Original Article

Prognostic significance of the Controlling Nutritional Status (CONUT) score in surgically treated breast cancer patients

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Background: Breast cancer is one of the most common malignancy in women with high mortality rate. Given the growing evidence shows that immune-inflammatory system influences the survival of patients with cancer, we assessed the prognostic significance of the preoperative Controlling Nutritional Status (CONUT) score in patients with breast cancer who underwent surgery.

Methods: We conducted a retrospective analysis of 1,367 breast cancer patients who underwent surgery between December 2010 and October 2012. All individual preoperative serum albumin concentration, total cholesterol concentration, and total peripheral lymphocyte count were counted to calculate CONUT. Higher CONUT score is in line with worse nutritional status. The optimal cut-off of CONUT score was set at 3 to categorize the investigated patients into two groups, namely a high- or low-CONUT score group. We adopted univariate and multivariate analyses (Cox proportional hazards regression model) statistical method.

Results: Patients in the high-CONUT score group had shorter overall survival (OS) and recurrence-free survival (RFS) in comparison with those in the low-CONUT score group, 66.43 *vs.* 69.30 months and 54.70 *vs.* 59.98 months respectively (all P value <0.05). Univariate and multivariate analyses revealed that the CONUT score was an independent predictor of OS (P=0.029 and 0.046, respectively) and RFS (P=0.001, P=0.013, respectively).

Conclusions: The CONUT score was identified as an independent prognostic indicator in surgically treated breast cancer patients, indicating that, compared with the low CONUT score, a high CONUT score may lead to poorer prognosis.

Keywords: CONUT; breast cancer; surgery; survival

Submitted Feb 28, 2020. Accepted for publication Sep 03, 2020.
doi: 10.21037/gs-20-294
View this article at: http://dx.doi.org/10.21037/gs-20-294

Introduction

Breast cancer is one of the most common malignancy in women with high mortality rate (1). By far, a set of canonical management of breast cancer has been constructed, including operation, neoadjuvant therapy, proper postoperative treatment and the recent hot immunotherapy (2,3). According to the specific situation of each individual, clinician would choose the optimal treatments (4). Years of development, mature process has been formed in clinic. Despite that multimodal treatment has significantly decreased its mortality rate, breast cancer is still a severe disease imperiling thousands of patients health with the global occurrence is still increasing (5). At the same time, the medical model of precision medicine is increasingly playing an important role. A core principle of precision medicine is that cancer treatment aims at emphasizing the clinical and biological characteristics of the individual tumor (6,7). Breast cancer is a highly heterogeneous malignant disease. Combining personalized treatment with individuals' conditions may embody the application of precision medicine in breast cancer and produce predictable results to improve prognosis.

Recently, inflammation and immunity have been the focus of research, depicting a promising future for cancer treatment (8). Likewise, several researches have revealed immune biomarkers as meaningful hallmarks of cancer (9,10). Further, there have been studies demonstrating that activation of the host immune system is beneficial for improving the patients' overall survival (11,12). Biomarkers such as the platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and C-reactive protein (CRP) have been verified as independent prognostic factors in various cancers, including breast cancer (13-17). Comparably, the Controlling Nutritional Status (CONUT) score is another emerging biomarker score which is calculated by three parameters: the serum albumin concentration, total cholesterol concentration, and total peripheral lymphocyte count; reflecting both the nutritional and immune context of the investigated patient (18). The CONUT score has reported positive outcome in several carcinomas, such as renal, gastric, prostate, and colorectal cancer (19-22). An interesting appearance was observed that patients in high CONUT group had longer survival than those in low group. Therefore, we presumed that the CONUT score could have similar impact in breast cancer and could be implemented in daily clinical practices to monitor the patient's disease condition, assessing possibility of early disease progression and to guide timely therapeutic intervention. It is an extension of precision medicine in clinical application.

In this study, we investigated the clinical applicability of the CONUT score as a new, accurate and sensitive prognostic biomarker in breast cancer and its significance to overall survival and recurrence-free survival.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/gs-20-294).

