IMAGING AND PATHOLOGY FEATURES TO PREDICT AXILLARY TUMOUR LOAD IN BREAST CANCER

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RUNNING TITLE

Axillary ultrasound and tumour load

ABSTRACT

AIM: The objective of our study was to investigate if imaging and pathology features could help in identifying high axillary tumour burden (ATB) in breast cancer patients, in order to individualize decisions on axillary lymph node (ALN) dissection (ALND).

METHODS: We retrospectively analysed patients treated in our Unit between 2011 and 2014 for whom surgery including ALND was the upfront treatment. We divided patients in two groups: low ATB (LATB) if ≤ 2 ALN were infiltrated and high ATB (HATB) if >2 ALN were infiltrated. Several imaging and pathology features were evaluated as predictors of ATB.

RESULTS: We included 105 patients in the study. Axillary ultrasound (AUS) features associated with HATB were any sign of ALN infiltration (76 vs 24%, p= 0.027) and >2 ALN described as suspicious (73% vs 27%, p=0.018); however, when the AUS described ≤2 suspicious ALN, 39% of these patients had HATB. The magnetic resonance imaging (MRI) feature associated with HATB was any sign of ALN infiltration (48% vs 52%, p=0.031). Regarding pathology features, a positive preoperative ALN cytology or biopsy (PPCB) was associated with HATB (53% vs 47%, p=0.008); p53 positivity (80% vs20%) and high histological grade (68% vs 32%) correlated with LATB (p=0.05 and p=0.02 respectively). In the multivariate analysis, only a PPCB was associated with HATB (p= 0.038).

CONCLUSIONS: AUS was useful detecting HATB but it performed worse identifying patients with LATB. Similar to other studies, proving axillary

infiltration with an AUS directed cytology or biopsy is the most important factor predicting HATB.

Key words: axillary tumor load, axillary ultrasound, breast cancer, p53, positive preoperative citology or biopsy

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MAIN DOCUMENT

INTRODUCTION

Axillary staging in breast cancer is essential for prognosis and in order to plan the treatment, but its management remains controversial. When the ACOSOG Z0011[1] and the Amaros[2] trials were published in the beginnings of 10's decade, several Breast Units stopped performing axillary lymph node dissection (ALND) in patients with one or two affected sentinel lymph nodes (SLN) as both studies proved that ALND was not superior to direct or indirect axillary irradiation. Since those trials appeared, several systematic reviews and meta-analysis supported these data[3,4].

In the other hand, a recent meta-analysis of randomized trials of ALND vs no ALND showed an improvement in overall survival (OS) and disease free survival (DFS) for patients submitted to ALND[5]. Also importantly, a randomized trial reported that irradiation of lymph node areas improved DFS and distant disease free survival (DDFS)[6]. These studies suggested that, at least in some

patients, treating the lymph node neoplastic burden by surgery or radiation could be helpful in achieving the best results in breast cancer treatment.

As a consequence of all these studies it is highly suggested that patients with a low neoplastic axillary burden could safely spare ALND as systemic treatments and indirect or direct radiotherapy would be adequate to treat the regional spread of the disease[7]. Patients with a high axillary tumour burden, especially those not responding to systemic treatments, could be the ones candidate to ALND.

The aim of our study was to evaluate if the information obtained through preoperative axillary ultrasound (AUS) and magnetic resonance imaging (MRI) reports, together with the pathology features of the tumour obtained in the diagnostic biopsy, could be useful to estimate the axillary tumour burden in patients with an infiltrated axilla; if reliable enough they could be useful to decide the best therapeutic option.

MATERIAL AND METHODS:

We planned a retrospective cohort study. Female patients with a first diagnose of invasive carcinoma treated in our Breast Functional Unit between July 2011 and December 2014 were identified from the Tumour Registry of Hospital del

Mar, prospectively maintained by the Epidemiology Department staff. Patients included in the study were those with ALN infiltration for who surgery including ALND was the first treatment, so that the pathology report quantified axillary neoplastic infiltration.

