

RESEARCH PAPER



Comparison of 21-gene assay and St.Gallen International Expert Consensus in the treatment decision for patients with early invasive breast cancers

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ABSTRACT

This study aimed to evaluate the impacts of 21-gene recurrence score (RS) and St. Gallen International Expert Consensus on treatment decision and prognosis of patients with invasive breast cancer. We retrospectively analyzed the therapy protocol and outcome of 134 cases based on age, body mass index (BMI), menopause, pathological types, tumor-node-metastasis (TNM) stages, percentage of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), Ki-67, molecular subtype, and tumor biomarkers. RS was calculated based on 21-gene assay following traditional (old RS cutoff) and updated (new RS cutoff) National Comprehensive Cancer Network (NCCN) guideline. In addition, we also compared treatment protocol of NCCN guidelines with St. Gallen International Expert Consensus. The results showed that BMI, PR, Ki-67, and molecular subtype are critical for the evaluation of risk factors. Based on the new cutoff, low, middle, and high RS were 18%, 66%, and 16%, respectively. In contrast, based on the old cutoff, low, middle, and high RS were 60%, 29%, and 11%, respectively. The agreement rate of NCCN guidelines and St. Gallen International Expert Consensus for adjuvant treatment was 50. However, there is minimal agreement (0.151, 0.071) in kappa coefficient of old and new cutoff. This study revealed that the combination of NCCN guidelines and St. Gallen International Expert Consensus might improve the benefits of adjuvant treatment in patients with early invasive breast cancer.

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Introduction

Breast cancer is one of the most common types of cancer in women.¹ The risk factors for breast cancer include genetic mutations, diet, reproductive history, and advancing age.² Treatment for breast cancer includes surgery, chemotherapy, and radiation; the choice of treatment depend on the stage of the cancer and age of the patients.³ In addition, the patients who are estrogen receptor (ER)-positive, human epidermal growth factor receptor type 2(HER2)-negative, and axillary lymph node (LN) – negative (ER+/HER2-/LN-) require hormone therapy,⁴ which is an adjuvant therapy based on ER and HER2 expression levels.^{5,6} Currently, the benefits of chemotherapy and endocrine therapy depend on the recurrence score (RS) based on the 21-gene assay.^{7,8} This include 16 specific genes and 5 reference genes detected by reverse-transcriptase polymerase chain reaction (RT-PCR) method. Gene expression analysis also determine the benefits of hormone therapy and chemotherapy, as well as the 10-year risk of distant metastasis in patients with invasive breast cancer (ER+/HER2-/LN-).^{9,10} National Comprehensive Cancer Network (NCCN) guidelines released the first version for breast cancer RS; the RS for low, middle, and high risk of recurrence were ≤ 17 , 18–30, ≥ 31 , respectively in 2017.¹¹ In this study, we considered the 2017 version of NCCN guidelines as the old criteria. In late 2018, NCCN updated

guidelines.¹² According to this new criteria, the RS for low, middle, and high risk of recurrence were ≤ 10 , 11–25, ≥ 26 , respectively. These different cutoff values have affected the therapeutic benefits provided the NCCN guidelines.

In addition to NCCN guidelines, some institutes use St. Gallen International Expert Consensus^{13,14} to decide the therapeutic strategy for patients with breast cancer. The comparative advantages and disadvantage of NCCN guidelines and St. Gallen International Expert Consensus for the treatment of patients with breast cancer patients remain unknown.

Here, we retrospectively reviewed the records of the patients in our hospital from January, 2015 to December, 2018. We compared the treatment benefits of the old and new RS cutoffs for patients with breast cancer patients. Additionally, we also calculated the agreement rate of NCCN guidelines and St. Gallen International Expert Consensus.

Patients and methods

Patients with breast cancer were enrolled from January 2015 to December 2018 based on the following criteria: Age: 18--75 years; axillary LN negative, ER+ and/or PR+, HER2-; and bone marrow, liver, kidney function, lung, and heart are normal range. Using RT-PCR, 21-gene assay was performed to evaluate the RS of the patients;,, *Ki-67*, *STK15*, *survivin*,