Methods

Patients

There were 1987 patients received curative surgery from December 2010 to October 2012 at the Sun Yat-sen University Cancer Center (SYSUCC; Guangzhou, China). The inclusion criteria were as follows: (I) breast cancer patients; (II) patients received surgery. The exclusion criteria were as follows: (I) synchronal malignancies; (II) ductal carcinoma in situ; (III) incomplete blood sample data and missing visit due to various reasons. Finally, we retrospectively retrieved the data of 1,367 breast cancer patients (see *Figure 1*).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of SYSUCC (B2020-215-01) and individual consent for this retrospective analysis was waived.

Sample collection and classification

All patients' information was retrieved from the Sun Yat-sen University Cancer Center (SYSUCC) medical records. Blood samples were collected and measured within 1 week before surgery. The CONUT score was calculated using the preoperative data on serum albumin concentration, total cholesterol concentration, and total peripheral lymphocyte count. The three parameters scores were grouped into four levels based on their concentrations (*Table 1*). The cut-off value for the CONUT was defined as 3, according to previous research on renal, gastric, and prostate cancer (19-21). The age parameter was classified into two groups based on its median value (48 years old). The

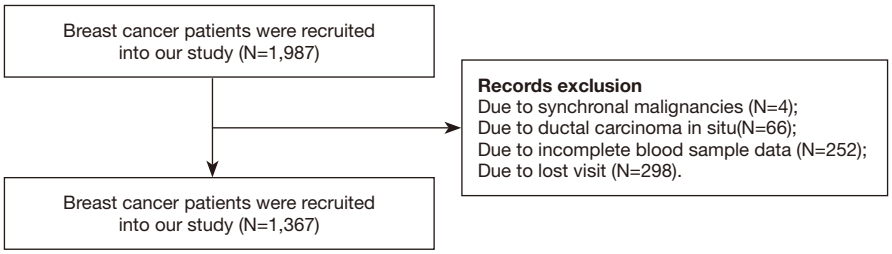

Figure 1 Flow diagram of study selection.

Table 1 Controlling nutritional status index score: assessment of malnutritional state (20)

Parameter	Malnutritional state			
	Normal	Mild	Moderate	Severe
Albumin (g/dL) [score]	≥3.50 [0]	3.00–3.49 [2]	2.50–2.99 [4]	<2.50 [6]
Total lymphocyte count (mg/dL) [score]	≥1,600 [0]	1,200–1,599 [1]	800–1,199 [2]	<800 [3]
Total cholesterol (mg/dL) [score]	≥180 [0]	140–179 [1]	100–139 [2]	<100 [3]
Total score	0–1	2–4	5–8	9-12

tumors were staged according to the 7th AJCC (American Joint Committee on Cancer) TNM staging system. The expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2) and Ki-67 were defined by the St Gallen criteria (23). We identified ER and PR positive if there were at least 1% positive heterologous tumor cell nuclei in the sample evaluated by immunohistochemistry (IHC). HER-2 status was assessed using a semiquantitative score (0–3+). Patients with 2+ IHC staining for HER2 underwent fluorescence in-situ hybridization (Fish) to confirm HER2 positivity or negativity. Ki67 was stratified into two group and the cutoff was 14%. The expression of tumor markers (CEA, CA153) was considered as positive if they were beyond normal range.

Follow-up

All patients were followed-up by outpatient examination or telephonic interviews. The last follow-up time was 27 September, 2019. Overall survival (OS) time was defined as the period from surgery to death from various causes or to the last follow-up date. Recurrence-free survival (RFS) was defined as the time from the date of surgery to the date of the first recurrence, death from any cause or last follow-up.

Statistical analysis

All analyses were conducted using the SPSS software version 23.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 6.0 (GraphPad, La Jolla, CA, USA). Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model. Two-tailed P values <0.05 were considered as statistically significant.

