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No Relationship Between Total Lymph Node Tumor Burden Using Osna and The Decision to Perform and Axillary Lymphadenectomy in Early Breast Cancer

Lloro PC[1], Garnica MDR[1], Jimenez BS[1], Lobalzo SR[2], Tudela AC[3], Calleja AJR[4], Ruiz FR[1] and Leo JCMD[1*]

[1]Obstetricia y Ginecología Hospital Universitario Costa del Sol.

[2]Área integrada de Gestión Laboratorio de Análisis Clínicos y Anatomía Patológica Obstetricia y Ginecología Hospital Universitario Costa del Sol.

[3]Oncología radioterápica Hospital Clínico Universitario Virgen de la Victoria.

[4]Unidad de Investigación e Innovación. Hospital Universitario Costa del Sol

[*]Corresponding author:

José C Maañón di Leo,
Obstetricia y Ginecología Hospital Universitario Costa del Sol, Spain

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One Step Nucleic Acid Amplification; Positive sentinel node; Axillary lymphadenectomy

1. Abstract

1.1. Purpose: This study intends to determine the correlation between total tumor load [TTL] analyzed by One Step Nucleic Acid Amplification [OSNA] and the clinical outcomes obtained in our clinical practice, and whether TTL is a useful tool for selecting patients who should undergo axillary lymphadenectomy

1.2. Methodology: The study has a retrospective cohort design, carried out at the Costa de Sol Hospital on 92 patients with [GC+] analyzed by OSNA, between 2012 and 2017.

1.3. Results: Survival analysis was performed by classifying patients into micrometastatic, macrometastatic with <25K copies and macrometastatic with >25Kcopies, with no statistical significance found between the groups [long-range test 0.266]

1.4. Conclusion: The recommendation of axillary lymphadenectomy [ALND] in clinically [or radiologically] negative axilla cases with high tumor burden determined by OSNA does not support data from aur studio.

1.5. Statements and Declarations: Authors declare that they have no financial or non-financial interests that are directly or indirectly related to the work submitted for publication.

2. Purpose

Some Scientific Societies have included in their recommendations the use of the One Step Nucleic Acid Amplification [OSNA] method and total tumour load [TTL] to select patients with early breast cancer to perform axillary lymphadenectomy [ALND] [1] in patients undergoing breast conservative surgery. Thus, the TTL, defined as the CK19 mRNA copy number, is the decisive criterion for the indication of lymphadenectomy, regardless of the number of metastatic nodes.

This means that in certain situations the OSNA method and TTL prevail over the de-escalation criteria for performing a ALND [2-4]. The Z0011 [2] study has demonstrated [with more than 10 years of follow-up, and also with worldwide clinical application], an axillary residual percentage after sentinel lymph node biopsy of 27%, and yet a percentage of axillary recurrences similar to lymphadenectomy. At the Breast Unit of the Costa de Sol University Hospital, we use the OSNA method to classify patients undergoing sentinel lymph node biopsy [SLNB] into lymph nodes with isolated tumour cells, micro-metastatic and macro-metastatic. On the other hand, in patients undergoing conservative surgery and affected lymph nodes, we followed the international guidelines and inclusion criteria of the Z0011 study. This study intends to determine the correlation between TTL and the clinical outcomes obtained in our clinical practice, and whether TTL is a useful tool for selecting patients who should undergo axillary lymphadenectomy.

3. Methods

The study has a retrospective cohort design, carried out at the Costa de Sol Hospital on 92 patients with positive sentinel lymph node [SLN+] analysed by OSNA, between 2012 and 2017, which allows a long follow-up of those who met ACOSOG Z0011 criteria and were not subjected to an ALND. The inclusion criteria [ACOSOG Z0011] were: conservative surgery, T1-T2 [up to 5 cm], clinical N0, no more than 2 nodes with macro metastases in the intraoperative outcome, patient who will receive complementary radiotherapy on breast volume, patient not undergoing axillary lymphadenectomy, no neoadjuvant chemotherapy, and intraoperative study using the OSNA method.

