Comprehensive Validation Study of Quality-of-Life Questionnaire Using Objective Clinical Measures: Breast Cancer Treatment Outcome Scale (BCTOS), Brazilian Portuguese Version

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Abstract

Quality-of-life questionnaires (QLQs) do not correlate with objective measurements of treatment sequelae. We performed a comprehensive validation study of the Brazilian Portuguese version of the Breast Cancer Treatment Outcome Scale (BCTOS), adding physical evaluations of the main sequelae related to breast-conserving therapy (BCT). Three hundred patients were evaluated. BCTOS represented a good QLQ for BCT patients, which correlated with objective measurements.

Introduction: When evaluating a quality-of-life questionnaire (QLQ), many validation studies do not correlate quality-of-life scores with objective measurements of complications associated with treatment. **Patients and Methods:** We performed a cross-sectional observational study with 300 patients submitted to breast-conserving therapy. The patients answered the European Organization for Research and Treatment of Cancer (EORTC) QLQs C-30 and BR23, as well as the Brazilian Portuguese version of the Breast Cancer Treatment Outcome Scale (BCTOS) questionnaire. Retest, internal consistency, factorial analysis, convergent/divergent analysis, and Rasch evaluation were performed. All patients underwent physical evaluations to assess lymphedema, handgrip strength, shoulder range of motion, breast cosmesis, and breast pain, and these groups were compared on the basis of BCTOS scores. Receiver operating characteristic curve determined the predictive value of BCTOS scores associated with clinical practice. **Results:** The internal consistencies of the BCTOS domains ranged from 0.785 to 0.895. Factor analysis grouped according to the original questionnaire. Convergent validation showed differences in the sexual functioning and sexual enjoyment domains of the EORTC BR23. Analysis of known groups found that in most domains, the scores were higher in patients with lymphedema, strength deficit, shoulder range-of-motion alteration, poor breast cosmesis, breast pain, and axillary lymphadenectomy. Using a cutoff of 1.26, lymphedema was associated with the edema domain; using a cutoff of 1.33, Late Effects Normal Tissue Task Force/Subjective, Objective, Management, Analytic pain was associated with the pain domain; and using a cutoff of 2.37, the cosmetic domain was associated with subjective cosmesis. **Conclusion:** The association of objective measurements in a validation study of quality of life qualified the study and allowed us to develop better parameters for comparisons of results of breast-conserving therapy between populations.

Clinical Breast Cancer, Vol. 19, No. 1, e85-100 © 2018 Elsevier Inc. All rights reserved.
Keywords: Breast-conserving surgery, Morbidity, Patient reported outcome measures, Survival, Validation studies

Introduction

The treatment of breast cancer has changed radically in the last 30 years, with increases in survival. In the 1990s, studies showed the safety of conservative treatment of breast cancer when associated with breast radiotherapy, allowing safe conservative treatment without worsening patient prognosis; this treatment strategy has

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Submitted: Aug 4, 2018; Revised: Oct 19, 2018; Accepted: Oct 21, 2018; Epub: Oct 27, 2018

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1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2018.10.004

persisted over 20 years of follow-up.[1,2] Of the women diagnosed at early and late disease stages, 57% and 13% will undergo conservative treatment, respectively, with the majority receiving radiotherapy.[3]

Radiotherapy is an integral part of the treatment of breast cancer. Its use aims to raise the rates of locoregional control, thus reducing relapse rates. In this sense, it is currently used at the level of breast plaster in patients submitted to mastectomy and at high risk of locoregional recurrence.[4] It is also routinely used in patients undergoing quadrantectomy because its use decreases rates of breast cancer recurrence.[2] In the context of breast cancer, axillary radiotherapy may be omitted in patients submitted to axillary lymphadenectomy, but in high-risk patients, it is still routinely used at the supraclavicular fossa level.[5] Its use determines radiodermatitis and tissue changes.

Axillary lymphadenectomy has a long-established role in the treatment of breast cancer; it is an important part of locoregional therapy, especially in the presence of metastatic axillary disease, but it is associated with definitive sequelae. In the last decade, the concept of sentinel lymph node investigation (SLNI) has been used effectively in breast cancer,[6,7] allowing the reduction of the number of lymphadenectomies and their complications.

The evaluation of sequelae after treatment depends on the treatment method used.[8,9] Lymphedema rate increases with advanced disease, radiotherapy, regional lymph node irradiation,[10] and axillary node dissection.[11] Its incidence is affected by methodology[9,12] and duration of follow-up, reaching its highest values at 10 years.[10,11] Handgrip strength and arm mobility decrease in the affected arm.[13,14] When sentinel lymph node dissection is performed, the number of sequelae is lower: at 7 years of treatment, two fifths of patients submitted to SLNI and seven tenths of those submitted to axillary lymphadenectomy experienced representative deficiencies (> 20 degrees) in shoulder movement during flexion, abduction, and rotation.[15]

In the treated patients, many of the acute symptoms disappear; however, emotional deficits in social relations and cognitive functions associated with specific symptoms and concerns arising from cancer impair patient quality of life.[16] Including measures of quality of life in clinical practice seems to be a great challenge. Using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ) C-30 and the BR23 module, it was observed that patients undergoing conservative treatment were more sexually active and more satisfied with body image 1 year after diagnosis. Likewise, differences in overall quality of life and social functioning gradually increased, becoming significant at 5 years.[17]

Of the instruments for the surgical evaluation of breast cancer, the EORTC QLQ BR23 evaluates the quality of life in cancer patients, the MBROS (Michigan Breast Reconstruction Outcome Study) evaluates reconstructive surgery, and the BREAST-Q evaluates patients submitted to mastectomy with and without breast reconstruction, with a recent version including breast conservative treatment. The BCTOS was created in 2001 to evaluate patients undergoing conservative breast cancer treatment,[18] at which time the standard for axillary treatment was axillary lymphadenectomy.

Only a few studies have objectively and subjectively assessed the aesthetic aspects of the breast and have correlated them with quality of life. Functional aspects of breast cancer surgery and their influence on quality of life are represented by breast and/or shoulder–arm morbidities.[19,20] There is no standardization for the quantitative evaluation of sequelae related to the treatment of breast cancer. In this sense, studies have been performed evaluating the cosmetic effects with the Breast Cancer Conservative Treatment Cosmetic Results (BCCT.core),[21] but there is a lack of studies comparing measurements related to QLQs associated with objective measurements of lymphedema, upper limb strength, and shoulder sensitivity and mobility, which motivated the present study.

Patients and Methods

This was a cross-sectional observational study of 300 patients submitted to conservative treatment of breast cancer, selected as a convenience sample from women treated at the Women's Outpatient Clinic of the Barretos Cancer Hospital from May 2015 to June 2016. The ratio of 1 SLNI to 3 lymphadenectomies was considered, and the patients were randomly selected.

The inclusion criteria included the following: patients with breast cancer treated at the Barretos Cancer Hospital; conservative surgical treatment of the breast; surgical treatment of the axilla (axillary lymphadenectomy or SLNI); cognition adequate to answer the QLQs; completion of radiotherapy within ≥ 12 months; Eastern Cooperative Oncology Group performance status of 0 or 1; and provision of written informed consent. The noninclusion criteria were patients with metastatic disease; patients undergoing chemotherapy; patients with bilateral breast cancer; breast cancer in men; and high number of comorbidities that limited the evaluation of the QLQs.

Sociodemographic and Clinical Characterization

The sociodemographic and clinical data were collected through information from each patient's medical record by means of a standardized clinical record. After providing written informed consent, the patients were referred to the physiotherapy outpatient clinic of the Barretos Cancer Hospital to apply the QLQs. After the application of the QLQs, the patients underwent systematic physiotherapeutic evaluations, which aimed to evaluate sensitivity, handgrip strength, shoulder range of motion (ROM), cosmesis, and lymphedema.

Instrument Being Validated

The BCTOS questionnaire, which is used in patients submitted to conservative treatment,[22] has 22 questions, with 8 questions related to breast shape and volume, 7 related to shoulder/arm movement, 4 related to arm volume, and 3 related to pain and tenderness in the breast. These questions are quantified from 1 to 4 points. One point is given when no difference is observed between the breast or the area of the treated breast and the untreated breast area, and 4 points are given when there is a large difference between the breast or the area of the treated breast and the untreated breast area. The questionnaire was translated by our group into Brazilian Portuguese,[23] and validation was necessary.

