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Pleomorphic Lobular Carcinoma *in Situ*: Issues in the surgical management

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Abstract:
Background :Lobular carcinoma *in situ* (LCIS) is considered a risk marker for invasive breast cancer with no requirement for surgical excision, while ductal carcinoma *in situ* (DCIS) is a precursor of invasive disease,demanding breast surgery and adjuvant treatment.Pleomorphic LCIS is a rarehistological subtype that presents a different pattern of clinical outcome compared to classic LCIS, due to frequent association with invasive disease and high recurrence in case of positive surgical margins. Considering this contrast, although there is no sufficient literature support to determine an optimal treatment, in clinical practice the tendence is to managePLCISsimilarly to DCIS, including with regard to surgical excision and adequate margins.Methods:Biomedical literature search on PubMed using terms 'pleomorphic' and 'lobular carcinoma in situ' in the articles titles of the past 10 years.Conclusion: Although there is still nosetted guidelines for PLCIS management, this lesion isconsidered more aggressive than classic LCIS demanding different approuch. To define the standard guidance that brings safety outcome to the patient presenting this disease, prospective studies and meta-analysis, including precise surgical margin information is necessary.

Keywords -*Lobular Carcinoma in situ, Management, Pleomorphic, Surgical treatment*

I. INTRODUCTION

Lobular carcinoma *in situ* (LCIS) has been removed from TNM cancer staging in 2017 and it's considered a benign entity ever since. [1] However, there are histological subtypes of LCIS, which are divided in classic (CLCIS) and non-classic. Among the non-classic subtypes, there is florid LCIS and pleomorphic lobular carcinoma *in situ* (PLCIS)and both have different histological pattern and clinical outcomes in diagnosed patients.Hence, non-classic LCIS, mainly the PLCIS, tend to be treated as carcinoma ductal *in situ* (DCIS), a precursor of invasive breast cancer that manage with surgery with adequate margin, adjuvant radiotherapy and endocrine therapy.

However, in breast cancer guidelines of 2023, PLCIS continue not to have a optimal defined management when diagnosed, leading to impasses in medical decision. [1]

The review intents to bring studies data from the last 10 years, all of them composed of case series report and reviews, to expose in which direction the treatment of non-classic LCIS, especially of PCLIS, is setting to.

II. METHODOLOGY

Electronic literature search on PubMed including keywords: 'pleomorphic' and'lobular carcinoma in situ'in the articles title between 2013 and 2023 yielded 13 suitable articles which were incorporated into this review. Further articles were identified by manual search through the references in previous studies.

III. DISCUSSION

LCIS is not part of TNM cancer staging anymore, instead of that,is consideredas a lesionof uncertain malignant potential – categorized as B3 by the UK National Health Service Breast Screening Program (NHS BSP). B3 lesions have different approach according to associated risks of "upgrade"to invasive disease and risk of subsequent carcinoma [2].CLCIS is a histological subtype considered a marker of increased risk of developing invasive breast cancer but not a precursor of malignant lesions [3]. This is corroborated by the fact that most common invasive disease associated with CLCIS is invasive ductal carcinoma instead of lobular carcinoma [4].

Since CLCIS is a risk marker, pure CLCIS in core biopsy generally does not require surgical excision. When it comes to breast conservative surgery (BCS) for invasive cancer and CDIS, if there is onlyCLCIS at surgical margin there is no need of re-excision [1].

PLCIS is a rare variant first described by Frost et al in 1996 [5], its histological pattern is marked by nuclear pleomorphism and/or an expansile growth cells that extends into the ducts with lacked cohesion. PLCIS subtype is high-grade in situ lesion that shares morphologic features of CLCIS and DCIS [6]. In common with CLCIS, it presents loss of E- Cadherin gene, while CDIS has positive staining for E- Cadherin [7]. But series reports shows that while upgrade rate overall of LCIS is 27%(range 0-60%), in PLCIS is higher with 41% provingto be more frequently adjacent to invasive carcinoma [2].

Due to the contrast, retrospective studies sought to compare outcomes depending on the surgical treatment, mainly margin status when it comes to recurrence rate. Desai et al [6]in 2018 compare drecurrence after surgery for PLCIS depending on final margin status of their report with other 5 case series [8,9,10,11,12]. These reports were published between 2011 and 2018 and each one considered from 16 to 78 patients diagnosed with PLCIS.