The following exclusion criteria were taken: patient undergoing axillary lymphadenectomy, intraoperative study using a method other than OSNA, and TTL of less than 250 copies [isolated tumour cells]. Pathologic examination of the sentinel lymph node was performed intraoperatively. Once the adipose tissue lymph node has been dissected, an imprinting cytology is performed before homogenizing it for study by molecular technique and the perinodal fat is included in paraffin for delayed histological study. The study is based on the mRNA amplification analysis of cytokeratin 19 and is performed using the molecular technique OSNA Sysmex. Descriptive analysis was performed using measures of central tendency and dispersion for quantitative variables, and frequency distribution for qualitative variables. To assess differences between groups, mRNA accounts were dichotomized with a cut-off point of 25,000 copies. The chi-square test was used for qualitative variables, and Student's T-test for quantitative variables. The patients classified by type of metastasis and number of copies were evaluated using the Kaplan-Meier method, taking as an adjustment variable the patients classified by type of metastasis and number of copies, assessing differences using the Log-Rank test. In the different analyses, the level of statistical significance was established at $p<0.05$. SPSS v28 software was used.

The median number of sentinel nodes obtained by the procedure was 2 nodes, with a median number of positive nodes of 1 [limits 1 -5] Table I. All patients met the criteria of the Z0011 study [Table 1].

55 patients were classified, using the OSNA method, as micro-metastatic, while 37 were classified as macro-metastatic. Using total tumor burden as a parameter, 7 of the patients classified as macrometastatic had less than 25K copies, and 30 of the patients showed more than 25K copies. In the unvariant analysis, taking as the response variable the OSNA counts [<25000 /=>25000], nor age [p=0.739], pathological tumour size [p=0.236], menopausal status [p=0.983], histological grade [p=0.933], Ki 67 [p=0.917], oestrogen receptors [p=0.420], progesterone receptors [p=0.314], number of affected lymph nodes [p=0.180], showed statistical association. Only the presence of vascular lymph invasion showed a statistical association [p=0.05] in the analysis. To perform the survival analysis, patients were classified as micro-metastatic, macro-metastatic with <25K copies and macro-metastatic with >25Kcopias, with no statistical significance found between the groups [long rank test 0.266] (Figure 1). During the study period, 6 patients suffered a relapse of their disease [Table 2]. Only one of them has presented an axillary relapse associated with supraclavicular and laterocervical, pulmonary and mediastinal relapse. There have been 2 systemic relapses, one breast relapse and 3 regional loco relapses with associated systemic disease. Finally, the number of patients needed to be treated under the CTT criteria to produce harm was 2.3 [NNH [Hazard Ratio, Cox Regression]]

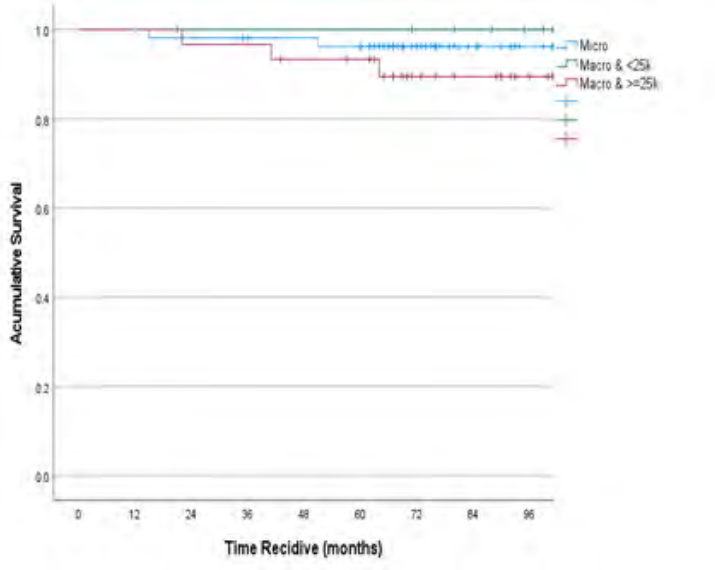

Figure 1: Survival Analysis. Created using SPSS v28

Table 1: Epidemiological characteristics

Epidemiological characteristics.	N: 92	%
Age years (mean ; SD)	55.5	10.6
Menopause		
Pre-menopause	29	31.50%
Post-menopause	63	68.50%
Bilaterality		
Yes	2	2.20%
No	90	97.80%
Histology		
Ductal	79	85.90%
Lobular	2	2.20%
Other	11	12%
Tumour size		
Pathologic mm (mean ; SD)	18.3	7.7
Histological Grade		
Grade I	22	23.90%
Grade II	41	44.60%
Grade III	29	31.50%
ILV		
No	60	65.20%
Yes	2	34.80%
Ki 67		
<=20%	54	61.40%
>20%	34	38.60%
Oestrogen Receptor		
Positive (>1%)	85	92.40%
Negative	7	7.60%
Progesterone Receptor		
Positive (>1%)	76	72.60%
Negative	16	1.40%
Her 2 Neu		
Negative 0	49	53.3
Negative +1	17	18.5
Positive +2	18	19.6
Positive +3	8	8.7
Sentinel lymph node		
Median number of SLNs (median ; IQR)	2	1
Number of SLNs affected (median ; IQR)	1	0
1	42	46.30%
2	31	33.70%
3	15	15.80%
4	3	3.20%
5	1	1.10%
Type of affectation		
Micro metastasis	55	59.80%
Macro metastasis	37	40.20%
OSNA Total Copies (TTL)		
Micro mtts	55	59.80%
Macro mtts <25K	7	7.60%
Macro mtts >25K	30	32.60%