Other QLQs

The EORTC QLQ C-30 is an overall quality-of-life questionnaire for cancer patients, validated for the Portuguese language and

composed of 30 questions divided into 3 dimensions: 5 functional scales (physical functioning, role, emotional functioning, cognitive functioning, social functioning), 3 symptom scales (fatigue, nausea/vomiting, pain), and 6 single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) and overall quality of life. Functional and symptom scales are classified on a scale ranging from 1 (no) to 4 (very much), and questions related to overall quality of life are classified on a scale ranging from 1 (very poor) to 7 (excellent). The score is converted to a scale of 0 to 100 points. High scores for overall quality of life indicate good quality of life, while high scores on the symptoms scale indicate increased symptomatology.[24]

The EORTC QLQ BR23 is a quality-of-life questionnaire specific for patients with breast cancer. Validated in the Portuguese language, it has 23 questions divided into 2 dimensions: functional scales (body image, future perspective, sexual functioning, sexual enjoyment) and symptoms scales (chemotherapy effect, concern about hair loss, breast and arm symptoms). As a score, it uses a 4-point scale (not at all, a little, quite a bit, very much). Like the QLQ C-30, the score is converted from 0 to 100 and is interpreted in the same way.[24]

Psychometric Properties Evaluated

Using classic psychometric theory analysis, reliability was measured by means of internal consistency and test−retest stability. A retest was conducted 21 to 30 days after the first questionnaire application in a sample of 50 patients in the form of telephone or face-to-face interviews. Correlation analysis among the BCTOS, the EORTC QLQ C-30, and the EORTC QLQ BR23 scores were conducted for the convergent/divergent validation. To compare known groups, the following groups were used: lymphedema, strength deficit, change in shoulder ROM, cosmesis assessed by BCCT.core, cosmesis evaluated by the research participant, breast pain evaluated by the research participant using the LENT (Late Effects Normal Tissue Task Force)/SOMA (Subjective, Objective, Management, Analytic) scale, age, and type of axillary surgery. Additionally, confirmatory factor analysis was conducted to test the original factor structure of BCTOS, with 22 items and 4 domains. In addition those classic psychometric measurements, further analyses were conducted using the Rasch method theory.

Objective Measures—Physiotherapeutic Evaluation

To assess lymphedema, volumetry of the upper limbs was performed by water displacement with the device proposed by Lette.[25] Lymphedema was diagnosed on the basis of water displacement methodology,[9] as it was a cross-sectional study. We compared the difference between the risk arm and contralateral arm. Lymphedema was considered when the volume increase in the risk arm had a value of $\geq$ 200 mL.[9,26]

Handgrip evaluation was performed by a hydraulic hand dynamometer (Saehan, model SH5001). Three measurements were performed,[26,27] and the largest measurement was recorded.[13] A difference was considered to be a 12% decrease in the risk side compared to the contralateral side.[27]

To measure the ROM of the shoulders, the participants were positioned in front of a simetrograph in the orthostatic position 3 m away from the camera used to capture the images. The ROM was assessed statically by photogrammetry by ImageJ software.[28] The movements of flexion, abduction, and extension of the shoulder were photographed bilaterally. A minimum of 10 degrees of difference was considered acceptable,[29,30] which in a previous study showed a strong correlation with goniometry.[31]

In the objective evaluation of cosmesis, the semiautomated BCCT.core software was used to analyze the distance between breast points, objectively comparing the symmetry of the treated and untreated breast,[32,33] which, after mathematical calculations, ranked the breast on a scale from excellent to poor. To create the photos, the thorax was marked with a point on the furcula and 25 cm below, at the midline. The patients were photographed in the anteroposterior position 1 m away. To compare the objective result of the breast cosmesis evaluation obtained via BCCT.core with the subjective evaluation of the patient, the participant was asked to classify her general breast result using the same scoring system used in BCCT.core: 1, excellent; 2, good; 3, fair; and 4, poor.[32]

To evaluate breast pain after radiotherapy, the patients were asked to quantify the pain in the irradiated breast according to the following graduation: 0, no pain; 1, occasional or minimal hypersensitivity; 2, intermittent and tolerable pain; 3, persistent and intense pain; or 4, refractory and excruciating pain. This graduation is part of the item referring to breast pain after radiotherapy of the LENT/SOMA scale, which evaluates the effects of radiotherapy.[34]

Statistical Analysis

Descriptive statistics were calculated according to the type of variable. For the categorical variables, frequencies and percentages were calculated. Means, medians, standard deviations, and minimum and maximum values were calculated for numerical variables.

The reliability and validity of the instrument were evaluated. Reliability was analyzed through internal consistency by the Cronbach α test, and results above 0.70 and below than 0.95 were considered suitable. In the test−retest reproducibility, the intraclass correlation coefficient (ICC) was used.[35] An ICC of $>$ 0.75 was considered excellent, ICCs between 0.4 and 0.75 satisfactory, and ICCs $<$ 0.4 poor.

Construct validation was performed, and exploratory and confirmatory factor analysis, known groups, and convergent/divergent validation were conducted. For the exploratory factor analysis, principal component analysis was used, with Varimax rotation, eigenvalues $>$ 1, and cumulative variance $>$ 60%. In a further confirmatory factor analysis, the original factor structure for the BCTOS was tested using maximum likelihood estimation. To test goodness of fit, we used the comparative fit index and the Tucker-Lewis index. For both, values $\geq$ 0.95 indicated a good fit and values $>$ 0.90 an acceptable fit.[36] Root mean square error of approximation values $<$ 0.08 were considered to reflect acceptable fit to the model, and values $<$ 0.05 were considered to be a good fit.

Regarding Rasch analysis, the fit of the data was assessed by testing the difference between the observed responses and the responses expected from the model. The fit of the items and persons to the Rasch model was evaluated using "outlier-sensitive fit" mean square statistics (outfit MNSQ) and "information-weighted fit" mean square statistics (infit MNSQ); the values should be between 0.6 and 1.4.[37] Values $>$ 1.4 (underfit) indicated that the item may not contribute to the same underlying construct as do other items in

the same scale; values < 0.6 (overfit) indicated that the item may be redundant in the same scale.

Additionally, ratio of chi-square to degree of freedom (df) ≤ 2 or 3 was considered as a good fit to the model.[38] Convergent/divergent validation was performed by the Spearman correlation method (nonnormal sample), with correlation coefficients > 0.4 being considered significant.

The Mann-Whitney test was used to compare known groups. To assess the predictive value of BCTOS scores associated with clinical practice, we performed a reverse evaluation. We selected domains with statistical association with the variables and constructed receiver operating characteristic (ROC) curves. The ROC curve determined be best cutoff point to separate groups. To classify the accuracy of the text, we adopted the area under the ROC curve, which was classified as excellent (0.90−1), good (0.80−0.90), fair (0.70−0.80), poor (0.60−0.70), and failing (0.50−0.60).

SPSS 20.0 software was used (IBM). Confirmatory factor analysis was accomplished by SPSS Amos 20.0. Winsteps Rasch 3.92.0 measurement software was used to complete the Rasch analysis. The significance level considered was $P < .05$.

Ethical Approval

The present study was approved by local research ethics committee under number 782/2014.

Results

During the active search process, 2615 medical records were randomly assessed before medical evaluation was performed. When the inclusion criteria were met, the patient was invited to be included in the study. Of the 335 women who met the inclusion criteria, 35 refused to participate, leaving 300 patients who consented to participate in the present study.

The mean (range; SD) age of the study population was 58.8 (25.6−87.5; 9.6) years. The average (range; SD) time from the first medical evaluation to participation in this study was 7.4 (1.2−20.6; 4.3) years. The mean (range; SD) educational level was 7.3 (0−33; 5.3) years, the mean (range; SD) size of the invasive tumor was 2.2 (0.1−10; 1.4) cm, and the majority of the patients (39.7%) were overweight, followed by obesity (30.3%) grade I, II, or III.

Regarding the main clinical characteristics of the group, 154 subjects (51.3%) had clinical stage II disease, and 262 (87.3%) had invasive ductal carcinoma. Regarding the type of surgical treatment, 165 (55%) underwent axillary lymphadenectomy and 66 (22%) SLNI, followed by axillary lymphadenectomy, totaling 231 women (77%) with axillary lymphadenectomy, while 69 women (23%) were subjected only to SLNI. Fifty-one women (17%) underwent oncoplastic surgery, and 37 (12.3%) had breast symmetrization. Of these, 29 (9.7) were concomitant to breast surgery, and 8 (2.7%) were performed later. All of the patients received radiotherapy to the breast, and 100 (33%) underwent radiotherapy to the supraclavicular fossa (Table 1).

Lymphedema (differential volume ≥ 200 mL) was observed in 62 patients (20.7%). A total of 155 women (51.7%) presented alterations in at least one type of shoulder movement, the most prevalent being alteration in shoulder abduction, affecting 118 women (39.3%), followed by flexion alterations (29.7%, 89 patients) and change in extension (10%, 30 patients). Palmar grip strength was altered in 115 patients (38.3%), and 191 (63.7%) had breast pain. By means of BCCT.core software, the majority of the results of the breast cosmesis were classified as fair (45%), and the majority of the patients classified the result as good (49%).