Among patients with positive or <1 mm margins (36in total), 10 presented recurrence, resulting in a 28% rate. In contrast, among patients with negative margins (72 in total), there was only 3 recurrences reported, resulting in a 4% recurrence rate. This indicates that having positive or very close margins is associated with a higher likelihood of recurrence compared to having negative.

Masannat et al also in 2018 [13] did the largest series of PLCIS in the medical literature using data base of two cohorts, GLACIER Study (A study to investigate the Genetics of LobulAr Carcinoma In situ in EuRope) and Multicenter UK based audit. From this data source, 176 patients with PLCIS with enough information for analysis were identified, in 130 cases, patients had invasive breast cancer associated with PLCIS, the main histological type was lobular invasive carcinoma. These tumors had high incidence of poorly differentiated cells (histologic grade 2/3) and immune his to chemistry predominance of ER positive and HER-2 negative. In this review, when diagnosed in core biopsy, PLCIS upgrade to invasive disease on surgical excision was 31.8% rate, which is higher than data for CLCIS and similar to DCIS. The results of this review support the view that PLCIS is a more aggressive form of lobular in situ neoplasia[14]and state in favor of the tendency to treat PLCIS like DCIS, which after Marinovich et al [15] meta-analysis in 2016 have surgical margin recommendation >2mm, although there was no evaluation of the outcomes with margin between 1 and 2mm.

As a more recent tendency, when it comes to Genetic analysis of non-classic LCIS variants, two studies published in 2020 [16,17], describe frequent alterations in genes ERBB2/ERBB3.

Harrison et al[16] in 2020 presented 19 cases of non-classic LCIS (17 PLCIS, 2 florid LCIS) of which 9 lesions were HR+/HER2−; the majority had ERBB2 alterations including mutations (13 cases) and amplifications (6 cases). Other significant alterations included mutations in PIK3CA (6 cases).

Shamir et al [17], in the same year, did a genomic analysis of 16 non-classic LCIS (10 PLCIS, 6 florid LCIS) and recognized high frequent alterations in genes such: CDH1, the gene related with Hereditary diffuse gastric cancer which is associated with lobular breast cancer (9/10 PLCIS, 6/6 FLCIS), PIK3CA (7/10 PLCIS, 2/6 FLCIS), ERBB2 (6/10 PLCIS, 2/6 FLCIS; six mutations, two amplifications), ERBB3 (1/10 PLCIS, 2/6

FLCIS), TP53, tumor suppressor gene related to Li Fraumeni syndrome (3/10 PLCIS). Frequent ERBB2/ERBB3 alterations in non-classic LCIS are consistent with more aggressive behavior and may have prognostic and therapeutic implications.

Considering this background, clinical guidelines in Oncology for invasive breast cancer point that, although no surgical margin is necessary for pure LCIS or proliferative disease with atypia, when it comes to pleomorphic LCIS the optimal width of margins is not known. [1] (Table 1). The lack of prospective studies and adequate sample size to promote statistical significance results is the reason for these undefined management.

TABLE

Margin status recommendations after breast conservative surgery (BCS) for invasive cancers and DCIS – NCCN Guidelines Version 4.2023 [1]

	No ink on tumor	2-mm margin	No margin necessary
Invasive breast cancer	X		
Invasive breast cancer + DCIS	X		
Invasive breast cancer + extensive DCIS	X		
Pure DCIS		X	
DCIS with microinvasion		X	
Pure LCIS* at surgical margin			X
Atypia at surgical margin			X

*For pleomorphic Lobular Carcinoma In Situ (LCIS), the optimal width of margins is not known.

IV. CONCLUSION

Considering the rarity of non-classic LCIS variants, mainly PLCIS, limited data exist, leading to difficult to state a guideline for management. Although considered more aggressive than classic, there are controversies in treatment and for the breast surgeon an important issue is the margin status.

As appropriate management has been debated, literature needs evidence from prospective studies, as randomized controlled trials,or meta-Analysis using quantitative and qualitative variables with necessary information of cases in order to define the standard margin that brings safety outcome to the patient presenting this disease.

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