Assessment of skin involvement in breast cancer: preoperative ultrasound and anatomopathological correlation

KEYWORDS Breast Cancer. Skin. Ultrasound. Pathology.

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ABSTRACT Introduction: The removal of the overlying skin carcinoma is often unnecessary and can compromise the aesthetic result of breast surgery. Objectives: To correlate the tumor-skin distance obtained from the ultrasound and pathologic examinations and establish a relationship between these parameters. Methods: This was a prospective correlational study of 39 women presenting 41 breast tumors who were diagnosed with invasive cancer. The distance between the lesion and skin was measured using preoperative ultrasound examinations and an anatomopathological evaluation. Results: The mean distance between the tumor and skin obtained from the ultrasound was 0.8 cm (0.15 - 2.43 cm). The pathologic examinations yielded a mean distance of 2.21 cm (0.5 - 5.0 cm). Conclusion: The tumor-skin measurements obtained from ultrasound correlated well with those obtained from pathologic examinations (r = 0.75). The distance obtained by sonography was consistently less than that obtained from a pathology specimen, and the average difference was 3.1-fold.

Introduction

The adequate assessment of the local extent of breast cancer is crucial during surgical planning to obtain tumor-free margins. Therefore, ultrasonography (US) has often been used to provide information on the size of a lesion and its relationship with anatomical breast structures. Measuring the proximity of the tumor to the skin using imaging methods is a subject of particular interest given the increasingly frequent use of conservative surgery and skin-sparing mastectomies (SSM) in the treatment of breast cancer [1].

US exhibits good sensitivity in assessing the relationship between the tumor and the skin. Its easy implementation, coupled with its low cost and absence of risk, make it an indispensable tool in surgical planning. Mammography (MG) may provide additional data regarding the superficial margin, especially when microcalcifications or skin thickening are present [2-5].

Magnetic resonance imaging (MRI) has been increasingly used during surgical planning for breast cancer, despite controversy regarding its actual benefits. The anatomical relationships between the lesion and breast, including the distance to the skin, chest wall, or nipple-areolar complex, are easily ascertained using this method. However, the risk of lesion overestimation, the high cost, and the lack of benefit in terms of reoperation rates for positive margins observed in randomised trials (MONET trial and COMICE trial) discourage the routine use of preoperative MRI [6, 7].

The use of SSM in the treatment of invasive tumors has revealed the importance of superficial margin analysis and the relationship between cancer and the skin. The goal of this technique is to separate all fibroglandular tissue, especially the tumor, from the skin flap to obtain cancer-free margins. However, dissection between the skin and the breast tissue is not always easy, especially in more superficial lesions. The inability to obtain free margins for these lesions increases the risk of local recurrence (LR). Thus, these patients may benefit from incisions that include the removal of the skin overlying the tumor, as proposed by Toth and Lappert in 1991 [8]. Moreover, in conservative surgeries, the removal of the skin overlying the tumor can impact the aesthetic result, deterring its indication, especially in small- and medium-volume breasts.

Moreover, the different positions of the breast observed in the most commonly used imaging tests (orthostatic MG, supine US, and prone MRI) present a challenge for surgical planning. The tumor may become somewhat displaced, and its relationship to surrounding structures can change [9, 10]. Undoubtedly, the shape of the breast when a patient is positioned in the US examination (i.e., in the supine position with arms abducted and hands behind their head) reduces relative distances within the breast. However, the magnitude of these changes is unknown. Our goal was to measure the tumor-skin distance using US examinations and compare this value with the distance observed in pathological examinations. This strategy will allow us to assess the impact of elastic forces on breast tissue and establish a relationship between the distance observed in US examinations and the distance observed in an anatomopathological specimen.

Materials and methods

The study was approved by the institution's ethics committee, and all patients signed free and informed consent forms. Patients presenting a breast tumor who were diagnosed with invasive cancer and were candidates for conservative or radical surgery (mastectomy) were included. The exclusion criteria consisted of having received neoadjuvant treatment, having no nodular lesions (tumors with indistinct margin, architectural distortions, and suspicious microcalcifications), clinical or ultrasonographic signs of skin involvement, and surgical treatment that did not include the removal of the skin overlying the tumor.