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cyclin B1, MYBL2, stromolysin 3, cathepsin L2, GBR7, HER2, GSTM1, CD68, BAG1, ER, PR, BCL2, SCUBE2, β -actin, GAPDH, RPLPO, GUS, and TFRC expression were determined.⁷ Total RNA was extracted from breast cancer samples and RT-PCR was performed. Ct value in 21 genes was recorded among 15–35 cycles. Ct values in five internal control genes were averaged, then delta Ct between single gene and internal control were changed into RS (0–100). *ER, GSTM1, and BAG1* are good prognosis markers. Their high expressions resulted in low RS. In contrast, *Ki-67, HER2, survivin, and CD68* group are bad prognosis genes; these high gene expression may lead to high RS. The patients received endocrine therapy alone or chemoendocrine therapy based on their RS. A low RS was below ≤ 17 (old RS cutoff) or ≤ 10 (new version RS cutoff). Midrange RS was 18–30 (old RS cutoff) or 11–25 (new RS cutoff). A high RS was ≥ 31 (old RS cutoff) or ≥ 26 (new cutoff). If RS is low, the patients only received endocrine therapy. Patients with midrange RS received endocrine therapy only or chemoendocrine therapy, as these patients did not benefit from chemotherapy alone. In contrast, patients with high RS received chemoendocrine therapy. However, these patients required chemotherapy as they may relapse in a short time. The primary endpoints of this study were the survival of patients with invasive cancer. The second endpoints were the absence of relapse and metastasis. This study was approved by our hospital ethical committees. All patients provided informed consent.

Calculation of St. Gallen International Expert Consensus

RS ranges from 1 to 100; a lower score indicated that the risk of relapse is minimal and the patients have low benefit from chemotherapy. We also set up the kappa coefficient as minimal, weak, moderate, strong, and almost perfect, as shown in Table 1. 21-gene assay was performed according to NCCN guidelines. It also was confirmed by American Society of Clinical Oncology (ASCO) and St. Gallen International Expert Consensus, which not only provided the relapse risk of within and beyond 5 years, but also predicted the benefits of chemotherapy or endocrine therapy in ER-positive patients with invasive breast cancer.

Statistical analysis

Chi-squared or Fisher's exact tests were used to determine the relationship between the histologic subtypes, patient demographics, clinic-pathological characteristics, and treatment. Continuous variables were compared using ANOVA test. Cohen's Kappa setting is between 0 and 1. 0.1–0.20 is slight agreement. Statistical analyses were performed using

Table 1. Kappa agreement setting.

Value of Cohen's kappa coefficient level of agreement
<0.20 minimal
0.21–0.40 weak
0.41–0.60 moderate
0.61–0.80 strong
0.81–1.0 almost perfect

Kappa coefficient is 0.223 (weak), $P < 0.001$.

SPSS software version 22. P -values < 0.05 were considered statistically.

Results

Clinical characteristics

Overall, 134 patients were enrolled in the study. Compared with old RS cutoff, when the new RS cutoff was used the number of low risk patients dramatic decreased from 80 (60%) to 24 (18%), the middle-risk patients increased from 39 (29%) to 89 (66%), and the high-risk patients are slightly increased from 15 (11%) to 21 (16%) (Figure 1). In addition, body mass index (BMI) and tissue differentiation stage showed significant difference in the new RS cutoff. We also found that PR and Ki-67 showed robust changes among low-, middle-, and high-risk groups in either old or new cutoffs. Luminal A and luminal B1 were tremendous elevation in middle-risk group. In contrast, there were no dramatic differences in age, menopause, pathology, tumor location, ER, and HER2 in either new or old RS cutoff (Table 2). These data indicated that different RS cutoffs may have a critical clinical significance in predicting prognosis and guiding therapy.

Comparison of agreement rate between St. Gallen International Expert Consensus and NCCN guidelines

To address the agreement rate of St. Gallen International Expert Consensus and NCCN guidelines, we evaluated the respective treatment protocol based on their RS. As shown in Table 3, 40 patients underwent endocrine therapy and 27 patients underwent for chemoendocrine therapy. The total match rate in St. Gallen International Expert Consensus and NCCN guidelines for adjuvant treatment was 50% (67/134). In contrast, uncertain rate in middle RS is 0%. These data showed that NCCN guideline and St. Gallen consensus were useful for therapy-related decisions in patients with early invasive breast cancer.

The match rate of kappa coefficient in old and new RS cutoff

To investigate the match rate of kappa coefficient in old and new RS cutoff in St. Gallen International Expert Consensus, we counted the match rate, and found it to be 44% (59/134); the kappa coefficient was 0.151 (minimal agreement) in old RS cutoff (Table 4). We also calculated kappa coefficient in the new RS cutoff (Table 5); we found that the agreement rate was 35% (47/134) and kappa coefficient was 0.071 (minimal agreement). These studies demonstrated that St. Gallen International Expert Consensus is also key indicator for breast cancer therapy.

