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Impact of BMI on Preoperative Axillary Ultrasound Assessment in Patients With Early Breast Cancer

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Abstract. *Background: The accuracy of axillary ultrasound (AUS) with fine-needle aspiration with varying patient body mass index (BMI) is still unclear. The aim of our study was to evaluate whether the US features of axillary lymph nodes changes with BMI of patients. Patients and Methods: A retrospective review was performed involving 144 out of 270 patients with early breast cancer who underwent breast surgery with sentinel lymph node biopsy. Diagnostic efficacy of AUS in preoperative axillary nodal staging was assessed in relation to BMI. Results: Negative predictive values of AUS for the overweight and obese groups were statistically significantly lower compared to the normal/underweight group (p=0.02 and p=0.003, respectively). Additionally, Spearman's correlation coefficient R between BMI and positive sentinel lymph node biopsy was 0.257, suggesting a significantly positive linear relationship between the two variables in the cohort overall. Conclusion: Our results demonstrate how in our cohort the negative predictive value of AUS was significantly influenced by adipose tissue and that the selection of the most suitable instrumental diagnostic technique might contribute to improving heterogeneous results.*

In 2013 obesity was defined by the American Medical Association as a complex, chronic disease (1). It is the result of complex relationship between genetic, socioeconomic and cultural influences and it is constantly expanding (2). Obesity is also evaluated with the well-known parameter named the body mass index (BMI). In 2016, the International Agency for Research on Cancer found sufficient evidence to support an association between excess body fat in 13 out of 24 cancer sites, including the breast (3-5).

Breast cancer is the most frequent malignant tumor in women, affecting about one in eight women in industrialized countries (6, 7). Overall 5-year survival is closely related to stage at diagnosis. In patients with early-stage tumors, it can reach up to 95%, falling to 84% in those with locally advanced disease and up to 23% in those with metastatic breast cancer (8). Obese patients with breast cancer have a higher risk of developing lymph node metastases and have a worse prognosis than normal weight patients (9).

Over the past two decades, trials have shown that axillary lymph node dissection (ALND) can be safely omitted in patients with early breast cancer with negative sentinel lymph node biopsy (SLNB) (10, 11). Axillary ultrasound (AUS) associated with fine-needle aspiration of suspicious lymph nodes is the gold standard in preoperative staging of the axilla to identify those patients with metastatic axillary lymph nodes who need to directly undergo axillary lymph node dissection (ALND) without SLNB.

It is unclear how the accuracy of both axillary clinical examination and AUS may vary in relation to the patient's BMI. However, a high BMI may interfere with several routine clinical examinations. In particular, a high BMI has been proposed as an independent risk factor for failure of sentinel node mapping (12, 13) even though the differences in the accuracy of axillary physical examination and AUS related to patient BMI are poorly understood and few studies have been published on this topic. As a consequence, these patients would be at higher risk for axillary nodal metastasis on SLNB even with a negative clinical examination and AUS.

The aim of our study was to evaluate if the AUS features of axillary lymph nodes change with BMI of the patients.

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Table I. *Clinical parameters of early breast cancer patients enrolled in our study stratified according to weight (normal, overweight and obese).*

Parameter		BMI			*p*-Value
		Normal	Overweight	Obese	
Age	Median (range)	55 (80-34)	58 (80-34)	62 (85-31)	**0.027**
T Stage, n (%)	T1	38 (61.29%)	27 (58.69%)	27 (75%)	**0.0001**
	T2	24 (38.71%)	19 (41.31%)	9 (25%)	
Type, n (%)	IDC	41 (66.13%)	33 (71.74%)	23 (63.89%)	0.44
	ILC	8 (12.9%)	4 (8.7%)	3 (8.33%)	
	Other	13 (20.97%)	8 (17.39%)	8 (22.22%)	
Subtype, n (%)	Luminal-A	37 (58%)	20 (43%)	22 (60%)	0.79
	Luminal-B	20 (31%)	20 (43%)	11 (30%)	
	HER2+	4 (6%)	3 (7%)	2 (5%)	
	Triple-negative	3 (5%)	3 (7%)	2 (5%)	

IDC: Invasive ductal carcinoma; HER2: human epidermal growth factor receptor 2; ILC: invasive lobular carcinoma. Statistically significant *p*-values are shown in bold ($p \leq 0.05$).