Preoperative US

All patients were subjected to an US examination with a 12 MHz linear transducer (Logic 6, GE Medical Systems, Milwaukee, WI, USA), performed independently by two doctors specialising in breast cancer diagnosis. Each assessment was performed with the transducer aligned with the major axis of the lesion, where the measurement between the most anterior hypo-echoic border of the lesion and the epidermis was obtained (Figure 1). The examiners routinely used the compression on the transducer. Each observer performed three different measurements of the area, and the average of these three distances was recorded as the final value. The intra- and inter-observer variability was also analysed. A tattoo was drawn with ink using a 13 x 4.5 mm needle at the skin projection with the shortest tumor-skin distance to provide a reference point for anatomopathological measurements (Figure 1).

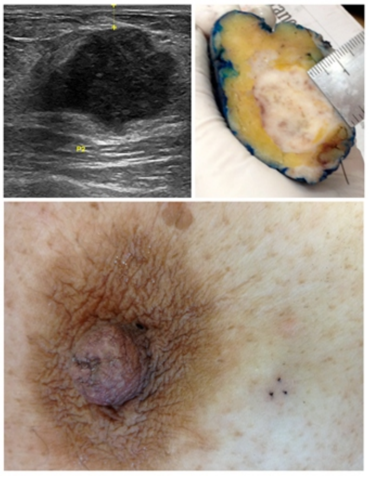

Figure 1: Correlation between the tumor-skin distances obtained from US (A) and Path examinations (B). The smallest distance obtained from US was the distance from the most anterior hypoechoic margin of the lesion to the skin. The distance obtained from the Path examinations was based on the use of tattoo ink as a reference, which was applied during preoperative US (C)

Surgery
All patients underwent surgery according to the institution protocol, which invariably included the removal of the skin overlying the tumor, as previously marked. The procedures were performed by resident physicians under the guidance of tutors of the Mastology Discipline in the Department of Gynaecology of the School of Medicine at our institution.

Anatomopathologic assessment
All surgical specimens were fixed in 10% neutral buffered formalin for at least 24 hours. They were then cleaved for macroscopic evaluation, and fragments were obtained to create slides and subsequently perform microscopic evaluations. The distance between the tumor and the skin at the previously marked location (ink) was measured using a standard millimetre ruler (Figure 1). Tumor-skin measurements less than 1.0 cm were re-analysed under a microscope by measuring the stained, corresponding H&E slides. The procedures were performed independently by two pathologists, and the measurements were correlated between the two observers, as in the US examinations.

Statistical analysis
The STATA 12 software was used to analyse the data. The reproducibility of the measurements obtained from US and pathological examinations was assessed using an intraclass correlation and Pearson's correlation (r). A simple linear regression was used to establish the relationship between the tumour-skin distance in the pathological examination and the US examination after analysing the normality of the data distribution using the Kolmogorov-Smirnov test. The standard Studentised Residual and Cook's Distance (Cook's D) were used to determine the presence of discordant or influential values, respectively. The significance level used for all tests was 5%.

Results
The study included 39 consecutive patients with 41 lesions that had been previously diagnosed as primary invasive breast carcinomas, and the patients were selected between January 2014 and January 2015. The characteristics of the patients and tumors are presented in Table 1.

Table 1: Clinical and pathological characteristics of patients (n = 41)

Table 1 - Clinical and pathological characteristics of patients	
	Number (41) (%)
Age (years) variation 39-77	
Mean: 59.2	
Tumour Type	
NSIC	37 (90)
ILC	1 (2)
CE	3 (7)
Size	
T1a	0 (0)
T1b	8 (19)
T1c	15 (36)
T2	7 (17)
T3	11 (26)
Lymph node status	
Positive	13 (31)
Negative	28 (68)
Histological grade	
G1	15 (36)
G2	19 (46)
G3	7 (17)
Hormonal status	
ER +	40 (97)
ER -	1 (2)
PR+	37 (90)
PR -	4 (9)
HER2 status	
HER2 +	3 (7)
HER2 -	38 (92)
Surgery Type	
Mastectomy	9 (21)
Conservative surgery	32 (78)

NSIC = non-special invasive carcinoma. ILC = invasive lobular carcinoma. SC = special carcinomas (tubular, medullary, and mucinous).

The average age of patients was 59.2 years (ranging from 39 to 77 years). The mean size of the lesions was 2.2 cm (ranging from 0.6 to 6.5 cm). In 23 (55%) patients, the lesions were less than 2.0 cm. Lymph node involvement was observed in 13 (31%) patients, and mastectomy was the surgery of choice in 9 (21%) patients (Table 1).