Discussion

Here, we evaluated the impacts of RS based on 21-gene assay and St. Gallen International Expert Consensus on the treatment decision for patients with the early-stage invasive breast cancer. We also compared the benefits of 21-gene RS

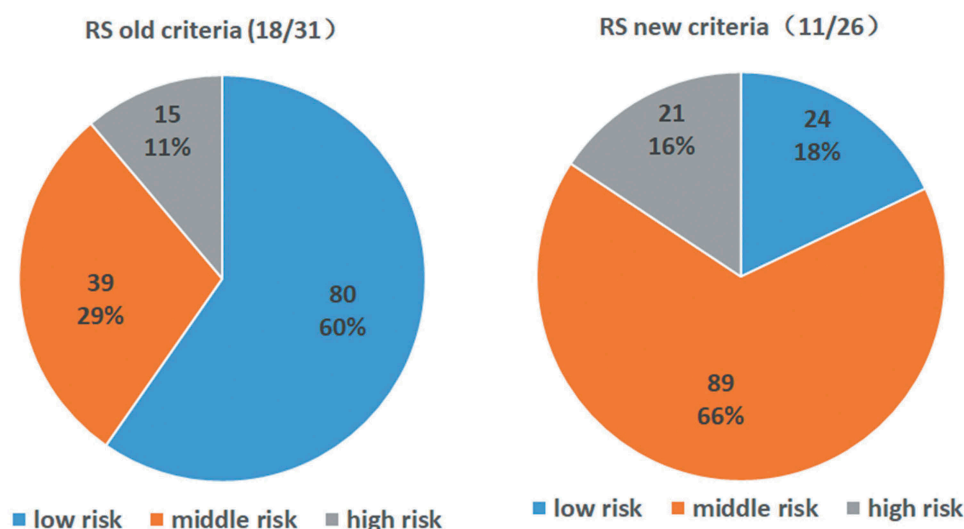


Figure 1. Comparison of RS new and old criteria. This graph presents percentage of low- (≤ 17), middle- (15–30), and high-risk (≥ 31) patients based on old criteria (left) and new criteria (right, low-risk ≤ 10 ; middle-risk, 11–25; high-risk, ≥ 26). RS, recurrence score.

Table 2. Clinical pathological characteristics of distinct risk groups.

	Old criteria			<i>p</i>	New criteria			<i>p</i>
	Low risk	Middle risk	High risk		Low risk	Middle risk	High risk	
Age				0.36				0.459
≤50	57(61%)	24(26%)	12(13%)		16(17%)	60(65%)	17(18%)	
>50	23(56%)	15(37%)	3(7%)		8(19%)	29(71%)	4(10%)	
BMI	22.64	22.79	21.41	0.241	23.15	22.67	21.3	0.036
Menopause				0.562				0.877
Yes	18(55%)	12(36%)	3(9%)		5(15%)	23(70%)	5(15%)	
No	62(61%)	27(27%)	12(12%)		19(19%)	66(65%)	16(16%)	
Pathology				0.498				0.747
IDC	54(62%)	25(29%)	8(9%)		17(20%)	56(64%)	14(16%)	
ILC	3(75%)	1(25%)	0		1(25%)	3(75%)	0	
Other	23(54%)	13(30%)	7(16%)		6(14%)	30(70%)	7(16%)	
Tissue differentiation				0.027				0.118
1	10(83%)	2(17%)	0		3(25%)	9(75%)	0	
2	33(56%)	17(29%)	9(15%)		11(19%)	35(59%)	13(22%)	
3	5(33%)	6(40%)	4(27%)		2(13%)	8(53%)	5(33%)	
Tumor location				0.878				0.593
Outward	21(62%)	10(29%)	3(9%)		5(15%)	25(73%)	4(12%)	
Inward	59(59%)	29(29%)	12(12%)		19(19%)	64(64%)	17(17%)	
Sites number				0.247				0.318
1	71(58%)	37(30%)	15(12%)		22(18%)	80(65%)	21(17%)	
2	9(82%)	2(18%)	0		2(18%)	9(82%)	0	
T stage				0.393				0.516
T1	62(62%)	26(26%)	12(12%)		20(20%)	64(64%)	16(16%)	
T2	18(53%)	13(38%)	3(9%)		4(12%)	25(73%)	5(15%)	
N stage				0.833				0.95
N0	65(60%)	31(28%)	13(12%)		19(17%)	73(67%)	17(16%)	
N1	15(60%)	8(32%)	2(8%)		5(20%)	16(64%)	4(16%)	
ER	72.85	71.49	61.2	0.326	77.63	71.89	60.62	0.074
PR	71.16	50.92	24.67	<0.001	70.75	63.27	34.29	<0.001
Ki-67	13.67	21.99	37.33	<0.001	14.21	15.8	36.5	<0.001
HER2(IHC)				0.374				0.33
0	42(58%)	22(30%)	9(122%)		12(16%)	47(64%)	14(19%)	
1	20(49%)	17(41%)	4(10%)		5(12%)	31(76%)	5(12%)	
2	18(90%)	0	2(10%)		7(35%)	11(55%)	2(10%)	
Molecular type				<0.001				<0.001
Luminal A	60(73%)	20(24%)	2(3%)		18(22%)	60(73%)	4(5%)	
Luminal B1	20(41%)	16(33%)	13(26%)		6(12%)	27(55%)	16(33%)	

BMI: Body mass index; IDC, Invasive ductal carcinoma; ILC, Invasive Lobular Carcinoma; ER, Estrogen receptor; PR, progesterone receptor; IHC, Immunohistochemistry.

and St. Gallen International Expert Consensus for adjuvant therapy. Our results showed that the new RS criteria slightly increased percentage of high-risk patients, but dramatically elevated percentage of middle-risk patients. However, the agreement rate of 21-gene RS testing and St. Gallen International Expert Consensus is almost consistent.