Patients and Methods

After approval of the Institutional Review Board of the University Hospital AUOP Paolo Giaccone of Palermo (IRB49/2019), the records of 270 consecutive patients who underwent surgery for invasive breast carcinoma at our Institution between January 2018 to June 2020 were retrospectively analyzed.

All patients with a histologically confirmed diagnosis of clinical early-stage breast cancer, cT1 or cT2 according to the TNM staging system (14), were selected and considered eligible for our study. Exclusion criteria of the study included previous neoadjuvant chemotherapy and previous ipsilateral axillary surgery.

The preoperative work-up consisted of physical examination, mammography and AUS for each patient, in order to determine the local extent of the disease. Any suspicious lesion detected in routine pre-operative evaluation by mammography or ultrasonography was assessed by needle core biopsy or fine-needle aspiration cytology (15). At the end of the preoperative diagnostic work-up, 126 patients were excluded because of metastatic axillary lymph nodes (cN1). Therefore, 144 patients were included in the study. The patients were stratified according to the BMI. The BMI was calculated as the weight divided by the square of the height in meters and was further categorized according to the World Health Organization criteria: Normal/underweight (BMI ≤25 kg/m^2), overweight (BMI 25-30 kg/m^2) and obese (BMI ≥30 kg/m^2) (16). Histological subtypes were categorized as ductal, lobular and other. The clinical and histopathological characteristics of the overall study population are summarized in Table I.

Axillary ultrasound. All the patients underwent pre-operative AUS to assess the morphological features of ipsilateral lymph nodes. Ultrasonography was performed using a 12-15 MHz linear transducer. Cortical thickening of the lymph node (defined as cortical thickness in excess of 3 mm), loss of fatty hilum and the presence of non-hilar blood flow were considered predictive of metastatic involvement of the lymph nodes. Moreover, a loss of ovality of lymph nodes at AUS was considered predictive of lymph node involvement. All suspicious lymph nodes underwent fine-needle aspiration cytology.

SLN mapping. All patients underwent a preoperative lymphoscintigraphy by means of a sub-dermal peri-areolar injection of ^{99}Tc-labeled human albumin colloid (10-12 MBq of ^{99m}Tc in 0.2 ml of albumin colloid), 18-24 hours before surgery (17). SLN was identified by obtaining scintigraphy images 15 to 180 minutes after the administration of the radiotracer and the cutaneous projection of the SLN was marked with indelible ink for identification. For the intraoperative identification of the SLN, a radio-guided surgical probe was used. In those cases, where the radio-guided surgical probe detected a weak radiotracer signal, a sub-areolar injection of 0.5-0.8 ml of vital stain about 10-15 minutes before surgery was performed.

Pathological examination. Nodes with a diameter of more than 5 mm were bisected longitudinally and frozen. SLNs with a diameter of less than 5 mm were frozen intact. The remaining tissue was formalin-fixed, paraffin-embedded and entirely sectioned at 100-μm intervals for the definitive histopathological examination. The presence of neoplastic cells was classified as micrometastases (≤2 mm), macrometastases (≥2 mm); single tumor cells or small clusters of cells (<0.2 mm) were defined as isolated tumor cells (18, 19).

Surgical procedure. All patients with SLN macrometastasis at frozen section immediately underwent completion ALND. In cases of SLN which were negative at frozen section but positive for macrometastases at definitive histopathological examination, the patients underwent a delayed completion ALND.