US measurements
The mean distance between the tumor and skin obtained from US examinations was 0.8 cm, with a minimum of 0.15 cm and a maximum of 2.43 cm. The measurements showed strong intra- and inter-observer correlations. In the individual analysis, the intraclass correlations obtained were 0.989 (0.982; 95% CI 0.994) for observer 1 and 0.991 (0.985; 95% CI 0.995) for observer 2. A comparison of the measurements made by observers 1 and 2 revealed an intraclass correlation of 0.96 (95% CI 0.93-0.98). The Pearson correlation (r) demonstrated a strong relationship between measurements, with $r = 0.994$, $p < 0.001$.

The Bland-Altman plot (Figure 2) revealed a mean difference between the US measurements of the two observers of -0.03 cm, with a 95% confidence interval of -0.23 to 0.17 cm.

Pathologic measurements
The pathologic findings revealed an average tumor-skin distance of 2.21 cm, with values ranging from 0.5 to 5.0 cm. The tumor-skin measurements observed in the pathologic examinations also

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showed a strong correlation between the two observers (r = 0.99, $p < 0.001$). The Bland-Altman plot (Figure 2) revealed a mean difference between the measurements of -0.04 cm, with a 95% confidence interval of -0.26 to 0.18 cm.

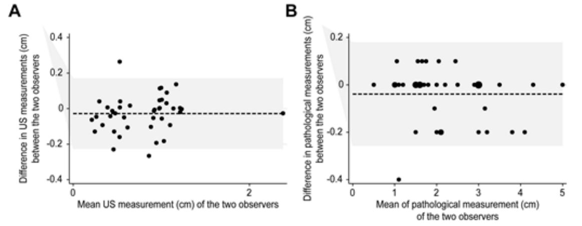

Figure 2: Bland-Altman plots showing the difference between observers for US (A) and Path measurements (B). Note the very small mean difference between observers for both methods (-0.03 for US and -0.04 for pathology)

The mean US and AP measurements obtained by the two observers were associated. Specifically, the Pearson correlation was r = 0.752, with $p < 0.001$ (Figure 3). A correlation was then performed based on the simple linear regression model.

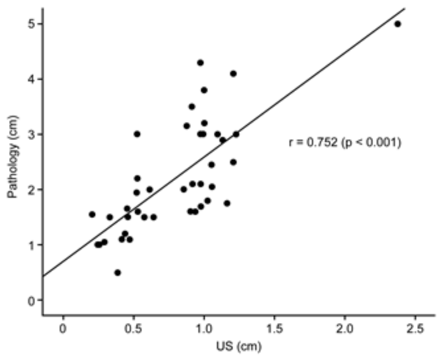

Figure 3: Scatter plot for the mean US and Path measurements

Table 2:. Results of the simple linear regression model to estimate the histological distance between the tumor and the skin

Coefficients	Estimate	Standard Error	95% Confidence interval	p
Intercept	0.69	0.24	[0.21; 1.17]	0.006
US	1.89	0.27	[1.36; 2.43]	< 0.001

N = 41

US: ultrasound

According to Table 2, the estimated model is given by the following:

$$\widehat{D}_{Patholgy_{i}} = 0.69 + 1.89 D_{US_i}$$

$D_{pathology}$ = estimated distance in the pathological examination; DUS = distance measured by US; i = 1, ..., 41

Thus, each increase of one unit of distance in the US measurement corresponded to an increase of 1.89 units in the pathologic measurement (Table 2).

Discussion

The assessment of the actual distance between the breast carcinoma and the skin can influence the decision to excise the dermis overlying the tumor in skin-sparing mastectomies. The present study aimed to establish a relationship between the tumor-skin distance observed during an US examination and the standard measurement, i.e., that obtained from the pathology specimen. Such information, as discussed by Cunnick and Mokbel [11], may influence the decision to remove or preserve the skin overlying the tumor during the surgical treatment of breast cancer. Specifically, Cunnick and Mokbel [11] considered that the risk of residual subcutaneous lesions was greater for tumors larger than 4.0 cm, especially for breast masses near the dermis.

Our data revealed that the tumor-skin distances obtained from the US examination were consistently smaller than those recorded from the pathology analysis, which averaged 0.8 cm and 2.2 cm, respectively. The elastic deformation suffered by the breast in the supine position, with the arms abducted and hands behind the head, largely explains this difference. Compared to the orthostatic position, the previously described positioning enlarges the area occupied by the breast in the chest and reduces its thickness, and the skin lies closer to the chest wall. This new conformation reduces the relative distances inside the breast, which return to normal in the surgical specimen.

The pressure of the US probe certainly contributed to the shrinkage of the tumor-skin distances in the US examination. This pressure compresses the breast, which decreases the distance between the tumor and the skin. Moreover, the insignificant variability between the measurements obtained shows that the compression was very similar between the two observers.