Results

The optimal cut-off value for the CONUT score

Based on their preoperative data, we calculated all patients scores and divided them into four levels, namely, normal [0–1], mild [2–4], moderate [5–8], and severe [9–12] (*Table 1*). According to previous study, the best CONUT cutoff was found to be 3. Therefore, the investigated 1,367 breast cancer patients were classified into a low CONUT score group (<3) or a high CONUT score (≥3) group.

Patient characteristics and Relationships between CONUT score with clinicopathological features

The median follow-up time was 5.86 years (range, 0.02–

8.82). The clinicopathological features of the entire study cohort and the relationships between the CONUT score and patient characteristics are shown in *Table 2*. Based on prespecified criteria, 308 (22.5%) and 1,059 (77.5%) were categorized into a high- and low-CONUT score group, respectively. The CONUT score was significantly associated with age (P<0.001), pTNM stage (P=0.027), Ki-67 (P=0.034).

Survival outcomes prognostication based on the CONUT score

Figure 2 demonstrate significant survival differences between the high- and low-CONUT breast cancer groups. The OS and RFS for patients in the high- and low-CONUT groups were 64.43 and 69.30 months (P=0.026) and 54.70 and 56.98 months (P=0.011), respectively. Multivariate analyses showed that N stage (P<0.001), M stage (P<0.001) and CONUT (P=0.046) matter were independent factor for OS (*Table 3*), while N stage (P=0.003), M stage (P<0.001), and CONUT (P=0.013) matter were independent factor for RFS (*Table 4*).

Discussion

Findings from the present study showed that patients with

Table 2 Clinicopathologic characteristics of the patients

Characteristic	Total (N=1,367)	CONUT		P
		Low	High	
Age (years)				<0.001*
<48	682 (49.9%)	476 (34.8%)	206 (15.1%)	
≥48	685 (50.1%)	583 (42.6%)	102 (7.5%)	
Histological type				0.599
Invasive ductal carcinoma	1,149 (84.1%)	893 (65.3%)	256 (18.7%)	
Others	213 (15.6%)	163 (11.9%)	50 (3.7%)	
Unknown	5 (0.4%)	3 (0.2%)	2 (0.1%)	
T stage				0.229
0	2 (0.1%)	1 (0.1%)	1 (0.1%)	
1	478 (35.0%)	371 (27.2%)	107 (7.8%)	
2	748 (54.7%)	588 (43.0%)	160 (11.7%)	
3	68 (5.0%)	51 (3.8%)	17 (1.2%)	
4	71 (5.2%)	48 (3.5%)	23 (1.7%)	
N stage				0.266
0	714 (52.2%)	567 (41.5%)	147 (10.7%)	
1	355 (26.0%)	272 (19.9%)	83 (6.1%)	
2	171 (12.5%)	126 (9.2%)	45 (3.3%)	
3	127 (9.3%)	94 (6.9%)	33 (2.4%)	
M stage				0.022*
0	1,340 (98.0%)	1,043 (76.3%)	297 (21.7%)	
1	27 (2.0%)	6 (1.2%)	11 (0.8%)	
pTNM stage				0.027*