No completion ALND was performed in women with metastasis-free SLN, isolated tumor cells nor in patients with SLN micrometastases, either at intraoperative or at final histopathological examination.

Statistical analysis. Comparing the diagnostic efficacy of AUS and SNB, we considered: True negative (TN) as the number of patients with metastases not found either during AUS or after SLNB; and false-negative (FN) as the number of patients with positive SLNB and negative AUS. The negative predictive value (NPV) was calculated as TN/(TN+FN), and represents the proportion of AUS-negative patients with negative SNB. Analysis of variance (ANOVA) test was used to evaluate the difference of the clinical characteristics of the

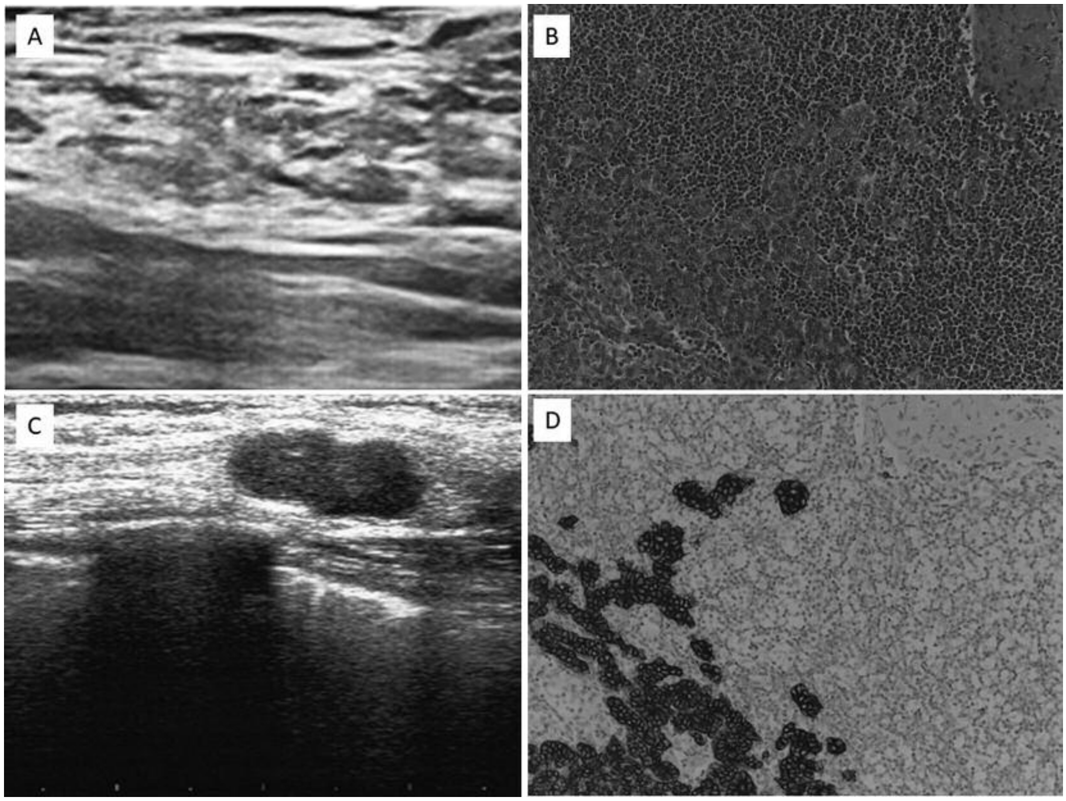

Figure 1. *Axillary ultrasound (AUS) and histopathological reports in an overweight/obese patient. Lymph node negative on AUS (A) diagnosed as metastasis at the pathological report (B). Lymph node positive on AUS (C) confirmed as metastasis at the pathological report (D). Hematoxylin and eosin staining, 200×.*

patients. The Mann–Whitney *U*-test was used for intergroup comparisons of two independent samples, while the chi-square test was used for categorical variables, and in particular to evaluate the FN and NPV differences, according to BMI strata. Spearman's correlation coefficient was calculated to evaluate the linear correlation between variables. All values were considered statistically significant when $p \leq 0.05$. Data were generated using MedCalc software for Windows, version 18.2.1 (MedCalc Software, Ostend, Belgium).