Table 2: Relapses

Patient	Type of recurrence	Time to Relapse (months)	Description	CTT
1	Loco regional and systemic	14	pT2 pN1 LVSI+, Luminal B	2100
2	Loco regional and systemic	111	pT1 pN1 LVSI+ Luminal A	1400000
3	Loco regional and systemic	40	pT2 pN1 Luminal B	630000
4	Systemic	63	pT2 pN1 Luminal B Her2+	15900000
5	Systemic	22	pT2 pN1 HER 2 enrich LVSI+	1720000
6	Mamary	50	pT1b pN1 Luminal A	1300

4. Discussion

The clinical relevance of an improvement in axillary staging using a method such as OSNA should be reassessed. Even more if the method is intended to be used to select patients who are candidates for axillary dissection in the post-Z0011 era [5-10]. Peg et al[11] analysed 697 patients who underwent ALND after SLN+. Despite the fact that the diameter of the included tumours was T1 - T3, they found a similar percentage of tumour residue [non SLN+] as in the study published by Giuliano et al. [29% Peg Vs 27.3% Giuliano] [12] This study was started before the publication of Z0011, with the aim of avoiding lymphadenectomies and only 2.8% of patients in the high-burden group did not receive axillary dissection. Evidently, the publication of the Z0011[2, 3] study changed the real impact that TTL could have. On the other hand, recent publications warn that TTL measured by the OSNA method [13] should not be used outside of a clinical trial. Ales Martínez et al analysed a total of 321 patients who underwent OSNA-assessed SLNB with a mean follow-up of 56 months. 71 cases showed a TTL greater than 15,000 copies. Using the Z0011 criteria, they obtained similar results to ours with a low rate of axillary lymphadenectomy. They also conclude, as we do, that if axillary management had been based on TTL values, they would have multiplied the number of axillary lymphadenectomies by a factor of 3.3. And that there is no relationship between TTL measured by the OSNA method and local and distant clinical outcomes [14]

In our study, the possibility of performing an excess lymphadenectomy was calculated as NNH, with a result of 2.3.

Different authors have proposed cut-off points for mRNA copies to decide whether, in the presence of a GC+, ALND should be performed [15]. Even the proposed cut-off point has recently been changed in the protocols of some scientific societies [1], probably due to the great dispersion of values around the mean in different publications [24,25]. Although the analysis of TTL by OSNA has shown in a meta-analysis published by Tiernan et al. [26], an overall sensitivity of 0.87 and a specificity of 0.98 when analysing metastatic compromise of the SLN, given the low prevalence of macrometastases, these values may lead to misinterpretations. For example, a positive predictive value of 0.79 implies that up to 21% of patients will be identified by the OSNA method as macrometastatic and undergo lymphadenectomy. Recently, the results of the SINODAR ONE study have been published [16] a prospective noninferiority multicenter randomized study aimed to assessing the role of axillary lymph node dissection in patients undergoing either breast-conserving surgery or mastectomy for T1–2 breast cancer and presenting one or two macrometastatic sentinel lymph. The histopathological examination was performed using the standard method or OSNA technique. Their results do not support the use of routine ALND.

5. Conclusion

The recommendation of ALND in clinically [or radiologically] negative axilla cases with high tumour burden determined by OSNA in patients meeting Z011 criteria does not support data from large randomized studies, and is consistent with the results of our study, despite being a retrospective cohort design. In these studies, without and with axillary RT [17-23] with a mean follow-up of 8-10 years, the axillary recurrence rate ranged from 1.5-3.8%, not being different from the rate observed with ALND. This fact, as well as the equality in disease-free survival and overall survival, and the fact that the decision to make systemic adjuvant treatment is based on the biological characteristics of the tumour, mean that the current trend is to reduce the need for axillary lymphadenectomy once again. what are the implications of not completing a lymphadenectomy in the presence of GC+? It does not seem that the false negatives of the SLNB, nor of the possible residual tumour compromise the true final objective, which is the local control of the disease. [17, 24, 25].

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