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	Total (N=1,367)	CONUT		P
		Low	High	
I	324 (23.7%)	255 (18.7%)	69 (5.0%)	
II	694 (50.8%)	550 (40.3%)	144 (10.5%)	
III	322 (23.6%)	238 (17.5%)	84 (6.1%)	
IV	27 (2.0%)	16 (1.2%)	11 (0.8%)	
ER				0.276
Negative	427 (31.2%)	323 (23.6%)	104 (7.6%)	
Positive	940 (68.8%)	736 (53.9%)	204 (14.9%)	
PR				0.823
Negative	534 (39.1%)	412 (30.2%)	122 (8.9%)	
Positive	833 (60.9%)	647 (47.3%)	186 (13.6%)	
HER2				0.986
Negative	973 (71.2%)	754 (55.2%)	219 (16.0%)	
Positive	386 (28.2%)	299 (21.9%)	87 (6.4%)	
Unknown	8 (0.6%)	6 (0.4%)	2 (0.1%)	
Ki-67				0.034*
≤14%	498 (36.4%)	370 (27.1%)	128 (9.4%)	
>14%	869 (63.6%)	698 (50.4%)	180 (13.2%)	
Molecular subtype				0.353
Luminal A	353 (25.8%)	264 (19.3%)	89 (6.5%)	
Luminal B/HER2-	404 (29.6%)	326 (23.9%)	78 (5.7%)	
Luminal B/HER2+	202 (14.8%)	160 (11.7%)	42 (3.1%)	
HER2 Enriched	185 (13.5%)	140 (10.2%)	45 (3.3%)	
Triple Negative	217 (15.9%)	166 (12.2%)	51 (3.7%)	
Unknown	5 (0.4%)	3 (0.2%)	2 (0.1%)	
Preoperative CEA				0.850
Negative	1,190 (87.1%)	924 (67.6%)	267 (19.5%)	
Positive	119 (8.7%)	93 (6.8%)	26 (1.9%)	
Unknown	57 (4.2%)	42 (3.1%)	15 (1.1%)	
Preoperative CA153				0.255
Negative	1,150 (84.1%)	900 (65.8%)	250 (18.3%)	
Positive	161 (12.3%)	117 (8.6%)	44 (3.2%)	
Unknown	56 (4.1%)	42 (3.1%)	14 (1.0%)	

*P<0.05. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2; CEA, carcinoembryonic antigen; CA153, cancer antigen 153.

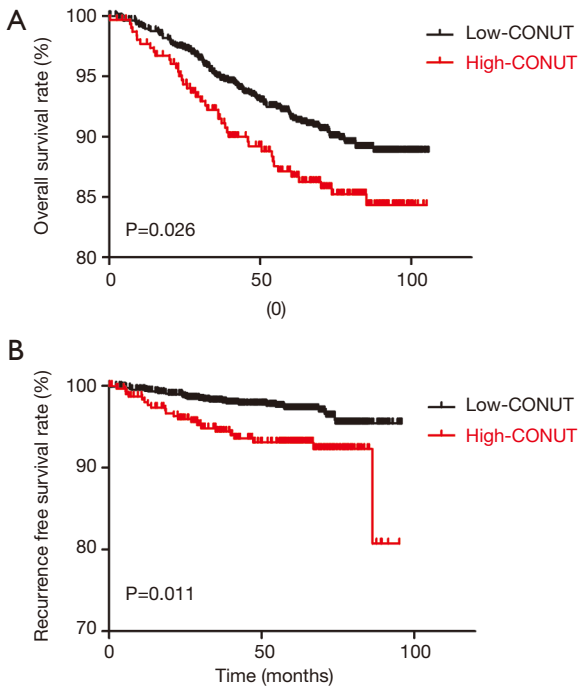

Figure 2 Kaplan-Meier for the stratified CONUT score groups in association to: (A) overall survival; (B) recurrence-free survival; and (C) distant metastatic-free survival.

high-CONUT score had poorer OS and RFS than those who with low-CONUT score and that the CONUT score was an independent prognostic factor for OS and RFS in surgically treated breast cancer patients; demonstrating that a high-CONUT score might be strongly associated with tumor progression and shorter survival.

Precision medicine request individualization (24,25) and will be modern medical trend (26). Immune-inflammatory system plays critical role in many physiological activity [such as wound healing (27), infection offence (28), vaccine (29)] and malignant cancers [perhaps affects tumor microenvironment (30)], and received fanatical attention. As we all known, nutritional status is thought to be associated with prognosis on oncology (31). For those reasons, it would be a proper biomarker which can reflect subjects' immune-inflammatory system and nutritional status, moreover, stay consistent with precision medicine.

Dozens of studies about immune-inflammatory system have been reported with various cancer prognosis, including breast cancer. However, there is no indicator that owns wide applicability. CONUT is a complex score and was first introduced as an efficient tool for early detection and continuous control of hospital undernutrition (18,32).