Patients who received systemic neoadyuvant treatment were excluded. In the Breast Cancer Unit of our institution some criteria are established to recommend neoadyuvant treatment in locally advanced operable carcinomas (some stages I, stages II-III) which could obtain a surgical conservative benefit as well as for testing a pathological complete response that will improve the prognosis and survival.

We constructed a new database with the Microsoft Access application, including Tumour Registry data prospectively obtained and new data retrospectively obtained that were necessary for the study. The prospectively collected data included patient's age, diagnostic biopsy date, diagnostic biopsy data, type of surgery performed, and histological and molecular data of the surgical specimen. The retrospectively collected data were obtained reviewing the clinical records and included imaging features described in the imaging reports and indication leading to ALND for each patient. The indications to perform an ALND during the study period included staging purposes -multicentric disease, T3 or T4 tumour-, preoperative positive ALN cytology or biopsy (PPCB), and a positive SLN.

Pathology Processing

Processing of breast surgery specimens followed the standardized protocol of our institution. Briefly, all specimens were inked and sectioned at 3 mm intervals and then fixed in 10% neutral buffered formalin for a period ranging from 24 to 48 hours. If possible, the entire specimen was submitted for paraffin processing. When not possible, the specimen was sampled through systematic mapping. H&E slides were evaluated. If carcinoma was present in only one section, its size was measured in this single slide. When multiple foci affecting multiple sections were found –that is, multifocal disease- carcinoma size was estimated adding the measurements of each focus taking into account the diagram of the specimen, the location of the involved blocks and the thickness of the sample submitted in each block. If re-excision was necessary because of involved margins, pathologists used the newly excised biopsy cavity as a landmark for additional size estimation. In addition to lesion extent, pathology type, histological grade and presence/absence of comedonecrosis were systematically reported. For SLN and ALND histological examination, routine technique was also developed. SLN were examined by serial sectioning; they were cut into 2-mm slices and for each slice, six sections of 4 μm were obtained, leaving 20 μm of separation between them. Three alternate sections were stained with routine hematoxylin–eosin (HE) and if negative, the remnant sections were studied immunohistochemically using cytokeratin. For ALND, 3-mm slices were obtained for each node and for each slice a single 4-μm section was stained with routine HE.

Following our Pathology department protocol, immunohistochemical analysis was systematically performed including estrogen receptor (ER), progesterone receptor (PR), p53 expression (p53), Her2-Neu expression (Her-2 Neu) and Ki67 proliferation index (ki67). ER, PR and p53 were reported in a semi-quantitative scale describing percentage of positive cells and intensity of staining. Ki 67 was reported describing the percentage of positive cells. Her-2-Neu expression by immunohistochemistry was reported as negative (0,1+), borderline (2+) or positive (3+). Specimens with Her-2-Neu borderline inmnohistochemistry expression were processed through in situ hybridation (ISH) to rule out Her-2-Neu gene amplification.

Statistical Analysis

We categorized patients in two groups depending on the number of lymph nodes found to be affected in the pathology specimen of the ALND: patients with a low axillary tumour burden (LATB) if only 1 or 2 nodes were affected and patients with a high axillary tumour burden (HATB) if there were more than 2. We chose this cut-off because it was the inclusion criteria used in Z0011 trial[1]. Both groups were compared regarding age, tumour size, number of lymph nodes retrieved in the ALND and number of ALN infiltrated. The imaging features identified in imaging reports and evaluated as axillary tumour burden predictors were: AUS reporting suspected ALN infiltration, number of lymph

nodes suspected to be infiltrated in AUS, type of features suggesting infiltration in AUS - cortical thickening of 3 mm or more, lymph node structure loss and extracapsular neoplastic infiltration- and axillary infiltration suspected in MRI (cortical thickening of 3mm or more, high activity, lymph node structure loss). The pathology features evaluated as axillary tumour burden predictors were a PPCB, size of the main tumour (pT) breast cancer pathology subtypes (infiltrating ductal carcinoma, lobular infiltrating carcinoma or other), breast cancer immunophenotypes (luminal A, luminal B, Her2 enriched or triple negative), histological grade, number of neoplastic foci (unifocal, multifocal or multicentric neoplasia), ER expression, PR expression; Her2 positivity showed by immunohistochemistry or by ISH, p53 expression, Ki67 expression and lymphovascular infiltration.

