk, 8 of them was recommended to receive chemotherapy by the doctor and the rest of them were eager to receive chemotherapy personally without the doctor's recommendation. Among the 97 patients categorized in low RS risk, 70 patients were deemed intermediate risk by St. Gallen, and only 6 patients with intermediate risk by St. Gallen received chemotherapy. Among these 6 patients, 4 of them chose chemotherapy for the patients' preferences. The rest 2 patients were recommended to receive chemotherapy by the doctor for Her-2 gene amplification verified by FISH.

Oncologist's confidence level in treatment recommendation before and after RS testing. After RS testing, more than one half of the oncologists increased their confidence level in treatment recommendation (Table 5).

Treatment recommendations in the control group without RS information. In the control group (Table 4),

Table 3. Concordance between RS and 2007 St. Gallen criteria

	St. Gallen low (n =28)	St. Gallen intermediate (n =106)
RS low (n = 97)	**27**	70
RS intermediate (n = 29)	1	**28**
RS high (n = 8)	0	8

Numbers in bold represent concordance between categories
Overall concordance: 55 of 134 = 41%

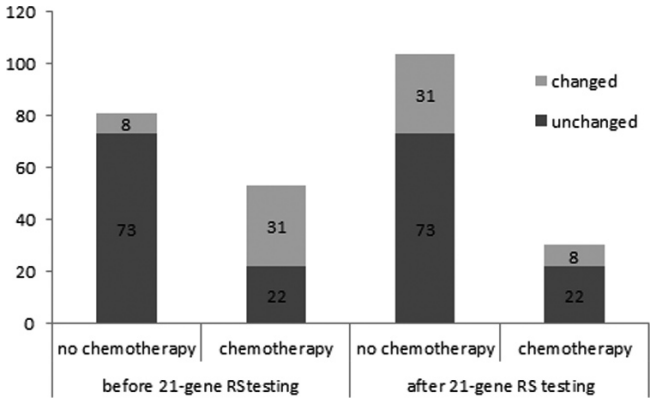

Figure 3. Chemotherapy decision before and after 21-gene RS testing (21-gene RS group, N=134)

67.6% (115/170) patients chose chemotherapy plus endocrine therapy. The chemotherapy percentage was much higher than that of 21-gene RS group (22.4%). Among the twenty-two patients in control group categorized in low risk by St. Gallen, half of them received chemotherapy. While, no patient in low risk by St. Gallen in 21-gene RS group received chemotherapy. Among the 119 patients in control group categorized in intermediate risk by St. Gallen, 73% (87/119) of them received chemotherapy. However, only 28.3% (30/106) patient in intermediate risk by St. Gallen in 21-gene RS group received chemotherapy.

Discussion

Adjuvant chemotherapy has been demonstrated by multiple clinical trials to be an efficacious treatment for breast cancer patients especially for those with positive lymph node metastasis [11]. But what kind of patients can get benefit from chemotherapy is still a question for all the breast cancer physicians. The effectiveness of adjuvant chemotherapy on hormone receptor positive, node-negative breast cancer is not so promising. It is a challenge for physicians to pick out the proper patient group who would benefit from the chemotherapy besides endocrine therapy. NCCN guidelines have

Table 4. Clinicopathological characteristics in patients receiving and not receiving adjuvant chemotherapy (all subjects)