Table 1 Number and Percentage of Patients According to Clinical Characteristics

Variable	Category	N	%
Clinical Characteristics			
TNM clinical stage	0	13	4.3
	I	70	23.3
	II	154	51.3
	II	63	21.0
Histology	DCIS	12	4.0
	Ductal invasive carcinoma	262	87.3
	Other	26	8.7
Axillary surgery	SLN	69	23.0
	SLN + lymphadenectomy	66	22.0
	Lymphadenectomy	165	55.0
Oncoplastic surgery	Absent	249	83.0
	Present	51	17.0
Symmetrization	Concomitant	29	9.7
	Late	8	2.7
	Absent	263	87.7
Chemotherapy	Neoadjuvant	29	9.7
	Adjuvant	221	73.7
	Absent	50	16.7
Hormone therapy	Absent	79	26.3
	Adjuvant	219	73.0
	Neoadjuvant	2	0.7
Supraclavicular radiotherapy	Absent	196	65.3
	Present	100	33.3
	Ignored	4	1.3
Functional Findings			
Pain (LENT/SOMA)	Absent	107	35.7
	Present	191	63.7
	Ignored	2	0.7
Cosmesis (BCCT.core)	Excellent	18	6
	Good	71	23.7
	Fair	135	45
	Bad	73	24.3
	Ignored	3	1
Cosmesis (self-reported)	Excellent	82	27.3
	Good	147	49
	Fair	49	16.3
	Bad	20	6.7
	Ignored	2	0.7

Abbreviations: BCCT.core = Breast Cancer Conservative Treatment Cosmetic Results; DCIS = ductal carcinoma-in-situ; LENT, Late Effects Normal Tissue Task Force; SLN = sentinel lymph node; TNM = tumor, node, metastasis classification system; SOMA = Subjective, Objective, Management, Analytic.

Table 2 Descriptive Items Answered in Each Graduation of BCTOS Questionnaire Items

Domain and Item	Mean (Standard Deviation)[a]	N	Missing	Graduation (Difference), N (%)			
				None	Slight	Moderate	Large
Functional Status							
Shoulder movement	1.7 (1)	300	0	180 (60)	50 (16.7)	47 (15.7)	23 (7.7)
Arm movement	1.9 (1.1)	299	1 (0.3)	154 (51.3)	52 (17.3)	56 (18.7)	37 (12.3)
Ability to lift objects	2.1 (1.2)	300	0	140 (46.7)	47 (15.7)	58 (19.3)	55 (18.3)
Shoulder stiffness	1.5 (0.9)	300	0	221 (73.7)	33 (11)	27 (9)	19 (6.3)
Shoulder pain	1.9 (1.1)	300	0	159 (53)	48 (16)	60 (20)	33 (11)
Arm pain	2 (1.1)	300	0	140 (46.7)	55 (18.3)	68 (22.7)	37 (12.3)
Arm stiffness	1.5 (0.9)	299	1 (0.3)	217 (72.3)	41 (13.7)	23 (7.7)	18 (6)
Cosmetic Status							
Breast size	2.7 (1)	300	0	41 (13.7)	97 (32.3)	88 (29.3)	74 (24.7)
Breast texture (hardening)	2.1 (1.1)	299	1 (0.3)	123 (41)	71 (23.7)	61 (20.3)	44 (14.7)
Nipple appearance	2.1 (1.2)	300	0	136 (45.3)	67 (22.3)	37 (12.3)	60 (20)
Breast shape	2.5 (1.1)	300	0	63 (21)	101 (33.7)	55 (18.3)	81 (27)
Breast elevation	2.4 (1.1)	300	0	81 (27)	85 (28.3)	60 (20)	74 (24.7)
Scar tissue	2.6 (1.1)	298	2 (0.7)	66 (22)	82 (27.3)	61 (20.3)	89 (29.7)
Fit of bra	1.9 (1.1)	298	2 (0.7)	159 (53)	52 (17.3)	47 (15.7)	40 (13.3)
Fit of clothing	1.7 (1)	300	0	183 (61)	49 (16.3)	36 (12)	32 (10.7)
Breast-Specific Pain							
Breast pain	1.8 (1)	299	1 (0.3)	155 (51.7)	69 (23)	52 (17.3)	23 (7.7)
Breast tenderness	1.9 (1.1)	300	0	146 (48.7)	66 (22)	53 (17.7)	35 (11.7)
Breast sensitivity	2.1 (1.1)	293	7 (2.3)	121 (40.3)	61 (20.3)	61 (20.3)	50 (16.7)
Edema							
Arm heaviness	1.8 (1)	300	0	160 (53.3)	58 (19.3)	56 (18.7)	26 (8.7)
Fit of shirtsleeve	1.6 (1)	300	0	189 (63)	56 (18.7)	32 (10.7)	23 (7.7)
Arm swelling	1.6 (0.9)	300	0	188 (62.7)	54 (18)	40 (13.3)	18 (6)
Breast swelling	1.3 (0.7)	300	0	244 (81.3)	29 (9.7)	21 (7)	6 (2)

Missing data indicate items without response.
[a]Variation from 1 to 4.

Regarding the BCTOS questions, the mean values of the scores ranged from 1.3 to 2.7; the items that obtained the highest values were breast size (2.7), followed by the items scar (2.6), breast shape (2.5), and breast lift (2.4). The items with the lowest values were shoulder movement (1.3), arm movement (1.5), and ability to lift objects (1.5). The percentages of items that were missing responses ranged 0 to 2.3%. Only the item referring to breast tenderness had a value of 2.3%; thus, no item was excluded. Table 2 shows these results.

In the internal consistency analysis (Table 3), the overall Cronbach alpha value was 0.926. When the Cronbach alpha value was evaluated for the domains, all presented values greater than 0.7, ranging from 0.785 to 0.895, thus indicating adequate internal consistency. When excluding an item, the Cronbach alpha values had a small negative change (0.593 to 0.887), leading to the conclusion that it is not necessary to exclude any item.

The retest was applied in 50 patients. In the evaluation of reproducibility, ICCs[35] of 0.861 (95% confidence interval [CI], 0.754–0.921), 0.878 (95% CI, 0.784–0.932), 0.820 (95% CI, 0.683–0.898), and 0.843 (95% CI, 0.723–0.911) were obtained for the functional, cosmetic, breast pain, and edema domains, respectively. All items had excellent correlation, with statistically significant differences ($P < .01$).

The exploratory factor analysis showed that in the Brazilian population, the items can be grouped into 4 domains, considering eigenvalues ≥ 1, with a total variance of 61.065% (Table 4). Using the Varimax rotation method with Kaiser normalization, the first domain had 8 items (3, 5, 6, 8, 11, 15, 16, and 19), the second domain had 7 items (1,2, 4, 12, 13, 14, and 20), the third domain had 4 (9, 17, 18, and 22), and the fourth had 3 items (7, 10, and 21). When comparing the grouping of domains through factor composition, only items 3 and 22 were not grouped as in the original study by Stanton et al[39] (Table 1; Supplemental Table 1 in the online version). Regarding the confirmatory factor analysis, fit indexes were considered good (comparative fit index = 0.951, Tucker-Lewis index = 0.940, root mean square error of approximation = 0.053, $\chi^2/df = 1.803$); all factor loadings were > 0.40 and statistically significant. Figure 1 depicts the model tested. Regarding Rasch method analysis, only item 4 (cosmetic status) presented values of infit and outfit outside the predefined limits. However, considering maximum fit values of 1.4, there were only

Table 3 Internal Consistency of BCTOS Through General Cronbach α and Each Domain If Excluded Item

BCTOS Domain	Cronbach α (95% Confidence Interval)	α If Excluded Item
General	0.926 (0.913–0.938)	
Functional Status	0.895 (0.876–0.913)	
Shoulder movement		0.877
Arm movement		0.873
Ability to lift objects		0.881
Shoulder stiffness		0.887
Shoulder pain		0.884
Arm pain		0.873
Arm stiffness		0.883
Cosmetic Status	0.846 (0.818–0.871)	
Breast size		0.825
Breast texture (hardening)		0.832
Nipple appearance		0.839
Breast shape		0.815
Breast Elevation		0.818
Scar tissue		0.830
Fit of bra		0.826
Fit of clothing		0.835
Breast-Specific Pain	0.787 (0.741–0.826)	
Breast pain		0.753
Breast tenderness		0.593
Breast sensitivity		0.777
Edema	0.785 (0.742–0.822)	
Arm heaviness		0.705
Fit of shirtsleeve		0.735
Arm swelling		0.678
Breast swelling		0.790

Abbreviation: BCTOS = Breast Cancer Treatment Outcome Scale.

Table 4 Factorial Composition of Items

Factor	Item	Component			
		1	2	3	4
3	Arm heaviness	*.623*	.214	.494	.187
5	Shoulder movement	*.745*	.226	.173	.118
6	Arm movement	*.735*	.201	.143	.251
8	Ability to lift objects	*.626*	.162	.226	.337
11	Shoulder stiffness	*.755*	.117	.073	.090
15	Shoulder pain	*.703*	.009	.174	.252
16	Arm pain	*.658*	.130	.294	.377
19	Arm stiffness	*.706*	.184	.165	.145
1	Breast size	.237	*.792*	.011	-.062
2	Breast texture (hardening)	.295	*.431*	.220	.408
4	Nipple appearance	.147	*.454*	.134	.399
12	Breast shape	.161	*.795*	.081	.135
13	Breast elevation (how high breast is)	.180	*.729*	.165	.103
14	Scar tissue	.061	*.676*	.134	.215
20	Fit of bra	.027	*.604*	.390	.157
9	Fit of shirtsleeve	.229	.216	*.737*	.004
17	Arm swelling	.337	.108	*.736*	.127
18	Breast swelling	.227	-.001	*.559*	.387
22	Fit of clothing	.119	.368	*.644*	.205
7	Breast pain	.387	.146	.157	*.661*
10	Breast tenderness	.263	.085	.159	*.807*
21	Breast sensitivity	.265	.324	.091	*.660*

Italicized value shows the grouped items.