We performed the statistical analysis with PAWS program 18th version (IBM^{R} SPSS^{R} software). Continuous data were compared by t-Student and U Mann-Whitney. Categorical data were compared with Chi2 and Fisher tests. We used a ROC curve regarding to the tumour size, a continuous variable. For all studies we considered a bilateral statistical significance if p-value was $\leq$0.05.

Ethical approval

This study obtained approval by the Ethical Committee for Clinical Research of our research centre, the *Institut Mar d'Investigacions Mèdiques* (IMIM). The study followed the recommendations of Helsinki Declaration.

RESULTS:

During the study period, 244 patients with infiltrated ALN were submitted to ALND in our unit; 139 patients who received systemic neoadyuvant treatment were excluded, leaving 105 patients for the study. In 15 patients ALND was made for staging purposes, in 28 patients because of a positive SN and in 62 patients because of a PPCB - positive cytology in 56 and positive core biopsy in 6-. Within these 105 patients, 60 were classified as LATB group and 45 as HATB group. **Figure 1** summarizes the recruitment flow of the study.

The characteristics of each group regarding age, average tumour size, number of lymph nodes retrieved in the ALND and numbers of infiltrated lymph nodes are summarized in **table 1**. There were no significant differences regarding age, number of lymph nodes retrieved and tumour size between the two groups, even though tumour size tended to be higher in the HATB group. As expected, the number of infiltrated lymph nodes was significantly higher in the HATB than in the LATB group.

AUS report described lymph nodes as being suspicious in 76 of 105 patients. The average number of suspicious nodes was 1.22 (SD 1.21) in LATB group and 2.17 (SD 1.72) in HATB group; this difference was significant (Mann-Whitney U p=0.003). Features of the suspicious nodes were described in 58 patients: cortical thickening in 40 (38.1%), lymph node structure loss in 14 (13.3%) and extracapsular neoplastic extension in 4 (3.8%) (**figure 2**). The results of the bivariate analysis of the imaging features evaluated as predictors of axillary tumour load are summarized in **table 2**. In the HATB group, suspicion of ALN infiltration and >2 ALN suspicious of being infiltrated was described more frequently and the difference was significant. Of note, when the AUS report described $\leq$2 ALN infiltrated, 39% of these patients had HATB. Regarding the description of features suggesting infiltration in the AUS, there were no statistical differences in any of the three descriptions evaluated; lymph node structure loss tended to be more frequently described in the HATB group. Regarding MRI, suspected ALN infiltration was more frequently reported in the HATB group and the difference was also significant (table 2).

Table 3 summarizes the bivariate analysis of the pathology features evaluated. A PPCB, P53 positivity and histological grade showed significant differences between the two groups. A PPCB was significantly more frequently found in the HATB group. P53 was positive in 14.2% of the samples (N= 14) and its positivity was significantly associated with the LATB group. Regarding histological grade, high tumour grade was significantly associated with the

LATB group also. None of the other pathology features showed significant differences between the two groups.

In the multivariate analysis the only factor that kept its significance as a predictor of HATB was a PPCB (p=0.038); p53 positivity was marginally significant (p=0.068) as a predictor of LATB (**table 4**).

DISCUSSION:

The main objective in the current treatment of breast cancer is to achieve the best overall and disease free survival with minimum secondary effects. In this sense, Z0011 trial[1] and other research trials[8,9] observed that it was possible to spare ALND in those patients with no suspicious ALN in clinical exploration and only 1 or 2 positive SLN.

Preoperative AUS was not systematically used in patients included in the Z0011 trial; however, it is a technique systematically used in many breast units as it is in ours. Upon the results of the present study it could be suggested that AUS performs good predicting HATB but it could be suboptimal predicting infiltration of only 1 or 2 ALN: in 39% of cases where AUS predicted a LATB the final pathologic exam confirmed more than 2 nodes with neoplastic disease. When

axillary disease is low, radiological techniques have less precision in detecting ALN infiltration, and features of suspicious nodes by AUS could be more easily disregarded. This is also confirmed in other previous studies[10,11,12.].