Table 3 Univariate and multivariate analyses of overall survival

Characteristic	Univariate analysis		Multivariate Cox regression analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age	1.135 (0.813–1.583)	0.457		
Histological type	2.171 (1.173–4.020)	0.014*	1.756 (0.942–3.272)	0.076
T stage	1.864 (1.559–2.227)	<0.001*	1.149 (0.918–1.437)	0.226
N stage	2.294 (1.981–2.655)	<0.001*	2.104 (1.713–2.394)	<0.001*
M stage	7.983 (4.499–14.166)	<0.001*	4.221 (2.275–7.834)	<0.001*
pTNM stage	3.574 (2.833–4.509)	<0.001*		
ER	0.598 (0.426–0.838)	0.003*	0.764 (0.457–1.279)	0.306
PR	0.543 (0.389–0.757)	<0.001*	0.813 (0.491–1.346)	0.421
HER2	1.795 (1.281–2.516)	0.001*	1.274 (0.878–1.848)	0.203
Ki-67	2.116 (1.413–3.169)	<0.001*	1.515 (0.990–2.320)	0.056
Molecular subtype	1.224 (1.093–1.370)	<0.001*		
CEA	3.157 (2.093–4.762)	<0.001*	1.341 (0.841–2.137)	0.218
CA153	1.901 (1.247–2.899)	0.003*	0.865 (0.539–1.390)	0.550
CONUT	1.502 (1.043–2.162)	0.029*	1.465 (1.007–2.132)	0.046*

*P<0.05. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2; CEA, carcinoembryonic antigen; CA153, cancer antigen 153.

Table 4 Univariate and multivariate analyses of overall survival and recurrence-free survival

Characteristic	Univariate analysis		Multivariate Cox regression analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age	0.890 (0.513–1.544)	0.679		
Histological type	0.651 (0.334–1.269)	0.208		
T stage	1.648 (1.203–2.256)	0.002*	1.198 (0.820–1.749)	0.350
N stage	1.735 (1.365–2.205)	<0.001*	1.532 (1.162–2.020)	0.003*
M stage	13.409 (6.008–29.931)	<0.001*	9.263 (3.852–22.278)	<0.001*
pTNM stage	2.593 (1.778–3.782)	<0.001*		
ER	0.524 (0.300–0.914)	0.023*	0.556 (0.232–1.331)	0.187
PR	0.553 (0.319–0.958)	0.035*	0.999 (0.419–2.382)	0.998
HER2	1.882 (1.077–3.288)	0.026*	1.642 (0.897–3.008)	0.108
Ki-67	1.934 (1.102–3.693)	0.046*	1.626 (0.815–3.243)	0.167
Molecular subtype	1.180 (0.997–1.425)	0.086		
CEA	2.636 (1.278–5.439)	0.009*	1.210 (0.538–2.725)	0.645
CA153	1.724 (0.837–3.554)	0.140		
CONUT	2.520 (1.442–4.402)	0.001*	2.104 (1.172–3.779)	0.013*

*P<0.05. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2; CEA, carcinoembryonic antigen; CA153, cancer antigen 153.

The CONUT score could provide a more comprehensive assessment in patient nutritional and immune status. According to united scoring method, CONUT score is divided into four subunits, 0–1 for normal, 2–4 for mild, 5–8 for moderate, 9–12 for severe. CONUT has been found in many studies to have substantial prognostic value for various types of cancers. In the subsequent retrospective analysis of 368 gastric cancer cases, Noriyuki Hirahara demonstrated the prognostic significance of CONUT in gastric cancer after curative gastrectomy. They also conducted a propensity score-matched analysis (PSM) in order to explore the significance. They reported that the CONUT is an objective, non-invasive, and readily available prognostic biomarker (20). In another one smaller cohort of 94 patients with oligometastatic prostate cancer, Zhang attested the relationship between high CONUT and poor PSA progression-free survival time (21). There are similar studies have been conformed in renal cancer and colorectal cancer (22,33). Thus, CONUT is exactly indicator which meets current needs. Though underlying mechanism is still unclear, no study has confirmed its value in breast cancer. We therefore assumed the CONUT score will be helpful in identifying high-risk patients timely, and in providing reasonable therapy after surgery.

