3D Breast Ultrasound: A Significant Predictor in Breast Cancer Reduction under Pre-operative Chemotherapy

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Abstract. *Background: The objective was the investigation of a possible predictive quantitative impact of initial tumor sphericity, measured by 3D sonography, on response to pre-operative chemotherapy. Patients and Methods: This 3D ultrasound study was conducted on 41 consecutive primary breast cancer patients who received pre-operative epirubicin and paclitaxel chemotherapy; the tumors were measured by 3D sonography and by pathology after chemotherapy. Sphericity was defined as the ratio of the smallest to the largest extent by 3D sonography. Results: A predictive impact of initial tumor sphericity on response to pre-operative chemotherapy was quantitatively identified for the first time. Sphericity was a significant predictor of pathological complete remission with a rank difference of 0.34 or about 1/3 i.e., spherical tumors were more likely to show successful remission. Conclusion: Tumor sphericity as defined from 3D sonography could be predictive of response to pre-operative chemotherapy regimens; prospective investigation is suggested.*

Using ultrasound as a noninvasive method to predict the possible outcome of a given treatment regimen would greatly benefit any patient collective while resulting in virtually no additional patient discomfort. This however, requires a thorough ultrasound analysis of response to pre-operative chemotherapy in breast cancer patients. Evidence points to at least equal long-term survival for pre-operative *versus* adjuvant administration of chemotherapy regimens (1, 2). The quality of life benefits accruing from the known (3-8) increase in the breast conserving surgery rate due to pre-operative therapy is substantial. Therefore, treatment individualization and optimization by identifying specific patient subgroups with different potential pre-operative response profiles is becoming more and more important. The noninvasive and readily available method of 3D ultrasound is already a fundamental part of clinical practice and may yield additional information about tumor response to preoperative chemotherapy.

Two tumors with the same volume can obviously have different degrees of asymmetry when considered as three-dimensional structures. Malignant tumors are significantly associated (9, 10) with a ratio of length to depth >1 (OR=2.5); here, the "depth" refers to the tumor dimension perpendicular to the skin surface, whereas the "length" refers to the larger of the two remaining dimensions. These findings provide an example of a wide relationship between morphology and tumor malignancy. It was thus an intriguing inquiry whether or not morphology might also be a predictive factor for response to pre-operative chemotherapy.

Therefore, this investigation proposed and tested the hypothesis that predictive information might be provided by the three-dimensional character of sonographic measurements, in particular the degree of equality of all three dimensions, which were defined and refered to as "sphericity".

Patients and Methods

Patient collective. This study was conducted in the OB/GYN department at the University of Cologne with (initially) 41 consecutive primary breast cancer patients between 2000 and 2003, who were selected for treatment with pre-operative combination chemotherapy of Epirubicin and Paclitaxel (Taxol). This treatment regimen was given to the patients whose tumors were either locally advanced (size ≥2 cm) or estrogenreceptor negative (ER–). Metastasis, previous malignancy,

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Table I. *Overall patient tumor characteristics.*

cT	Number	%	cN	Number	%	Histology	Number	%
T1	3	7.9	N0	4	10.5	Ductal	29	76.3
T2	30	78.9	N1	19	50.0	Lobular	5	13.2
T3	1	2.6	N2	1	2.6	Ductolobular	1	2.6
T4	4	10.5	Nx	14	36.8	Medullar	1	2.6
						Inflammatory	1	2.6
						Not Classified	1	2.6
Total	38	100	Total	38	100	Total	38	100

and pregnancy were exclusion criteria. The diagnosis of primary breast cancer was made on the basis of mammography, mamma sonography and MRI. Three of these patients were lost to follow-up for reasons unrelated to their disease stage or treatment, leaving a total of 38 for analysis. All the patients signed informed consent for this institutional review board (IRB) approved protocol.

The study protocol specified that patients receive up to six cycles of chemotherapy with Epirubicin (intravenous 1 hour infusion, dose 90 mg/m^2) and Paclitaxel (dose 175 mg/m^2). Deviations from the chemotherapy protocol occurred in two out of the 38 patients.

After the completion of pre-operative therapy, the patients who were considered appropriate candidates for breast conserving surgery were offered segmental mastectomy (lumpectomy). The patients who were considered inappropriate for breast conserving surgery or who did not desire it underwent total mastectomy. Study protocols were approved by the institutional review committee and met official guidelines. Further details of the study protocol as well as measurements of the tumor biological factors and their impact on outcome have been previously described (11).

The primary tumor characteristics and lymph node status were evaluated clinically, *via* ultrasound, mammography and MRI (12). Table I summarizes the patient tumor characteristics. The median age was 49.7 years (30-69).

Clinical diagnostics. Thorax X-rays and upper abdominal sonography were performed in all the patients, as well as tomography and skeletal scintigraphy as required (13, 14). Following pre-operative therapy, the tumor stage and lymph node stage were re-classified.

Three-dimensional sonography measurements of the tumor were recorded both before and after treatment. A standardized, two-step procedure was used to obtain a three-dimensional tumor measurement using a Voluson 730 Expert (GE Ultrasound Germany, Solingen, Germany). First, the ultrasound probe was rotated in the plane of the breast surface until the maximum lateral tumor dimension was determined. This dimension and the depth was recorded. The third dimension was then obtained by rotating the ultrasound probe through a 90 degree angle.

Tumor sphericity. As a three-dimensional tumor morphology characteristic, tumor sphericity Σ was defined as the ratio of the smallest to the largest sonographic dimension, so that $0<\Sigma\leq 1$. The sphericity prior to therapy was denoted by Σ_0. Accordingly, the tumors that presented as highly symmetrical had values of Σ_0 closer to unity.