As a consequence of the Z0011 trial results, some authors suggested that breast centers performing systematic AUS for breast cancer preoperative staging could be overtreating patients. The argument for this statement would be that AUS could be able to detect very low axillary neoplastic burden that physical exploration would not detect; patients that would be submitted to SN and for who ALND could be spared following the Z0011 criteria, would be submitted to a direct ALND in these centers performing preoperative AUS[13].

This affirmation is not supported by the results of our research neither the results of other studies: a PPCB is a proven risk factor for a high axillary tumour burden[14,15]. New ongoing trials may add information on advantages and disadvantages of this approach, in order to clarify the utility of AUS[16].

In our study a MRI report that informed of suspected axillary neoplastic infiltration was significantly associated with HATB in the bivariate analysis but it lost its significance in the multivariate analysis. It remains to be established the role of preoperative axillary MRI, if any, in this setting. In our study, these results should be taken with caution because of the lower number of cases

where MRI was performed comparing with AUS. The combination of both techniques could not also be calculated because of the small sample.

We also evaluated pathology features to predict axillary tumour load as it is well known that different breast cancer inmunophenotypes show different metastatic patterns[17,18]. We concluded that p53 positivity burden together with a high histological grade were associated with a low axillary tumour load. This conclusion is in concordance with the results of a previous research of our group[19]. Positive p53 breast cancers, although its aggressiveness, could explain a low axillary involvement because they would mainly start hematological dissemination during tumour growth[20]. In the present study the differences were significant in the bivariate analysis but not in the multivariate analysis; new current studies in our institution with more patients should clarify if these pathology features could be of any help when evaluating preoperatively the axillary tumour load.

The multivariate analysis included all the imaging and pathology features evaluated and the only feature that kept its significance was the existence of a PPCB; this was associated with the HATB group. As said, this is concordance with many other studies and supports the indication made by many international guidelines recommending ALND in this setting[21].

Our study has some limitations. First, it is a single institution analysis with a limited number of patients. Second, ALND was realized because of different indications, so the results regarding AUS should be analysed independently[22]. Third, during the study period the AUS report was not systematized and as a consequence, the imaging features evaluated could not be retrieved for all the patients evaluated and an information bias could not be discarded.

In conclusion, our study showed that in our institution AUS performed better predicting HATB than predicting LATB. It also suggested that p53 positivity and histological grade could be of some help when trying to predict LATB. In concordance with other studies, a PPCB was significantly associated with HATB. Future prospective studies are needed to determine if surgical decisions should be individualized depending on the pathology features and the axillary evaluation through imaging. Meanwhile, it is reasonable to perform ALND when a PPCB is obtained as the evidence in nowadays supports that the probability of HATB is high.

DISCLOSURE:

The authors refer no conflict of interest to declare.

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Figure 1 legend:

ALN: axillary lymph node

ALND: axillary lymph node dissection

SN: sentinel node

FNA: fine needle aspiration

LATB: low axillary tumour burden

HATB: high axillary tumour burden

FIGURE 1: RECRUITMENT FLOW

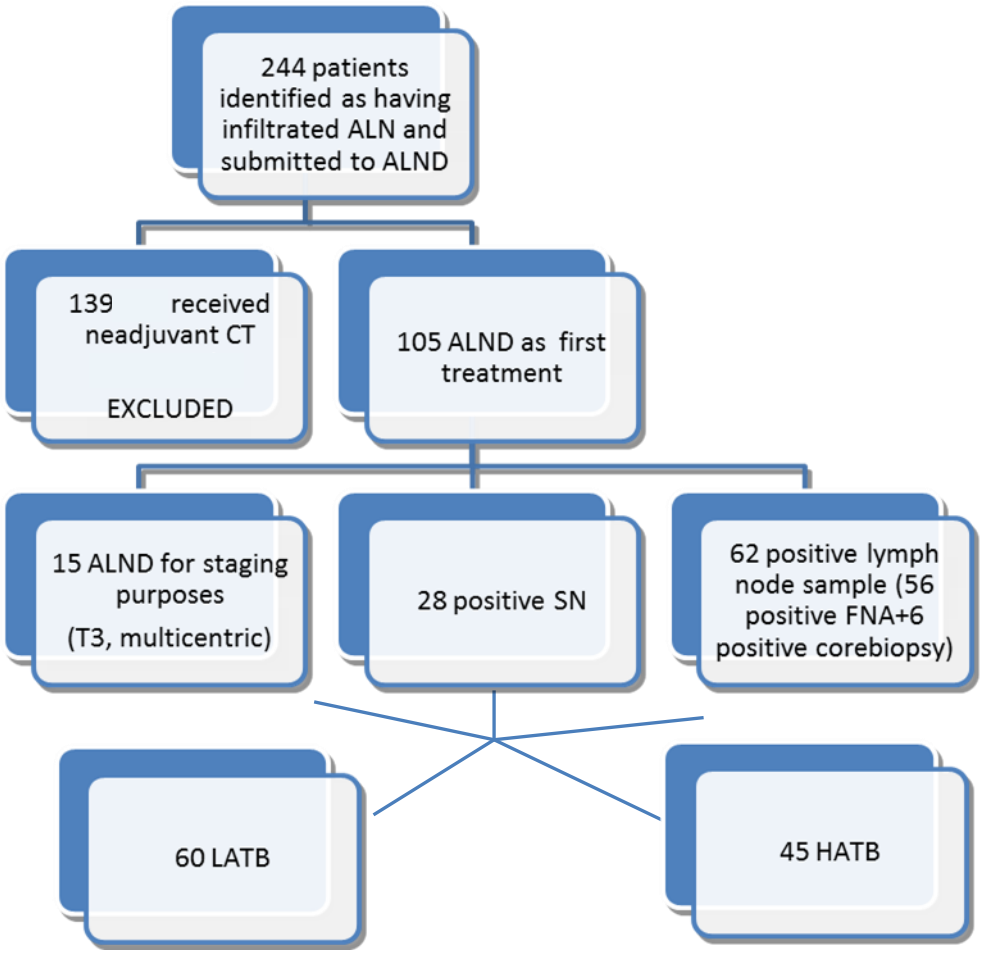

Figure 2: SUSPICIOUS NODE BY AXILLARY ULTRASOUND

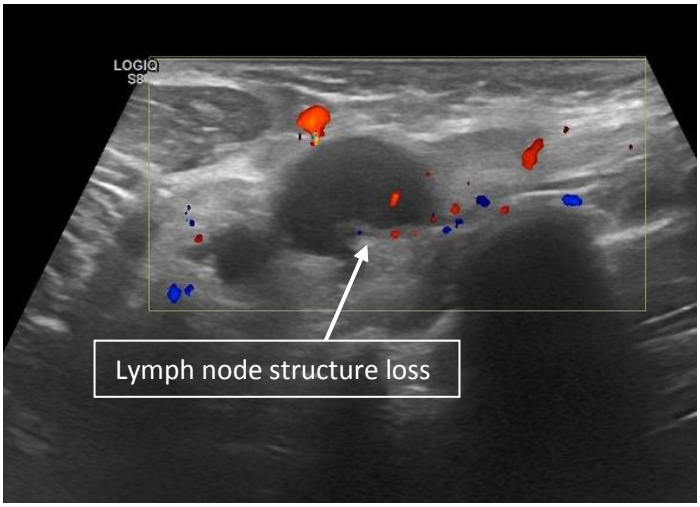

Table 1 : Description and comparison of features of both groups.