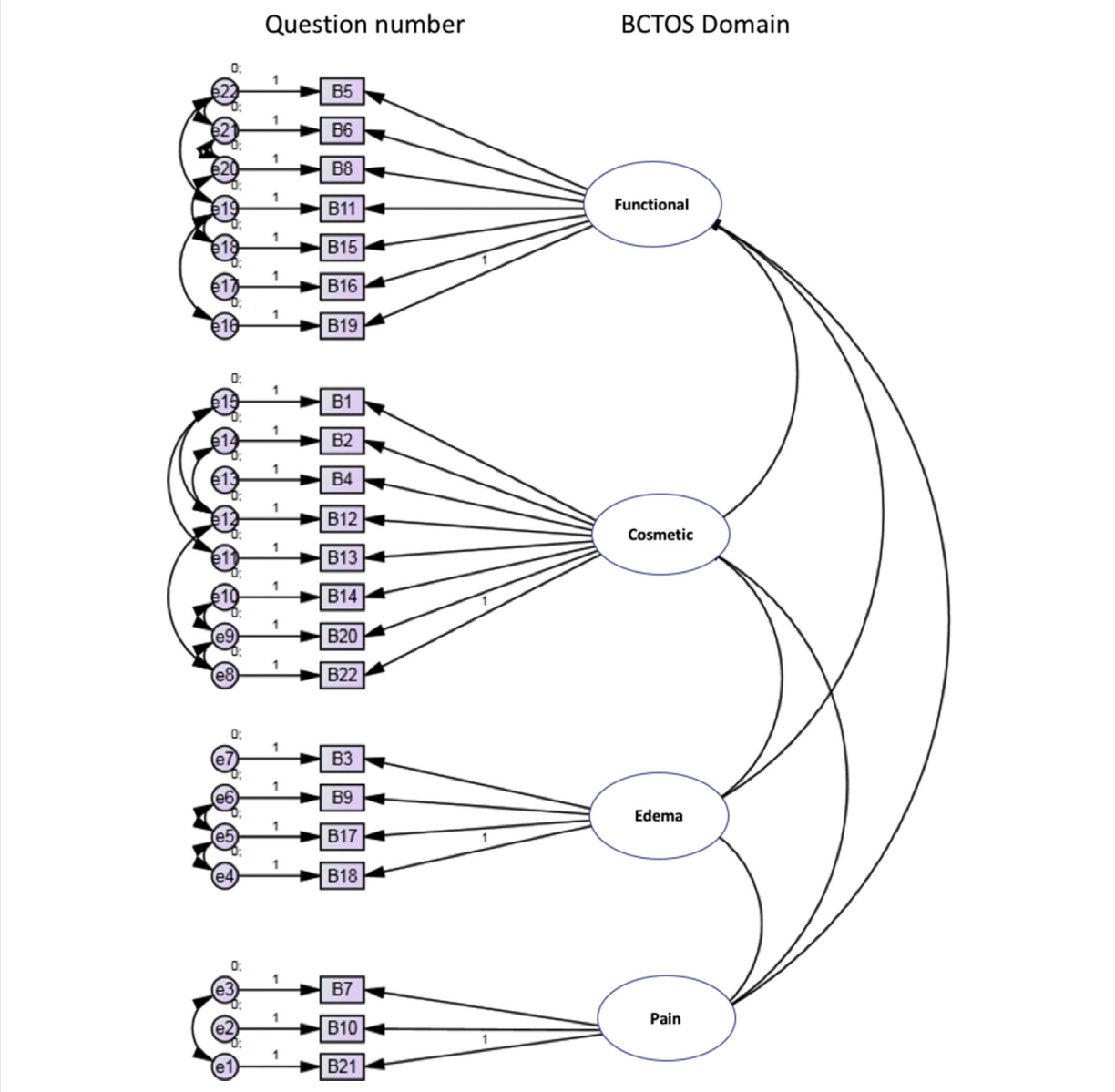
marginal findings (infit = 1.41, outfit 1.45). Table 5 depicts the Rasch analysis of the items.

Upon evaluating the correlations of the BCTOS domains with QLQ C-30 and QLQ BR23, correlations were observed in most domains (Table 6), except for the diarrhea, sexual function, sexual enjoyment, and hair loss domains. When comparing the results of the present study with a German translation study,[40] where the functional, cosmetic, and pain domains were evaluated, regarding the global, physical, functional, and emotional domains of the QLQ C-30 and the image, in the breast and arm symptoms domains of the QLQ BR23, significant similarities were observed in both studies for all variables.

Among the domains expected to have strong or moderate correlations, the functional domain of the BCTOS had a positive correlation with the financial difficulties domain of the EORTC QLQ C-30 (r = 0.413) and the arm symptom domain of EORTC QLQ BR23 (r = 0.747), and negative correlations with the physical functioning (r = −0.609) and role (r = −0.526) domains of the EORTC QLQ C-30. The cosmetic state domain of the BCTOS correlated positively with the breast symptom domain of the EORTC QLQ BR23 (r = 0.434) and negatively with the body image domain (r = −0.440) of the EORTC QLQ BR23. The breast-specific pain domain of the BCTOS had a positive correlation with the EORTC QLQ C-30 pain domain (r = 0.482) and the EORTC QLQ BR23 breast symptom domain (r = 0.651). The BCTOS edema domain was positively correlated with the arm symptom domain of the EORTC QLQ BR23 (r = 0.608). In the divergent validation, the functional domain of the BCTOS had weak correlations with the hair loss domain of the EORTC QLQ BR23, and the cosmetic, breast-specific pain, and edema domains had poor correlations with the items nausea and vomiting, appetite loss, and diarrhoea of the EORTC QLQ C-30.

Table 7 presents the comparison of the BCTOS scores with known groups. The analysis of the known groups showed that the instrument was able to discriminate patients with lymphedema, with statistically significant differences in the functional state, cosmetic state, and edema domains. Considering the groups of strength deficit, the analysis showed that the instrument was able to discriminate the functional state, breast-specific pain, and edema domains with statistically significant differences. The analysis to verify if the BCTOS was able to discriminate if the patient had altered ROM showed that the scores of the BCTOS domains were higher in patients with altered shoulder ROM, with statistically significant differences. The cosmetic and edema domains of the BCTOS were able to discriminate patients with fair or poor breast cosmesis from patients with excellent or good cosmesis, evaluated objectively by the BCCT.core software, while all BCTOS domains were able to discriminate breast cosmesis in the excellent or good

Figure 1 Factorial Analysis



categories from the fair or poor cosmesis categories, as subjectively evaluated by the patient. The mean scores of the BCTOS domains were higher, with statistically significant differences, in patients who reported breast pain and in women aged < 60 years. The analysis to verify if the instrument was able to discriminate patients in relation to the type of axillary surgery (sentinel lymph node vs. axillary lymphadenectomy) demonstrated a statistically significant difference in 2 domains: cosmetic state and edema.

When exclusively comparing the patients submitted to SLNI regarding lymphedema, strength deficit, and ROM alteration in relation to the BCTOS domains, differences were observed in the alteration of ROM with the functional ($P = .03$) and edema ($P = .03$) domains. However, when patients undergoing axillary lymphadenectomy were selected, patients with lymphedema had statistically significantly higher mean scores in the functional ($P = .04$) and edema ($P < .001$) domains. Patients with strength deficit had higher scores in the functional ($P = .001$), breast-specific pain ($P = .01$), and edema ($P = .01$) domains; and in patients with ROM alteration, mean scores were higher in all domains: functional ($P < .001$), cosmetic ($P = .003$), breast-specific pain ($P = .001$), and edema ($P < .001$).

In evaluating the ROC curve area, domains, and cutoff points, we observed the main results (Table 7, Figure 2), as follows. A good area was observed in the pain domain with LENT/SOMA pain criteria (ROC curve area = 0.846; 95% CI, 0.800−0.886; $P = .0001$) using a cutoff of > 1.33, with sensitivity and specificity of 81.3% and 73.1%, respectively. A regular area was observed in the edema domain with lymphedema (ROC curve area = 0.787;

Table 5 Rasch Item Analysis

Item or Domain	Measure	SE	Infit MNSQ	Outfit MNSQ
Functional Status				
15	−0.27	0.09	1.19	1.22
11	0.86	0.11	1.14	1.21
8	−0.76	0.09	1.13	1.10
19	0.90	0.11	1.01	0.89
5	0.18	0.11	0.94	0.91
6	−0.35	0.11	0.86	0.86
16	−0.55	0.11	0.83	0.84
Cosmetic Status				
4	0.26	0.08	1.41	1.45
22	0.91	0.08	1.25	1.04
14	−0.56	0.07	1.06	1.14
2	0.24	0.07	1.12	1.10
20	0.57	0.08	1.10	0.89
13	−0.31	0.07	0.84	0.87
1	−0.66	0.07	0.77	0.83
2	−0.45	0.07	0.75	0.71
Breast-Specific Pain				
21	−0.54	0.10	1.14	1.09
7	0.45	0.10	1.11	1.12
10	0.09	0.10	0.72	0.72
Edema				
18	1.14	0.13	1.39	1.27
9	−0.19	0.10	1.11	1.02
3	−0.78	0.10	0.88	0.86
17	−0.17	0.10	0.79	0.77

Abbreviations: MNSQ = mean squares; SE = standard error.