Statistical tests. Distribution-free tests (Mann-Whitney test, Spearman correlations) were used to test the association between pre-operative tumor sphericity and outcome or tumor biological characteristics. The nominal level of significance was $p=0.05$.

Results

Tumor sphericity as a predictive factor. The distribution of Σ_0 appeared bimodal, with peaks around one-half and one (Figure 1), the mean was 0.66 and standard deviation 0.20. The distribution after therapy was also bimodal (Figure 2), but with a shift toward sphericity (mean=0.83, standard deviation 0.19, $p<0.001$, Wilcoxon Signed Rank Test).

Initial tumor sphericity Σ_0 was a significant predictor of pathological complete remission (pcR) with a rank difference of 0.34 or about 1/3 ($p=0.008$, Mann-Whitney test), *i.e.*, more nearly spherical tumors were more likely to have successful pCR.

Sphericity was significantly higher in the ER-negative tumors ($p=0.027$, Mann-Whitney test), but was not significantly associated with progesterone receptor (PR), KI-67 antigen (KI-67) or human epidermal growth factor receptor 2 (HER2) status.

Discussion and Conclusion

In breast cancer, improved therapy concepts and individualization of pre-operative therapy are vital. The rate of pCR as determined by histology remains the primary indicator and the "gold standard" for evaluation of treatment efficacy and has in this study been correlated to the initial sphericity of the tumor.

A significant predictive impact of the initial tumor sphericity on the response to pre-operative chemotherapy in the present patient collective of locally advanced patients, in terms of pCR, was demonstrated. A significant predictive value of macroscopic primary tumor morphology should come as no surprise, since morphology at presentation is the consequence of tumor biological processes that also could have an impact on response to pre-operative therapy. This

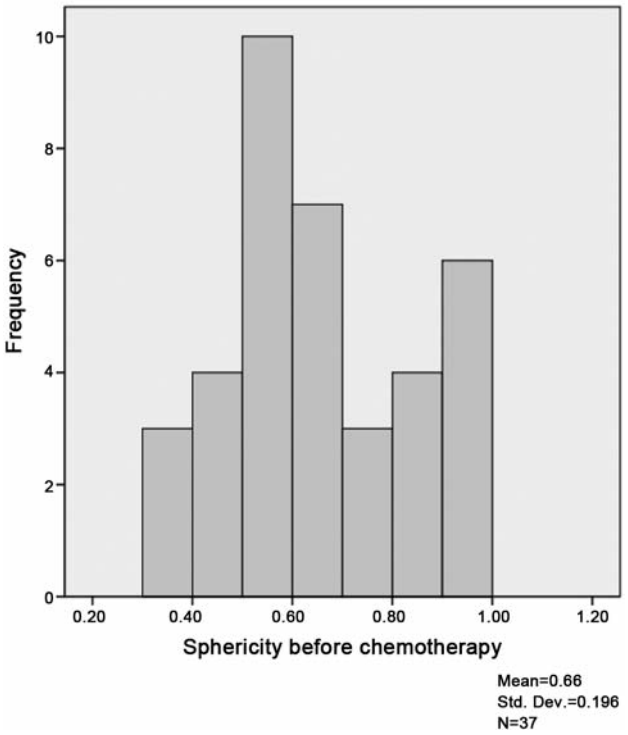

Figure 1. *Sphericity before chemotherapy.*

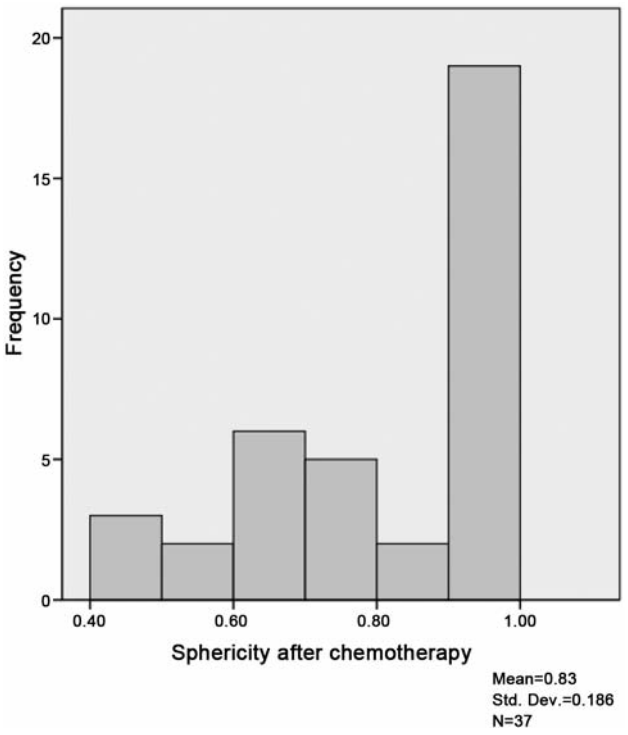

Figure 2. *Sphericity after chemotherapy.*

idea was supported by the association between sphericity and ER status. Associations of sphericity with additional tumor biological factors KI-67, HER2/neu and PR were not significant in the current collective, but might be seen in a larger collective.

Improved prediction of therapy success using such a routinely available measurement as tumor sphericity, possibly within a multivariate response prediction model, could have useful consequences in the clinical decision process for adjuvant *versus* pre-operative therapy. Supporting retrospective studies on existing data may be possible, since sphericity is a factor that can be recovered and quantified from existing sonographic measurements. Further investigations of sphericity, either prospectively or retrospectively, could well be warranted, for example, with respect to response to pre-operative therapy modalities or as a possible indicator for long-term survival in the adjuvant setting.

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