	LATB n=60	HATB n=45	p
Age	58.4(14.56)	61.3(14.07)	0.46
ALN retrieved in the ALND	17.9(7.70)	15.7(9.34)	0.45
Tumour size (mm)	26(17.90)	30(20.87)	0.29
Number of infiltrated ALN	1.5 (0.732)	8.8 (5.833)	**<0.001**

LATB: Low axillary tumour burden
HATB: High axillary tumour burden
ALN: Axillary lymph nodes
ALND: Axillary lymph nodes dissection

Table 2: Imaging features and axillary tumour burden

	LATB	HATB	p
Suspected axillary node infiltration reported in first US			
- No	26 (70%)	11 (30%)	**0.027**
- Yes	31 (48%)	34 (52%)	
Number of nodes suspicious of being infiltrated			
- 1 o 2	37 (61%)	24 (39%)	**0.018**
- >2	4 (27%)	11 (73%)	
Lymph node cortical thickening >3mm			
- Not reported	36 (55%)	29 (45%)	0.643
- Reported	24 (60%)	16 (40%)	
Lymph node structure loss			
- No	55 (68%)	36 (32%)	0.082
-Yes	5 (36%)	9 (64%)	
Suspected extracapsular neoplastic infiltration			
- No	58 (57%)	43 (43%)	0.769
-Yes	2 (50%)	2 (50%)	
Suspected axillary lymph node infiltration reported in the MRI			
- No	21 (72%)	8 (28%)	**0.031**
- Yes	30 (48%)	32 (52%)	

LATB: low axillary tumour burden

HATB: High axillary tumour burden

Table 3: Pathology features and axillary tumour burden

PATHOLOGY FEATURES	LATB	HATB	p
PPCB			
- Yes	30 (47%)	34 (53%)	**0.008**
- No	30 (73%)	11 (27%)	
TUMOUR SIZE			
pT1	32 (60%)	22 (40%)	
pT2	22(58%)	16(42%)	0.530
pT3	5 (42%)	7 (58%)	
PATHOLOGY SUBTYPE			
Ductal Infiltrating carcinoma	48 (59%)	33 (41%)	
Lobulillar infiltrating carcinoma	4 (33%)	8 (67%)	0.19
Other	8 (67%)	4 (33%)	
IMMUNOPHENOTYPES			
-Luminal A	15 (56%)	12 (44%)	
-Luminal B	34 (57%)	26 (43%)	
-HER-2 ENRICHED	1 (33%)	2 (67%)	
-BASAL LIKE	6 (60%)	4 (40%)	0.87
HISTOLOGICAL GRADE			
I	4 (27%)	11 (73%)	
II	26 (59%)	18 (41%)	
III	21 (68%)	10 (32%)	**0.02**
NUMBER OF FOCI			
Unifocal	34 (53%)	30 (47%)	0.38
Multifocal/ Multicentric	23 (62%)	14(38%)	
ER EXPRESSION			
-negative	7 (58%)	5(42%)	0.929
-positive	53 (57%)	40 (43%)	
PR EXPRESSION			
-negative	14 (58%)	10 (42%)	0.89
-positive	46 (57%)	35 (43%)	
HER 2			
-negative	46 (55%)	37 (45%)	0.48
-positive	11 (65%)	6 (35%)	
P53			
-Positive (10% o +)	12 (80%)	3 (20%)	**0.05**
-Negative (<10%)	48 (53%)	42 (47%)	
Ki67			
<15%	14 (49%)	15 (51%)	
>14%	46 (60%)	30 (40%)	0.257
LYMPHOVASCULAR INFILTRATION			
No	34 (64%)	19 (36%)	0.119
Yes	25 (49%)	26 (51%)	

LATB: Low axillary tumour burden HATB: high axillary tumour burden

PPCB: Preoperative positive axillary lymph node citology or biopsy

Table 4: Pathology features and High axillary tumour burden – Multivariate analysis

PATHOLOGY FEATURES	p
PPCB	**0.038**
IMMUNOPHENOTYPES	0.277
HISTOLOGICAL GRADE	0.458
P53	0.063
SUSPECTED AXILLARY NODE INFILTRATION REPORTED IN AUS	0.228
SUSPECTED AXILLARY NODE INFILTRATION REPORTED IN MRI	0.514