A few clinical practice guidelines including the American Society of Clinical oncology (ASCO), Cancer Care Ontario's Program in Evidence Based Care (CCO's PEBC), NCCN, and the St. Gallen International Breast Cancer Consensus are used to decide the therapeutic strategy of patients with the invasive breast cancer.¹⁴ The application of these guidelines has been shown to provide treatment benefits in terms of recurrence-free

Table 3. Adjuvant treatment protocol agreement rate of St. Gallen International Expert Consensus and NCCN guidelines.

		NCCN guidelines			Total
		Endocrine	Uncertain	Chemotherapy + endocrine	
St. Gallen Consensus	Endocrine	40	1	9	50
	Uncertain	20	0	16	36
	Chemotherapy + Endocrine	8	13	27	48
	Total	68	14	52	134

Match rate of St. Gallen International Expert Consensus and NCCN guidelines for adjuvant treatment was 67/134 = 50%.

Table 4. Agreement rate of 21 genes assay and St. Gallen International Expert Consensus for adjuvant treatment protocol.

		St. Gallen consensus treatment suggestions			
		Endocrine	Uncertain	Chemotherapy + endocrine	Total
21-gene assay Old criteria	Low risk	37	18	25	80
	Middle risk	10	14	15	39
	High risk	3	4	8	15
	Total	50	36	48	134

Match rate is 59/134 = 44%, Kappa coefficient is 0.151 (minimal agreement).

Table 5. Agreement rate of 21-gene assay new criteria and St. Gallen International Expert Consensus for adjuvant treatment protocol.

		St. Gallen consensus treatment suggestions			
		Endocrine	Uncertain	Chemotherapy + endocrine	Total
21-gene assay new Criteria	Low risk	12	6	6	24
	Middle risk	34	24	31	89
	High risk	4	6	11	21
	Total	50	36	48	134

Agreement rate is 47/134 = 35%, Kappa coefficient is 0.071 (minimal agreement).

and overall survival.^{15,16} However, different guidelines have some advantages and disadvantages.¹⁴ Among four guidelines, NCCN and St. Gallen International Expert Consensus specially focused on how to define and treat patients at high-risk of developing breast cancer.^{11,17,18} Therefore, the comparison of different guidelines may improve the therapeutic benefit and prognosis of patients with the early-stage breast cancer. In addition, biomarker assay and clinic-pathologic profiles also help to clarify the treatment strategy and prognosis. Our results showed the impacts of PR, Ki-67, luminal A subtype, and luminal B1 subtype in low-, middle-, and high- risk groups had a significantly varied based on old and new RS cutoff criteria. Tissue differentiation stages and BMI changed dramatically based on different RS cutoff criteria. These results indicated that different RS cutoff criteria have impacted on the treatment decision. Chen et al.¹⁹ reported that the 21-gene RS can affect chemotherapy decision in patients with invasive ductal carcinoma of the breast. Varga et al.²⁰ also showed that different risk stratification has an impacted on the clinical choice. Our findings are consistent with those of these previous reports.

NCCN guidelines and St. Gallen International Expert Consensus may be beneficial for treatment-related decision

in patients with early-stage breast cancer.¹⁴ We compared the agreement rate of NCCN guidelines and St. Gallen International Expert Consensus in treatment-related decision for 134 patients with breast cancer based on old and new RS cutoff criteria. It was found that the agreement rate is 50%, which overlapped in low and high RS cutoff patients. There was no any agreement in middle RS cutoff patients. We also further characterized kappa coefficient in St. Gallen International Expert Consensus and NCCN guidelines of old and new RS cutoff criteria. Both kappa coefficients fall into minimal agreement. This finding showed that agreement rate and kappa coefficient of NCCN guidelines and St. Gallen International Expert Consensus had diverse effects on treatment of patients with early breast cancer. Indeed, 21-gene assay can guide treatment-related decision for patients with breast cancer.^{21–23} St. Gallen International Expert Consensus also has great benefits for treatment-related decision in patients with cancer.²⁴ Our study confirmed these advantages for treatment-related decision in patients with early-stage invasive breast cancer.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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