Results

The average patient age was 59 (range=31-85 years). All 144 tumors were ≤3 cm (pT1-pT2). Patients and tumor characteristics are shown in detail in Table I. No significant difference in the average age was detected comparing the three BMI groups. Furthermore, according to the Molecular Subtypes of Breast Cancer classification (20), our study population included 73/138 (52.9%) luminal-A cases, 54/138 (39.1%) luminal-B, 7/138 (5%) triple-negative and 4/138 (2.8%) human epidermal growth factor receptor 2 (HER2)-enriched. Interestingly, patients with luminal-A disease were significantly more represented in the normal/underweight cohort ($p=0.04$) when compared to the overweight group. Six patients were considered as having missing data.

Among the 144 women included in the study, 62 were considered normal/underweight, 46 overweight and 36 obese. The SLN was positive for metastasis in 36 patients in the overall study population (25%). Almost all patients in the three BMI groups underwent breast-conserving surgery (98.6%). Synchronous completion ALND was performed in 26 patients (18%). The AUS FN rate for the entire series was 25% (36/144), in which the SLN was positive for metastasis (Figure 1). According to BMI stratification, the AUS FN rates were 12.1% (8/62) for the normal/underweight group, 30.4% (14/46) for the overweight group and 38.9% (14/36) for the obese group, respectively. NPVs were 87.1% (54/62), 69.5% (32/46) and 61.1% (22/36), respectively. In our study, in accordance with our hypothesis, NPV values for the overweight and obese groups were significant lower compared to the normal/underweight group ($p=0.02$ and $p=0.003$, respectively). Additionally, Spearman's correlation coefficient R between BMI and positive SLNB was 0.257, suggesting a significant ($p=0.001$) weakly positive linear

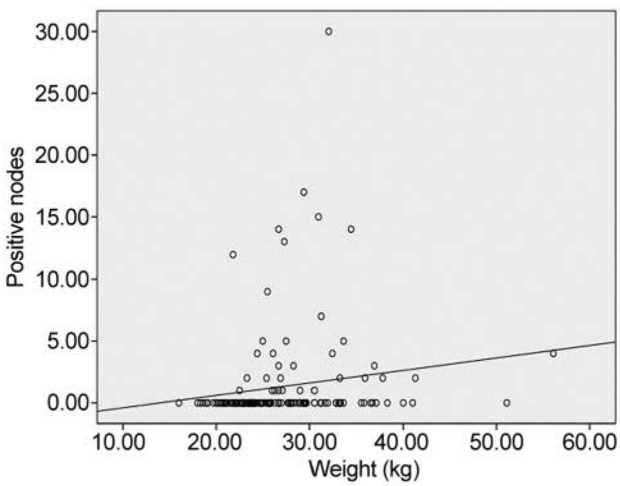

Figure 2. *Association between patient weight and number of positive nodes retrieved al the final histological examination (p=0.0001). Spearman's correlation coefficient was 0.257.*

relationship between the two variables considering the entire cohort (Figure 2).

Discussion

In the past decades, surgical treatment for breast cancer has evolved from the Halstead radical mastectomy to breast conservation or skin-sparing mastectomy with immediate reconstruction. ALN status remains the most important prognostic factor, despite the implementation of new genomic analyses and advances in routine pathology, and frequently affects the choice of therapy (21, 22). As an alternative to complete ALND, lymphatic mapping with SLNB, has been applied to patients with breast cancer.

Axillary adenopathy with suspicious ultrasound characteristics and positive needle biopsy allocates patients to neoadjuvant chemotherapy or upfront ALND. Patients with no suspicious nodes on AUS imaging and those with negative AUS-guided biopsy might even be spared the SLNB procedure.