To our best effort, we explore the relationship between CONUT and clinicopathologic characteristics. We observed that in our study, there are 1,149 (84.1%) patients were Invasive ductal carcinoma. There are 324 (23.7%), 694 (50.8%), 322 (23.6%) and 27 (2.0%) patients were clinical stage 1,2,3 and 4 respectively. At the same time, there are 353 (25.8%) patients for Luminal A, 404 (29.6%) for Luminal B/HER2-, 202 (14.8%) for Luminal B/HER2+, 185(13.5%) for HER2 Enriched and 217 (15.9%) for Triple Negative. As we all know, TNM stage is pivotal prognostic indicator. In *Table 2*, we noticed that TNM stage was related to CONUT (P=0.027). The relationship between chronic inflammation and cancer development had been studied. And some had validated chronic inflammation participated in invasion and metastasis of cancer (34,35). Our results provided more robust inflammatory responses in response to more aggressive tumors and higher tumor burdens. Given the importance of TNM stage and distant metastasis in predicting breast cancer patient outcomes, our finding suggested that CONUT might function as a prognostic breast cancer biomarker.

China is a populous country with more than 1.6 million

people being diagnosed and 1.2 million people dying of the disease each year (36). Breast cancer mortality varies from worldwide. In several reports about the mortality of China and worldwide, we observed that China held a higher mortality than worldwide, 69.5/100,000 *vs.* 12.9/100,000 (Segi Standard Population) (37,38). Apart from some aligned with known risk factors for women, there are various reasons for this. The economic status is the key. Dozens of patients cannot afford cost of treatment; therefore, it is possible to quit imperative treatment. China is largest developing country in the world and a vast country, the mortality varies between urban and rural area (39). In rural area, due to the lack of popularization, many patients do not pay enough attention to the occurrence of disease, resulting in the late stage at first diagnosis. And some patients choose traditional Chinese medicine instead of going to professional tumor hospital.

Results of this study paves the way for deeper investigation about immune-inflammatory-nutritional indicators in breast cancer. Our study initially explored the relationship between CONUT and the prognosis of breast cancer patients. We found that patients with high-CONUT score had shorter OS and RFS than those with low-CONUT score. CONUT is an independent predictor in breast cancer. Our results provided another perspective about precision medicine in breast cancer. Specific treatment is not only based on TNM stage, pathological type, different subtype, but also on host basic health status. Poor basic health status is a hazard for host who maybe more vulnerable about progression. Those patients could benefit from a preoperative nutritional intervention. A more intensive attention about nutritional status will be helpful in monitor disease changes.

Despite our meaningful findings, our limitations were obvious. First, our study is a retrospective analysis of a single-center design and could cause selection bias. Second, we focused on preoperative health status and failed to renew data during the whole process. Third, the underlying mechanism is unclear. Fourth, we recruited breast cancer patients are from china and we did not procedure a comparison with other countries and other races. Therefore, lots of efforts are required in order to elucidate the molecular mechanisms.

In summary, we identified the CONUT score as an independent prognostic indicator for OS and RFS in breast cancer patients after curative surgery. Patients with high CONUT score would have a greater risk of poorer survival as compared to those a low CONUT score.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/gs-20-294

Data Sharing Statement: Available at http://dx.doi.org/10.21037/gs-20-294

Peer Review File: Available at http://dx.doi.org/10.21037/gs-20-294

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs-20-294). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Research Ethics Committee of SYSUCC (B2020-215-01) and individual consent for this retrospective analysis was waived.

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Cite this article as: Huang ZZ, Song CG, Huang JJ, Xia W, Bi XW, Hua X, He ZY, Yuan ZY. Prognostic significance of the Controlling Nutritional Status (CONUT) score in surgically treated breast cancer patients. Gland Surg 2020;9(5):1370-1379. doi: 10.21037/gs-20-294