The elasticity modulus, or Young's modulus, is a value that defines the degree of deformation to which a body is subjected when tension is applied [12]. This value is directly proportional to the stiffness of the material. We believe that the deformities experienced by the breast during US depend primarily on the breast's composition, the cohesion of the interior tissues (ligaments), and its coating (skin). Breasts that predominantly consist of fat, loose ligaments, and flaccid skin will suffer greater deformation than glandular breasts with firm ligaments and tight skin. Among the 41 patients in this study, the ratio of the AP/US distances ranged from 1.5- to 8-fold, with an average of 3.1-fold. We believe that the variability in breast characteristics explains the differences observed. Thus, flaccid breasts whose deformities are greater will present smaller US tumour-skin measurements, whereas firmer breasts will have US measurements closer to those observed in pathology. In fact, we observed that the average AP/US ratios in patients under 50 or over 60 years old were 2.7- and 3.4-fold, respectively.

Carbonaro et al. [9] analysed the change in position suffered by the tumor inside the breast during MRI scans in the prone position vs. the supine position. They observed average displacements of 3-6 cm in the three orthogonal axes. Conversely, the distance between the tumor and the skin exhibited less variation, with an average displacement of 0.7 cm. Similar data were observed by Pallone et al. [10], who reported an average displacement of 0.4 cm. Our data reveal an average difference of 1.4 cm between the same distance (tumor-skin) measured based on preoperative US and histopathology. These data confirm the hypothesis that the deformation suffered by the breast in the supine position decreases the relative distances inside the breast. Nevertheless, the degree of deformation will depend on the features of each breast and the positioning of the patient.

The use of SSM for the treatment of invasive tumors has increased, which highlights the importance of discussing the proper selection of patients for this procedure. The challenge of precisely dissecting between the margins of the dermis and the breast inevitably leaves residual glandular tissue [13]. For tumors located on the surface, the use of this strategy risks leaving an invasive lesion in the skin flap, which will result in the LR of the disease. Although surgical margins should routinely be assessed, the spread of the disease is sometimes discontinuous and may lead to false negatives in intraoperative pathological examinations, especially with ductal carcinoma in situ. Cao et al. evaluated the superficial margins of 168 SSM cases and observed neoplastic involvement in 64 of the cases (38%). Of these cases, 25 exhibited sectioned carcinoma, possibly because they were located very close to the skin. According to the authors, the presence of focally involved anterior margins does not merited re-operation,

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although these margins were associated with an LR rate of 10%, and free margins resulted in an LR rate of only 4% [14].

A number of authors have analysed skin involvement in mastectomy specimens [15-17]. Both the dermis adjacent to the lesion and subdermal lymphatic vessels have been observed to contain neoplastic invasion, and the skin involvement rate ranged from 4.4% to 20% [14, 15]. According to Ho et al. [16], tumor size, skin tethering, and the presence of perineural invasion are the factors most associated with dermal involvement. However, these authors emphasised that clinical signs alone are insufficient to predict skin involvement. Of 30 mastectomy specimens, 5 demonstrated involvement of the skin adjacent to the tumor, and only 3 of these specimens exhibited clinical signs of skin involvement. Wertheim and Ozzello [17] analysed 1,000 mastectomies and reported 101 cases in which the skin was directly compromised by the cancer. Specifically, 29 of these samples showed no signs of dermal involvement during macroscopic examinations. These authors also reported that larger tumors that resulted in nipple and axillary involvement increased the risk of dermal compromise [17]. However, the distance between the tumor and the skin was not assessed.

The present study compared the tumor-skin distance based on preoperative US measurements obtained by the two observers and found very consistent results. Eom et al. [18] measured the tumor-skin distance using US and correlated these distances with the risk of lymph node involvement. Specifically, the authors stated that transducer compression on the skin could affect the distance obtained during US, especially for small breasts [18]. Moreover, the intra-observer and inter-observer agreements were high ($r = 0.99$). Therefore, we believe that obtaining the distance between the tumor and the skin using US is a simple, reliable, and reproducible procedure that will not significantly differ by observer.

To our knowledge, studies that are similar to the present study in which the risk of skin involvement was based on tumor-skin distance have not been published in the literature. Nevertheless, the present study is limited by the small number of cases and the absence of patients with compromised skin in pathological examinations but not in US examinations. The exclusion criteria adopted (indistinct margins lesions and suspected skin infiltration on physical or US examination) may have contributed to this situation.

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