Recent studies have examined the accuracy of some diagnostic methods to detect axilla-limited disease. A normal ALN usually exhibits an ovular shape, uniformly hypoechoic cortex, with a maximal thickness of less than 3 mm, smooth margins and intact central fatty hilum. On the other hand, suspicious findings of ALN include, irregular margins and encroachment or displacement of the fatty hilum, cortical thickness in excess of 3 mm and eccentric thickening. However, it has been demonstrated that the size of the lymph node on imaging cannot reliably help distinguish between normal and abnormal nodes (23). Focal morphological changes of ALN are the most important features differentiating benign from metastatic lymph nodes. For example, the presence of an asymmetric focal hypoechoic node with cortical lobulation or a completely hypoechoic node can be a guideline for performing fine-needle aspiration cytology in the preoperative staging of breast cancer (24).

A recent study has showed that cortical thickness greater than 3.5 mm in the most suspicious node diagnosed three or more positive axillary nodes for which ALND should be performed, with high sensitivity and specificity of 75.6% and 82.7%, respectively (25).

In 2016, Dihge *et al*. explained how the accuracy of AUS examination is influenced by BMI (26). They assessed the performance of AUS in obese (BMI ≥30 kg/m^2) and non-obese patients. The performance of US alone was significantly improved both in specificity and sensitivity in obese patients rather than those with a BMI of less than <30 kg/m^2. For AUS-guided biopsy, no difference in performance was observed with respect to BMI.

The impact of obesity on the accuracy of preoperative AUS was also assessed by Shah *et al*. (27), who found similar sensitivity for detecting nodal metastases in obese and non-obese patients, while the specificity was superior in obese patients. The same authors suggested that while normal ALNs may be more challenging to identify in obese patients, abnormal hypoechoic nodes with thickened cortices are still readily differentiated from the surrounding fat. The clinical implication is that AUS is also a feasible diagnostic method in primary breast cancer in obese patients. Contrary to these findings, in our study, only 12.1% of the cases with positive axillary lymph nodes in the normal weight group were not preoperatively diagnosed. This percentage was increased to 30.4% and 38.9% in the overweight and obese groups, respectively.

The accumulation of lipids within the lymph node can cause both an increase in volume and eco-structural changes that usually occur in chronic reactive and regressing lymphadenopathy. This modification, known as lipoplastic lymphadenopathy, can cause a discrepancy in its final stages between clinical evidence and US evaluation of the lymph node due to the replacement of the entire lymph node parenchyma with adipose tissue. Furthermore, in regions particularly rich in subcutaneous fat such as the axilla, a lymph node totally replaced by fat can also simulate a lipoma, assuming the same oval shape and echoic structure of normal fat, resulting in a FN US examination (28).

Finally, according to some, the abundant adipose tissue present in the lymph nodes of obese individuals can be the cause of a reduced lymphatic flow, with consequent greater mapping error than in the non-obese population (13).

Conclusion

Our results demonstrate how the NPV of preoperative AUS can be significantly influenced by adipose tissue. Despite some limitations, such as the retrospective nature of our data and the lack of node-positive patients because of the exclusion of those treated with neoadjuvant therapy, our study shows that the AUS NPV is significantly dependent on BMI in women with early-stage breast cancer. Further prospective studies will better identify in which categories of patients the NPV of preoperative AUS might be improved by also evaluating the molecular profile of the tumor.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

IM: Data analysis and interpretation, statistical analysis, article preparation. AG: Quality control of data and algorithms, data analysis and interpretation, statistical analysis. GG: Article preparation and editing. SL: Data acquisition, article preparation and editing. ML: Study concepts, study design, article review. AR: Study and design, article review. SV: Data acquisition, article editing. CC: Study concepts and design, quality control of data and algorithms, article review.

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