95% CI, 0.729−0.826; $P = .001$), using a cutoff of 1.26, with sensitivity and specificity of 84.6% and 63.1%, respectively. A regular area was observed in the cosmetic domain with subjective cosmesis (ROC curve area = 0.766; 95% CI, .714−0.813; $P = .001$), using a cutoff of 2.37, the sensitivity and specificity of which were 75.4% and 72.1%, respectively. A bad area was observed in the functional domain with shoulder mobility alteration (ROC curve area = 0.698; 95% CI, 0.642−0.750; $P = .001$), using a cutoff of 1.71, with sensitivity and specificity of 58.1% and 77.6%, respectively. The other variables had a bad or failing ROC curve area.

Discussion

QLQs integrate evaluation instruments reported by the patient. To evaluate breast cancer patients undergoing conservative breast treatment, we have the BCTOS[18,41-43] and the BREAST-Q, which was published recently, in 2016.[44]

The BCTOS, which was developed on the basis of a review of the literature and the opinions of experts, is a unique instrument to be used in the evaluation of the quality of life in patients exclusively submitted to breast-conserving therapy (BCT),[18,39] aiming at aesthetic measurement (breast shape) and functional state (pain and mobility) after treatment, along with the edema domain, which was not previously analyzed.[39] Created in 2001 and consisting of 22 items, it was translated into German in 2010.[40] This questionnaire underwent a process of translation into Brazilian Portuguese, considering that this is a validation study. According to the current criteria suggested by the EORTC for inclusion of a question in a QLQ, it should address at least 5 points from among these: (1) item difficult to understand < 5%; (2) embarrassing item < 5%; (3) mean score > 1.5; (4) prevalence of scores 2, 3, or 4 in > 30% of patients; (5) lack of base effect (if > 90% in items 1 or 2); (6) absence of ceiling effect (if > 90% in items 3 or 4); (7) interval > 2 points on a scale of 1 to 4; and (8) absent response < 10%.[45] Using these criteria, we observed (3) mean scores < 1.5 in items 11 (shoulder stiffness) and 18 (breast swelling); (4) prevalence of 33.7% of a score of 2 in item 12 (breast shape); and (7) differences of < 2 points on the scale 1−4 in items 3 (arm weight, 2−3), 5 (shoulder movement, 2−3), 6 (arm movement, 2−3), 8 (ability to lift objects, 3−4), 13 (breast lift, 1−2), 20 (bra adjustment, 2−3), and 21 (breast tenderness, 2−3). It should be considered that the present questionnaire was a translation, meaning that items (1) and (2) could not be considered; however, in the translation process,[23] when the questionnaire was administered to 16 patients, the following terms were difficult to understand: rigidity in item 19, tenderness in item 21, and adjustment in item 22. Thus, each item would represent 6.25%. Considering these aspects, only item 21 would have 6 points; items 3, 5, 6, 8, 11, 12, 13, 18, 19, 20, and 22 would have 7 points; and the other items would have 8 points, such that all items should be present in the final questionnaire.

In this case, evaluation of internal consistency revealed high internal consistency in all domains. The original study by Stanton et al[22] and the German version of Heil et al[40] also had high internal consistency in the domains of functional state, cosmetic state, and breast-specific pain, with values of 0.91, 0.89, and 0.81 in the Stanton et al study and 0.90, 0.84, and 0.85 in the Heil et al study. Neither assessed the internal consistency of the edema domain.

Regarding the test−retest reproducibility of the BCTOS, no studies have evaluated this question. The application of the retest was performed via a telephone call. Correlations were considered excellent in both moments, thus showing a good stability of the questionnaire.

When the domains were evaluated through factor analysis, in the study conducted by Stanton et al,[39] the BCTOS items were grouped into 3 domains; the study suggested a subscale for edema containing 4 items: arm weight (item 3), adjustment of the shirt-sleeve (item 9), arm swelling (item 17), and breast swelling (item 18). This subscale was based on the symptom's clinical importance.[22,39,46] For our study, 4 domains were considered according to eigenvalues > 1 and variance levels > 60%. In the validation study of the German version of the BCTOS, 3 domains were determined by eigenvalues > 1.5, and the edema domain/subscale was not considered in the factorial composition of the items.[40] In the grouping of the functional state, cosmetic state, and breast-specific pain domains, according to the factorial load, the items in the present study were grouped as in the study by Stanton et al, except for item 22 (clothing adjustment), which in the present study was grouped in the edema domain rather than in the cosmetic state item, as in the original study. In the original English-language version,[39] items 17 and 18 had values of 0.23 and 0.29 in the

Table 6 Correlation of Each BCTOS Domain With Domains of EORTC QLQ C-30 and QLQ BR23

Questionnaire	BCTOS Domain							
	Functional	Functional *P*	Cosmetic	Cosmetic *P*	Pain	Pain *P*	Edema	Edema *P*
QLQ C-30								
Global health status	−0.435	< .001	−0.374	< .001	−0.411	< .001	−0.293	< .001
Physical functioning	−0.609	< .001	−0.456	< .001	−0.441	< .001	−0.452	< .001
Role functional	−0.526	< .001	−0.360	< .001	−0.427	< .001	−0.398	< .001
Emotional functioning	−0.444	< .001	−0.355	< .001	−0.421	< .001	−0.292	< .001
Cognitive functioning	−0.379	< .001	−0.263	< .001	−0.389	< .001	−0.257	< .001
Social functioning	−0.392	< .001	−0.272	< .001	−0.343	< .001	−0.319	< .001
Fatigue	0.475	< .001	0.376	< .001	0.468	< .001	0.381	< .001
Nausea and vomiting	0.154	.008	0.104	.071	0.164	.004	0.216	< .001
Pain	0.568	< .001	0.320	< .001	0.482	< .001	0.406	< .001
Dyspnea	0.260	< .001	0.191	.010	0.191	.001	0.211	< .001
Insomnia	0.392	< .001	0.239	< .001	0.267	< .001	0.216	< .001
Appetite loss	0.250	< .001	0.194	.010	0.170	.003	0.139	.016
Constipation	0.220	< .001	0.173	.030	0.261	< .001	0.093	.106
Diarrhea	0.085	.143	0.060	.301	0.065	.263	0.083	.151
Financial difficulties	0.413	< .001	0.243	< .001	0.333	< .001	0.309	< .001
QLQ BR23								
Body image	−0.313	< .001	−0.440	< .001	−0.310	< .001	−0.270	< .001
Sexual functioning	−0.017	.774	−0.083	.152	−0.028	.634	−0.096	.096
Sexual enjoyment	0.075	.376	−0.017	.841	0.036	.674	−0.009	.910
Future perspective	−0.287	< .001	−0.253	< .001	−0.298	< .001	−0.222	< .001
Systemic therapy side effects	0.547	< .001	0.326	< .001	0.451	< .001	0.330	< .001
Breast symptoms	0.566	< .001	0.434	< .001	0.651	< .001	0.418	< .001
Arm symptoms	0.747	< .001	0.356	< .001	0.559	< .001	0.608	< .001
Upset by hair loss	0.161	.071	0.242	.006	0.260	.003	0.137	.126

Abbreviations: BCTOS = Breast Cancer Treatment Outcome Scale; BR23 = 23-question quality-of-life questionnaire specific for breast cancer; C-30 = 30-question overall quality-of-life questionnaire; EORTC = European Organization for Research and Treatment of Cancer; QLQ = quality-of-life questionnaire.

factor analysis, and because they are indicators of lymphedema, they were evaluated together in the same study, but with a lower casuistry in another publication,[22] where they were included in the fourth domain and associated with items 3 and 9, suggesting the necessity of a later study.[22,39] The German version grouped the questionnaire items into only 3 domains (functional, cosmetic, and pain), maintaining the 22 questions, with items 3, 9, and 17 included in the functional domain and item 18 (breast swelling) included in the breast pain domain.[40] The present study was able to group 3 of the 4 items proposed by the author in the original questionnaire into the edema domain. It is worth considering that in the original study, 184 patients were evaluated, with only 54 having lymphedema measurements, resulting in the second publication, where lymphedema was quantified (1, absent; 2, < 2 cm; 3, 2−4 cm; 4, > 4 cm), where only 10 (18.5%) of the patients had lymphedema.[22] In the German study, lymphedema was not measured.[40] In our study, of the 300 women evaluated, where the volumetry criterion was used, with a 200 mL difference, 20.7% (62) had lymphedema.