	21-gene RS group (N=134)		Control (N=170)	
	Chemotherapy (N=30)	No chemotherapy (N=104)	Chemotherapy (N=115)	No chemotherapy (N=55)
Age				
Median(range),years	44.5 (32-67)	50 (29-69)	48 (26-72)	53.5 (35-77)
Age category, N(%)				
≤50 years	23 (77)	57 (54.8)	74 (64.3)	20 (36)
>50 years	7 (23)	47 (45.2)	41 (35.7)	35 (64)
Histology, N(%)				
IDC	30 (100)	87 (83.6)	100 (87.0)	53 (96)
ILC	0	14 (13.5)	12 (10.4)	2 (4)
IDC+ILC	0	3 (2.9)	3 (2.6)	0
Tumor size, N(%)				
≤2cm	23 (77)	91 (87.5)	83 (72.2)	51 (93)
>2cm	7 (23)	10 (9.6)	32 (27.8)	4 (7)
Not applicable	0	3 (2.9)	0	0
Tumor grade, N(%)				
Grade 1	0	30 (28.8)	11 (9.6)	12 (22)
Grade 2	21 (70)	57 (54.8)	58 (50.4)	31 (56)
Grade 3	9 (30)	8 (7.7)	29 (25.2)	1 (2)
Not applicable	0	9 (8.7)	17 (14.8)	11 (20)
Ki-67 category, N(%)				
≤20%	8 (27)	88 (84.6)	66 (57.4)	40 (73)
>20%	22 (73)	14 (13.5)	39 (33.9)	7 (13)
Not applicable	0	2 (1.9)	10 (8.7)	8 (14)
St Gallen risk category				
Low	0	28 (26.9)	11 (9.6)	11 (20)
Intermediate	30 (100)	76 (73.1)	87 (75.7)	32 (58)
21-gene RS category				
Low	6 (20)	91 (87.5)	-	-
Intermediate	16 (53)	13 (12.5)	-	-
High	8 (27)	0	-	-

included the 21-gene signature assay for lymph node-negative, HR-positive patients since 2008. And all the node-negative breast cancer patients with HR-positive, HER-2 negative and >0.5cm have been recommended to RS testing to guide risk stratification and chemotherapy benefit by NCCN since 2011 [4]. The St. Gallen conferences made the definition of risk categories for patients with operated breast cancer according to clinicopathologic characteristics and make the chemotherapy recommendation according to the risk categories in 2007 [12]. And the Panel agreed that validated multigene tests, if readily available, could assist in deciding whether to add chemotherapy in cases where its use was uncertain after consideration of conventional markers for node-negative and HR-positive patients in 2009 [13]. In 2011, St. Gallen Panel made the surrogate definitions of intrinsic subtypes of breast cancer and made systemic treatment recommendations according to different subtypes [7]. The biological characteristics of breast cancer are attracting more and more researchers' attention.

Several studies demonstrated that the 21-gene assay was a more accurate predictor of relapse than standard clinical features for individual patients with HR-positive operable breast cancer treated with chemoendocrine therapy and provide complementary information in treatment planning [14].

To date, the validity of the 21-gene assay had been assessed in many countries around the world [15-18], but its validity in Chinese population had not been assessed yet. This is the first prospective study to confirm the clinical impact on adjuvant decision-making of 21-gene assay in Chinese breast cancer patients. In China, the RS testing has not been used widely so far, as the payment was not covered by social medical insurance or by third-party payers. So patients who decided to receive adjuvant chemotherapy definitely on clinicopathologic data (lymph node positive, tumor large, et al.) were not recommended to do RS testing and not enrolled in this pilot study. The distribution of RS group in our study (72% low, 22% intermediate, 6% high) is not so comparable with other studies [15, 8]. Kelly et al. showed the distribution of RS to be 52% low, 39% intermediate and 9% high in their study. And the RS distribution in NSABP B-14 clinical validation study was 51%, 22% and 17%, respectively. The results greatly depended on the characteristics of the patients enrolled. In our study, 21% of the patients (28/134) were categorized into low risk by 2007 St Gallen risk categories. Eighty-five percent of tumors were not larger than 2cm. And only 13% of the tumors were in grade 3. After the knowledge of RS, there were 29% patients changed their adjuvant therapy, including 6% (8/134) changed to receive chemotherapy besides endocrine therapy and 23% (31/134) changed to reject chemotherapy after that. The change percentage is similar with findings from other prospective studies by Eiermann et al. (30%) [18], Lo et al(32%) [19] and Albanell et al(32%) [20]. The majority of change in our study is from a chemoendocrine therapy recommendation to endocrine therapy alone. The oncologists seemed to be hesitant omitting chemotherapy before RS testing. About 40% patients were advised to receive chemotherapy before RS testing. The chemotherapy recommendation percentage decreased to 22% after RS testing. Meanwhile, the RS result increased the oncologist's confidence's level in treatment recommendation. Most of the patients in our study followed the oncologist's recommendation with ten patients persisting on chemotherapy by their own preference. About one-fourth of patients avoided the probable overtreatment after RS testing.