The present study represents what to our knowledge is the largest number of patients with lymphedema, indicating that 3 of the 4 factors initially proposed really fit the proposed domain. As a strength, we confirmed for the first time the original factor structure of BCTOS using confirmatory factor analysis. Moreover, Rasch method analysis confirmed the findings of the factor analysis because all items adequately fit the models tested. Thus, according to the factor and Rasch analyses conducted in the present study, no item should be excluded from the BCTOS.

The EORTC QLQ C-30 and BR23 have scores ranging from 0 to 100, where higher scores are associated with higher prevalence. In the BCTOS, the scores range from 1 to 4, and the assessment is performed in comparison to the untreated side. The higher the value, the greater the difference, which facilitates the identification of differences, even if the patient has already adapted to them. This difference between the questionnaire scores justifies the weak correlations of the cosmetic state domain with the sexual functioning and enjoyment domains. In addition, the timing of the questionnaires is different. The EORTC questionnaires ask patients to respond by considering the last week in most items, or the last 4 weeks on items referring to image and sexual enjoyment in the EORTC QLQ BR23, while the BCTOS asks the patients to formulate their response according to the time at which the questionnaire was applied. Although there are differences regarding the questionnaire scores, when moment is taken into account, along with the difference between one side versus the other, which the

Table 7 Comparison of BCTOS Domains According to Known Characteristics

Variable	Category	Functional	Cosmetic	Breast-Specific Pain	Edema
Population					
Age	< 60 (n = 156)	1.95 (0.83)	2.35 (0.75)	2.14 (0.94)	1.71 (0.69)
	≥ 60 (n = 136)	1.62 (0.76)	2.12 (0.77)	1.71 (0.71)	1.45 (0.69)
	P[a]	< .001	.006	< .001	< .001
Type of axillary surgery	SLN (n = 69)	1.75 (0.87)	1.92 (0.67)	1.84 (0.88)	1.28 (0.43)
	Axillary lymphadenectomy (n = 231)	1.81 (0.79)	2.34 (0.77)	1.99 (0.84)	1.69 (0.75)
	P[a]	.256	< .001	.167	< .001
Sequelae					
Lymphedema	Present (n = 62)	2.01 (0.88)	2.51 (0.74)	2.12 (0.99)	2.16 (0.76)
	Absent (n = 235)	1.74 (0.79)	2.18 (0.76)	1.90 (0.85)	1.44 (0.6)
	P[a]	.015	.002	.178	< .001
	ROC curve area	0.611	0.632	0.555	**0.787**
Handgrip strength loss	Present (n = 115)	2.0 (0.78)	2.29 (0.78)	2.14 (0.94)	1.70 (0.72)
	Absent (n = 185)	1.67 (0.76)	2.21 (0.76)	1.83 (0.84)	1.53 (0.70)
	P[a]	< .001	.402	.005	.013
	ROC curve area	.623	.529	.596	.583
Shoulder mobility alteration	Absent (n = 143)	1.5 (0.64)	2.10 (0.70)	1.73 (0.75)	1.40 (0.60)
	Present (n = 155)	2.08 (0.85)	2.37 (0.80)	2.17 (0.96)	1.78 (0.75)
	P[a]	< .001	.002	< .001	< .001
	ROC curve area	**0.698**	0.605	0.631	0.663
BCCT.core	Excellent and good (n = 89)	1.74 (0.77)	1.93 (0.67)	2.01 (0.9)	1.47 (0.68)
	Fair and bad (n = 208)	1.83 (0.83)	2.38 (0.77)	1.94 (0.89)	1.65 (0.72)
	P[a]	.427	< .001	.486	.013
	ROC curve area	0.529	0.669	0.525	0.588
Subjective cosmesis	Excellent and good (n = 229)	1.71 (0.76)	2.07 (0.69)	1.83 (0.82)	1.53 (0.67)
	Fair and bad (n = 69)	2.09 (0.9)	2.80 (0.73)	2.39 (0.97)	1.84 (0.78)
	P[a]	.002	< .001	< .001	.001
	ROC curve area	0.623	**0.766**	0.669	0.627
Breast pain	Absent (n = 107)	1.38 (0.58)	1.89 (0.60)	1.31 (0.49)	1.31 (0.53)
	Present (n = 191)	2.04 (0.82)	2.43 (0.78)	2.32 (0.86)	2.32 (0.86)
	P[a]	< .001	< .001	< .001	< .001
	ROC curve area	0.760	0.703	**0.852**	0.701

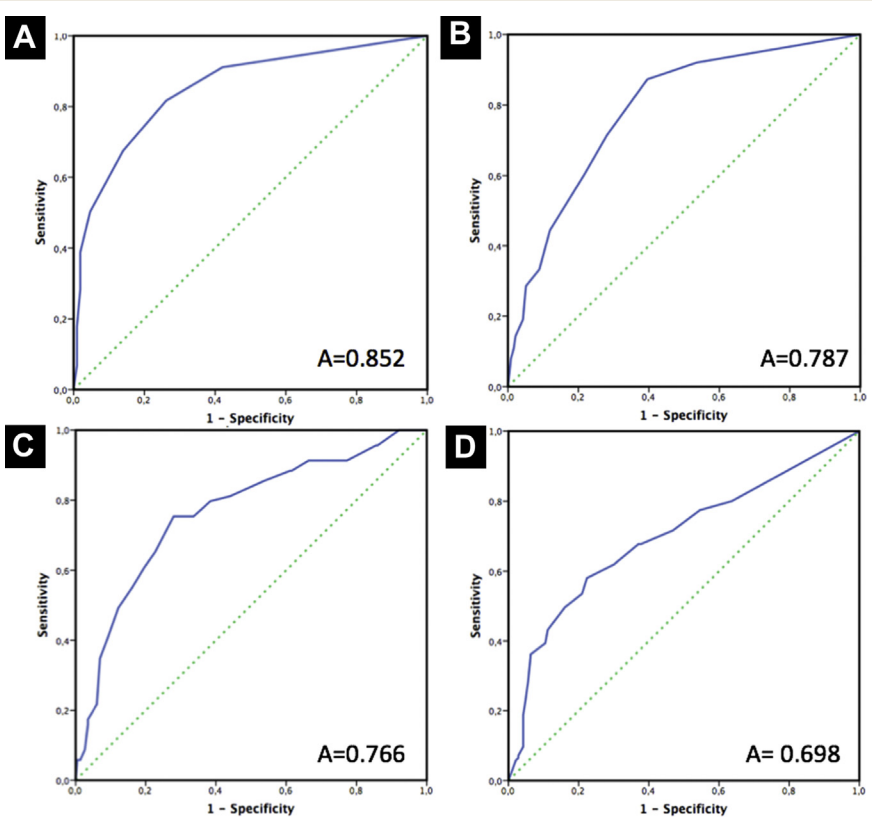
Abbreviations: BCTOS = Breast Cancer Treatment Outcome Scale; ROC = receiver operating characteristic; SLN = sentinel lymph node.
[a]Mann-Whitney test.

other 2 questionnaires do not consider, there were convergent correlations in the domains physical function, role, and financial difficulties of the EORTC QLQ C-30 and arm symptoms of the EORTC QLQ BR23 with the functional state domain of the BCTOS; body image and sexual enjoyment of the BR23 with the BCTOS cosmetic state; QLQ C-30 pain and breast symptoms of the BR23 with BCTOS breast-specific pain; and financial difficulties of the EORTC QLQ C-30 and arm symptoms of the BR23 with BCTOS edema. The original study by Stanton et al[39] did not compare the BCTOS with the EORTC questionnaire, instead making comparisons with the Short Form 36-Item Health Survey (SF-36) and a depression scale, which does not allow us to compare findings. A German study compared the results of the EORTC QLQ C-30 and BR23, observing that in both studies, the same variables selected in the German study were shown to be significant, and with the same positive or negative associations, with a small difference between the numbers, indicating that the relationships between the questionnaires are independent of the language.[40]

Comparisons of Known Groups

In the evaluation of known groups, it is necessary to compare not only the results obtained in the questionnaire but also the characteristics of the population and the criteria used to separate the groups. Thus, for example, in the evaluation of lymphedema, a difference of > 2 cm between the treated and untreated arms was considered to be lymphedema in the original BCTOS study,[22] whereas in our study, volume (difference of 200 mL) was used. According to each methodology considered for the diagnosis, ie, volumetry (volume or percentage), perimetry, spectroscopic bioimpedance, self-report, and descriptions in medical records, a

Figure 2 ROC Curve Related to Domain and Specific Sequelae. (A) Pain Domain With LENT/SOMA Pain. (B) Edema Domain With Lymphedema (200 mL). (C) Cosmetic Domain With Subjective Cosmesis. (D) Functional Domain With Shoulder Mobility Alteration



Abbreviations: LENT = Late Effects Normal Tissue Task Force; ROC = receiver operating characteristic; SOMA = Subjective, Objective, Management, Analytic.

difference in percentages against prevalence was observed. This study was cross sectional, and for water displacement, a relative difference between the limbs was used, but for longitudinal studies, it is better to use the relative differences in the same risk limb.[46]

Likewise, in general, QLQs show specific events, and many of the complications related to treatment are time dependent and are also related to the surgical procedure and radiotherapy performed.[10,11] Thus, considering that 46.7% of lymphedemas appear in the first 2 years,[11] the studies performed with the BCTOS comparing patients in the preoperative and postoperative periods up to 1 year with patients in the early stage of disease and where axillary lymphadenectomy was not the routine procedure may have a small number of patients with lymphedema—an item that may not be as sensitive to this domain. It should be noted that the validation study[40] and subsequent studies performed in the German language did not consider the edema domain.[33,47] In this study, we sought to evaluate patients with a long follow-up period, which averaged 7.4 years (range, 1.2−20.6 years) and was associated with the intentional selection of patients in a 1:3 proportion (1 sentinel lymph node for 3 patients undergoing axillary lymphadenectomy). Because of the advanced disease stage at diagnosis, many patients (33.3%) underwent supraclavicular fossa radiotherapy, which tended to select patients with a higher probability of treatment-related complications. Similarly, in the literature, it is difficult to characterize a cutoff point for changes in shoulder mobility and strength on the affected side as associated with shoulder pathologies such as rotator cuff syndrome, because although they are more frequently present on the side being treated, they are also present in the general population.[8] In the original study, where quantitative measurements were performed, only cosmesis and edema were evaluated, and in the German studies, only cosmesis was evaluated.[22,33,47] The German validation study evaluated the influences of some covariates on quality of life but did not demonstrate the rate of complications related to the treatment or its impact in relation to the questionnaire.[40]

Lymphedema

Lymphedema (differential volume $\geq$ 200 mL) was present in 62 patients, of whom 60 underwent axillary lymphadenectomy. In the study by Nguyen et al,[48] a cohort study where lymphedema was assessed from medical records, the incidence rates of lymphedema at 5 years were 6% in patients with conservative surgical treatment of the breast associated with SLNI and 14.7% in patients with lymphadenectomy and BCT. In our study, the evaluation of

lymphedema was performed using the volumetry method,[49] and the overall rate was 20.7%, although it was 2.9% among patients with SLNI and 26% in patients with axillary lymphadenectomy. The lymphedema rates found in our study were close to the risk of developing lymphedema.[12] In patients with lymphedema, the mean scores of the functional state, cosmetic state, and edema domains of the BCTOS questionnaire were significantly higher, indicating that quality of life is impaired by lymphedema and that this instrument is able to discriminate patients with lymphedema.

Krishnan et al[22] correlated arm edema, performed by means of perimetry, with the BCTOS domains, except for the edema domain, and with the mental health and physical health domains of the SF-36. They found significant correlations of arm edema with functional state and cosmetic state domains, but they found no correlations between arm edema and SF-36 domains. The study conducted by Lee et al[50] evaluated quality of life in breast cancer patients with lymphedema who survived more than 1 year after surgery. The questionnaire used was the SF-36, and the method of evaluation of lymphedema was arm circumference, noting that patients with lymphedema did not have significant differences in quality of life compared to patients without lymphedema but that they differed when the quality of life of these patients treated for breast cancer was compared to that of the general population.

Some studies evaluating QLQs evaluate scores associated with clinical attention in breast cancer patients. Considering acceptable an area under the curve value of $>$ 0.70 (fair result) to 0.80 (good),[51-53] Snyder et al[51] compared the QLQ C-30 with Supportive Care Needs Survey—Short Form 34, Iskandarsyah et al[52] evaluated the Distress Thermometer, and Nesvold et al[53] evaluated a Kwan arm problem scale. The use of a cutoff allowed us to use the quality-of-life questionnaire in clinical practice while excluding other instruments for evaluation; or on the basis of a score, it gives us an idea of what it represents in clinical practice. Evaluating our study using a cutoff of 1.26 in the domain edema was associated with a clinical lymphedema evaluated by a 200 mL volume difference.

Shoulder Mobility and Handgrip Strength

Although considered as a factor associated with the treatment of breast cancer,[8] few studies have attempted to systematically quantify a cutoff point associated with strength deficit and altered shoulder mobility. Patients who participated in our study and who had altered shoulder ROM had significantly higher values in the 4 domains of the BCTOS, and those with handgrip strength deficits had higher values for the functional state domains breast-specific pain and edema. Rietman et al[54] assessed long-term limb morbidity after treatment for stage I and II breast cancer and found that the shoulder movement, handgrip strength, and quality of life of these women were impaired after treatment. Axillary lymphadenectomy was a predicting factor for morbidity and poor quality of life. A similar result was observed in the present study because when we separately analyzed the force deficit and the ROM in the patients submitted to lymphadenectomy and SLNI, those with axillary lymphadenectomy had higher scores of the BCTOS when they had strength deficits and ROM alterations; in contrast, in patients submitted to SLNI, only the functional state and edema domains had statistically significant scores in patients with ROM alterations.

The rates of strength deficit were similar: 37.7% in the axillary lymphadenectomy group and 40.6% in the SLNI groups. In relation to handgrip strength, the population with deficits of strength and axillary lymphadenectomy also had significantly higher scores in the functional state, cosmetic state, and edema domains, while patients with SLNI had no differences in scores when they had strength deficits.

Lymphadenectomy with radiotherapy is a risk factor for the reduction of ROM. When compared to lymphadenectomy and SLNI, changes in shoulder ROM occurred in 8% to 20%, versus 0 to 4% in 12 months.[55] In this study, as reported in the literature, alterations in ROM were present in a greater number of patients submitted to axillary lymphadenectomy, and all scores were significantly higher, whereas only the functional state and edema scores were higher in patients with altered shoulder mobility after SLNI. Recchia et al[43] evaluated the correlation of shoulder dysfunction with quality of life after treatment for breast cancer and found a moderate correlation between shoulder dysfunction and quality of life. However, to assess shoulder dysfunction, the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire was used.

Breast Cosmesis

When evaluating breast cosmesis, the criterion used to assess cosmesis should also be evaluated. In the original study of the BCTOS, a nurse evaluated the cosmesis, which assesses breast size, difference in breast symmetry, breast fibrosis, and the presence of telangiectasia; smaller numbers indicate better cosmesis, and higher numbers indicate worse cosmesis, observing an objective correlation of 0.69 ($P < .001$).[22] Using the German version of the questionnaire and comparing the BCTOS with BCCT.core, where 4 items are evaluated in both instruments, in which smaller values imply better cosmesis, a concordance of values ranging from 35% to 44% was observed, where the κ coefficient of agreement was approximately 0.21, ranging from 0.04 before surgery, 0.34 near surgery, and 0.19 within 1 year after surgery. In this study, patients reported a better judgment regarding the software.[47] It is a fact that poor breast cosmesis has a negative impact on the quality of life of patients treated for breast cancer. However, when cosmesis is evaluated subjectively, the women report better enjoyment with the cosmetic result because 76.8% classified the results as good or excellent; in contrast, when objectively evaluated, only 29.9% fit the classification. In a study in which the result of the cosmesis was evaluated by the patient and the doctor on a scale from 0 to 3, there was also a significant difference between the evaluations of the patients and the physicians, and the cosmetic result was considered good or excellent by 76.3% of patients and 47% of physicians.[56] The same was observed in our study; a regular relation was observed with cosmetic domain and subjective cosmesis (ROC curve area = 0.766), but it was not observed in relation to objective evaluation (ROC curve area = 0.669). In addition, our study showed that poor breast cosmesis has a negative impact on quality of life and that the BCTOS questionnaire is a tool capable of discriminating the difference between good or excellent breast cosmesis from fair or poor breast cosmesis, mainly according to the woman's degree of satisfaction, because the scores of the 4 domains were statistically higher in patients with fair or poor breast cosmesis by self-evaluation, whereas only the domains of cosmetic state and edema were

statistically significant in patients with fair or poor breast cosmesis when analyzed by the BCCT.core.

Breast Pain

In a systematic review and meta-analysis of chronic breast pain factors in breast cancer survivors, the risk factors for breast pain were identified as age < 50 to 55 years, low schooling, higher body mass index, lymphedema, axillary lymphadenectomy, and receipt of radiotherapy or chemotherapy. Regarding the types of surgical treatment, there was no difference in the risk of developing chronic pain.[57] On the basis of the aforementioned meta-analysis, our study population had a high risk for chronic pain because the mean age was 51.2 years, the mean educational level was low (7.3 years), 91 participants had a body mass index of $\geq$ 30 kg/m^2, lymphedema was present in 20.7%, 77% underwent axillary lymphadenectomy, and 83.4% received chemotherapy and 100% breast radiotherapy. In a study that aimed to investigate the prevalence of pain, according to the EORTC QLQ C-30 and BR23, pain was prevalent in 46.3% of the participants.[58] Because pain is subjective, to evaluate breast pain, we used the item referring to breast pain of the LENT/SOMA scale,[8,59] observing a 64% prevalence of breast pain, whether mild or severe. The scores of the 4 domains of the BCTOS were higher in patients with breast pain, and the BCTOS had a positive correlation with the pain domain of the EORTC QLQ C-30. In addition, a good relation was observed with the pain domain and LENT/SOMA pain (ROC curve area = 0.846).