Table 5. Oncologist's confidence level changed post-RS testing

Confidence level	RS risk		
	Low (n=97)	Intermediate (n=29)	High (n=8)
Increased	52	16	5
Unchanged	40	11	3
Drops	5	2	0

The reasons for most intermediate RS patients (16/29) to receive chemotherapy were as following: the first, the TAILORx study randomized node-negative and ER-positive patients between 11 and 25 to endocrine therapy alone or chemoendocrine therapy [9]. The physicians would like to recommend intermediate risk patients with a little high RS to chemotherapy. Secondly, eight of intermediate RS patients chose chemotherapy by individual preference for their eagerness to get benefit from chemotherapy.

Comparing the St. Gallen risk category with 21-gene RS in our study, we observed significant correlation in St. Gallen low group and RS low group. Almost all of patients (27/28) categorized into St. Gallen low group got a low RS. The percentage is a bit higher than other studies (24/32) [21]. The oncologists may have more confidence to omit chemotherapy for patients in St. Gallen low risk group when 21-gene RS testing was not available. More data are expected from future studies.

As a continuous score, BCSM calculated by Adjuvant! Online was compared to RS directly without the categorization of low, intermediate or high risk. There was poor correlation between BCSM and RS in our study(r=0.10). The result is similar with findings from the study by Kelly CM et al [15]. Several studies chose cutoffs for estimated BCSM in order to create similar category as RS, the overall concordance was about 50% [21]. The oncologists got little information for chemotherapy decision-making from BCSM.

Our study shows that the RS results influenced chemotherapy decisions more than the standard clinicopathologic criteria such as the St. Gallen Consensus Statement and Adjuvant! Online. More than one half of the oncologists increased their confidence level after RS testing. A prospective Germany study reported physicians' confidence increased in 45% of node-negative patients [18]. Furthermore, patients' preferences are also important in treatment decision-making especially for those in intermediate RS risk. To date, the oncologists are still not so sure about the chemotherapy benefit for such patient group. The result of TAILORx study is worth waiting.

From the economic view, 21-gene testing is still expensive for developing country patients especially for the rural population. Cancer treatment is an enormous burden for rural family. The physicians still rely largely on classic clinicopathologic information to make the treatment decision. How to get more information from the clinicopathologic characteristics is a challenge for physicians in rural hospital. Similar with previous studies [15], tumor grade, PR expression and Ki-67 index were significantly different between the three RS cohorts. Patients with higher tumor grade, lower PR expression and higher Ki-67 index had more probability to be categorized into high RS group in this study. It is consistent with the 21-gene recurrence score calculation [8]. In Kelly CM et al's study, none of invasive lobular carcinoma(ILC) was categorized into high RS [15]. Our study also observed the association between low RS and invasive lobular histology. All of the 14 ILC patients of the RS group had low RS in this study. Considering the biological, molecular and clinical difference between ILC and invasive ductal carcinoma, further study is warranted in the usage of RS testing in ILC patients.

Our study has several limitations. First, the follow-up period was not long enough for the survival analysis. We will follow up all patients in this study in the following years to get more survival information. Second, we didn't choose control group in the same period as 21-gene group. The chemotherapy percentage in control group(67.6%) was much higher than that of 21-gene RS group in the retrospective part of this study although the baseline characteristics were approximately balanced. There were still a bit more patients with larger tumor or higher grade in the control group and the oncologists might be less confident in endocrine therapy alone before the application of 21-gene RS testing in our department. All of these might influence the chemotherapy decision-making. Up to now, the 21-gene RS studies in node-positive estrogen receptor-positive breast cancer patients have been carried out and RS has been demonstrated to be a predictor of the benefit of chemotherapy [17,18]. Our pilot study enrolled only node-negative patients because RS testing is not widely used in China by far.

In conclusion, our study demonstrates a reduction in the use of adjuvant chemotherapy in Chinese women with node-negative hormone receptor-positive breast cancer, based on use of the RS. The RS had an impact on the physicians' treatment decision-making.

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