Age is a predictor of breast pain because the younger the women, the greater the reports of breast pain after breast cancer treatment.[56] Pain had a negative impact on the quality of life of younger patients after modified mastectomy and among those who received radiotherapy.[60] In our study, patients aged < 60 years also had higher BCTOS domain scores compared to patients aged $\geq$ 60 years. Age was also significantly correlated as a factor, influencing functional state, cosmetic state, and breast-specific pain domains in the validation study of the German-language BCTOS; the edema domain was not evaluated in this study.[40]

Type of Axillary Treatment

Currently, SLNI indications are more frequent. Patients treated for a long time usually undergo axillary lymphadenectomy, regardless of clinical stage of disease. However, supraclavicular fossa radiotherapy is associated with clinical stage. The association of lymphadenectomy and radiotherapy of the supraclavicular fossa elevates the risk of lymphedema.[11] In the original study, a historical series of treated patients (1982−1999) was evaluated; SLNI was not yet a methodology accepted by all, with 40.6% having stage II disease, and there was no description of the use of radiotherapy in fossa.[39] However, objective evaluation was performed in only 54 patients, where the lymphedema rate was 18.5%.[22] In the German validation study, clinical stage was not reported, 81% presented tumors of stage T0−1, and 50% had axillary stage N0 disease, where axillary lymphadenectomy was performed in only 26% of the patients; there were no descriptions regarding treatment in the supraclavicular fossa or the rate of sequelae associated with treatment.[40] In the present study, 21.0% of the patients had stage III disease, 77% underwent lymphadenectomy, and 33% had supraclavicular fossa radiotherapy; using objective criteria, 20.7% had lymphedema, 51.7% had alterations in mobility, and 38.3% had changes in strength. In patients submitted to SLNI, the lymphedema, strength change, and ROM rates were 2.9%, 40.6%, and 42.6%; in patients undergoing axillary lymphadenectomy, these rates were 26.2%, 37.6%, and 54.8%.

Quality of life was more affected in patients with lymphedema after axillary lymphadenectomy than in those with lymphedema after SLNI because the functional state and edema scores were significantly higher in patients with lymphedema and radical lymphadenectomy compared to those without lymphedema and radical lymphadenectomy, while there was no difference in the scores of patients submitted to SLNI with and without lymphedema. In patients with SLNI, the changes in ROM was associated with worse functional and edema scores; however, in the presence of axillary lymphadenectomy, which has the highest complication rates, BCTOS presented higher scores in all domains.

Limitations

Some limitations were found in the present study, such as low level of education, which made the majority of patients prefer to use the questionnaire as an interview. BCTOS is a simple questionnaire that is easy to understand, but we did not measure the time spent completing each questionnaire. A questionnaire requiring less time may have better clinical applicability and responsiveness, which can indicate the capacity of the instrument to evaluate changes over time, which was also not performed in the present study. In addition, because the subjective evaluation through the BCTOS is performed in a comparative manner, it can be biased toward for patients with bilateral cancer—a fact that we excluded in our inclusion criteria.

We believe that the way patients were selected indirectly led to a higher rate of complications, and that these complications were associated with significant differences observed in the quality-of-life questionnaire, thus valuing the use of quantitative and qualitative measurements in validation studies of QLQs. Therefore, in both the creation and evaluation of questionnaires, the use of populations where the frequency of a variable is low may contribute negatively to the construction of a QLQ, to the point of excluding an important item in the initial analysis of reliability. Perhaps the high rate of lymphedema observed in our population had a positive influence on the questionnaire, thus supporting the association initially considered in the original study[22,39] and not considered in the German validation study.[40]

Conclusion

The BCTOS is a valid and reliable instrument in its Brazilian Portuguese form, with good correlation with the original questionnaire. In the Brazilian Portuguese version, the BCTOS showed high indices related to internal consistency and test−retest reproducibility. Factor analysis showed similar results compared to the English version, validating the edema domain for the first time. BCTOS was able to correlate with the main treatment-related sequelae through objective measures, ie, lymphedema, changes in strength, alterations in shoulder mobility, breast cosmesis, and breast pain. Thus, despite being considered an old questionnaire created in a different manner compared to current

questionnaires, the BCTOS is valid in the evaluation of patients submitted to BCT.

Clinical Practice Points

- The Brazilian Portuguese version of the BCTOS is a valid instrument of quality of life for patients submitted to BCT.
- This study was the first to validate the lymphedema domain proposed in the original version. It was possible because of the criteria used for patient selection and the high numbers of sequelae.
- It is important to correlate quality-of-life instrument domains with objective measurements (and not always what the patient thinks or correlates with objective findings), which leads to possible questionnaire subjectivity.
- Using other objective instruments of sequelae measurement, it was possible to correlate quality of life, objective instruments, and sequelae related to breast cancer treatment
- For developing a quality-of-life questionnaire, it is important to add other objective instruments and to report them because their conditions reflect on the final questionnaire version's question selection.

Acknowledgments

We thank Annette L. Stanton (PhD, UCLA), whose authorized us to translate and use the BCTOS. We thank Maria João Cardoso (MD, PhD, Fundação Champalimaud), who kindly provided us with the BCCT.core. We also thank the Researcher Support Center of Barretos Cancer Hospital (Núcleo de Apoio ao Pesquisador do Hospital de Câncer de Barretos), especially Viviane Andrade, Larissa Kuil, and Lais Corsino Durant, who assisted in the selection of patients and the application of QLQs. Supported in part by São Paulo Research Foundation (FAPESP, Fundação de Amparo a Pesquisa do Estado de São Paulo, Brasil) 2014/08197-0.

Supplemental Data

A supplemental table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2018.10.004.

Disclosure

The authors have stated that they have no conflict of interest.

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Supplemental Data

Supplemental Table 1 Factorial Composition of Items and Comparison With Factorial Composition of Original Study and German Version

	Functional			Cosmetic			Specific-Breast Pain			Edema	
No.	Current	Original	German	Current	Original	German	Current	Original	German	Current	Original[a]
1	0.237	−0.020	−0.024	**0.792**	**0.860**	**0.817**	−0.062	−0.040	−0.006	0.011	
2	0.295	0.160	−0.025	**0.431**	**0.550**	0.132	0.408	0.140	**0.572**	0.220	
3	**0.623**[b]		**0.721**	0.214		−0.07	0.187		0.185	0.494	
4	0.147	0.040	−0.136	**0.454**	**0.420**	**0.578**	0.399	0.080	0.105	0.134	
5	**0.745**	**0.960**	**0.644**	0.226	−0.010	0.06	0.118	−0.090	0.129	0.173	
6	**0.735**	**0.860**	**0.748**	0.201	−0.110	−0.002	0.251	0.040	0.07	0.143	
7	0.387	0.300	0.09	0.146	0.030	−0.221	**0.661**	**0.470**	**0.805**	0.157	
8	**0.626**	**0.540**	0.372	0.162	0.040	0.08	0.337	0.170	**0.405**	0.226	
9	0.229		**0.518**	0.216		0.302	0.004		−0.145	**0.737**	
10	0.263	0.010	−0.04	0.085	−0.050	−0.06	**0.807**	**0.970**	**0.808**	0.159	
11	**0.755**	**0.920**	**0.766**	0.117	−0.020	0.06	0.090	−0.050	−0.02	0.073	
12	0.161	−0.100	−0.08	**0.795**	**0.840**	**0.874**	0.135	0.070	−0.100	0.081	
13	0.180	−0.030	0.04	**0.729**	**0.740**	**0.817**	0.103	0.040	−0.08	0.165	
14	0.061	−0.080	0.166	**0.676**	**0.480**	**0.480**	0.215	0.290	0.02	0.134	
15	**0.703**	**0.790**	**0.671**	0.009	0.050	0.04	0.252	−0.010	−0.02	0.174	
16	**0.658**	**0.450**	**0.832**	0.130	0.040	−0.121	0.377	0.260	0.0005	0.294	
17	0.337		**0.574**	0.108		−0.134	0.127		−0.110	**0.736**	
18	0.227		−0.205	−0.001		0.166	0.387		**0.670**	**0.559**	
19	**0.706**	**0.680**	**0.830**	0.184	0.090	0.03	0.145	0.040	−0.158	0.165	
20	0.027	0.090	0.002	**0.604**	**0.830**	**0.614**	0.157	−0.080	0.162	0.390	
21	0.265	0.040	0.02	0.324	0.200	0.218	**0.660**	**0.660**	**0.629**	0.091	
22	0.119	0.060	0.08	0.368	**0.820**	**0.446**	0.205	−0.160	0.06	**0.644**	

Original study is that of Stanton et al,[39] and that of German version is Heil et al.[40]
Bolded value shows the items and the value of the items grouped in the factorial analysis of each study.
[a]Considered but not presented in original study.
[b]Different grouping than original study.