Breast Cancer

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Upgrade on Breast Ductal Carcinoma in Situ

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1. Introduction

Breast Ductal Carcinoma in Situ (DCIS) is defined as a pre-invasive lesion composed of proliferative malignant ductal cells limited to ducts and lobes, without invasion of the basal membrane [1].

Without trespassing basal membrane, DCIS has no capacity to develop metastases (M1). It is a pre-neoplastic lesion, understood as a non-necessary precursor of Infiltrating Ductal Carcinoma (IDC) [2]. Even though, there are series that describe cases developing M1 after diagnosis of DCIS (less than 1%), maybe due to patients with under-diagnosed CDI as a logical explanation [3].

The classification of different pathologies on breast is subdivided according to the Relative Risk (RR) to proliferate to IDC. Thus we find entities classified as:

Non-proliferative: simple cyst, fibroadenoma, apocrine metaplasia, mild ductal hyperplasia and simple columnar alteration. RR between 1.2 and 1.4

Proliferative: usual ductal hyperplasia, sclerosingadenosis / radial scar, columnar hyperplasia and papilloma. RR between 1.7 and 2.2.

Proliferative with atypia: atypical lobular hyperplasia, atypical ductal hyperplasia or lobular carcinoma in situ. RR equal or greater than 4

The intraductalneoplasia (DIN) classification defined by Tavassoli[4] is maintained to date. It allows us to define the lesions according to relative risk increase, considering so-called DCIS those lesions from DIN1c:

DIN1a: Corresponds to conventional / usual ductal hyperplasia and flat atypia (proliferative lesion).

DIN1b: a typical ductal hyperplasia (proliferative lesion presntinga

DIN1c: atypical hyperplasia that exceeds 2 mm in extension or the grade 1 DCIS that also exceeds those 2 mm in surface extension.

DIN2: combines the terms of grade 2 DCIS, micropapillary or cribiform DCIS and apocrine or clear cell intraductal carcinoma.

DIN3: would correspond to grade 3 DCIS and anaplastic intraductal carcinoma.

The incidence of DCIS has significantly increased since the use of screening mammograms. More than 90% of cases of DCIS are detected only by imaging techniques [5].

DCIS and IDC risk factors are mainly shared, including the family history of breast cancer, increased breast density and obesity among others. The risk is increased as well in those patients with genetic disorders such as BRCA1-2, causing early appearance of DCIS either IDC in affected patients. Despite these data, the prevalence of DCIS remains lower than that of IDC in general population [6].

2. Diagnosis

The definitive diagnosis is given by the pathological study of a suspicious lesion [7], but to obtain the sample of study, normally by stereotaxic biopsy or surgical biopsy, it is usually thanks to mammographic suspicious images. 90% of DCIS are diagnosed from biopsied microcalcifications screened in mammography. It rarely debuts as a palpable nodule (<5%) [8].

Since the introduction of mammography as a complement to breast physical examination and the implementation of screening programs, the most frequent radiological sign that can make us suspect that we are facing this entity is the calcium pattern, often

in the form of clustered microcalcifications, heterogeneous, with a usually segmental pattern of distribution.

Normally what is mammographically manifested is nothing more than a small part of a set of intracanalicular lesions that progress to the nipple, usually in a non-continuous way, with interfocal gaps of up to 1 cm, which affect a whole mammary segment [9].

The 20-30% of breast cancers diagnosed by screening mammography are DCIS. Most of the cases (150 per 1000 mammograms in the first round versus 0.83 / 1000 in successive rounds) are detected in the first mammograms performed at the entrance to the screening program, even more since the introduction of digital mammography and Tomosynthesis [10].

The improvements on screening mammography permits identify everyday more and more intraductallesions that may progress to invasive cancer, but it is known that not all of them would. For this reason systematic mammography is questioned for the entire population. We may be over diagnosing and over-treating patients who would never develop breast cancer, leading to an increase in health system costs, and especially associated morbidity and mortality.

The reality is that nowadays we are not able to select those cases with real potential of progression to infiltration. Research must move forward to provide better knowledge of these lesions biology (the role of the underlying stroma, identify progression factors, use of genetic platforms...) and create groups upon risk that will allow selecting those patients who really need to be treated.

Performing acomplementary breast magnetic resonance imaging (MRI) is advised, although it is not routinely indicated, to help us define the extent of the process, especially to detect cases of multifocal-multicentric or bilateral lesions [11].

The MRI allows us to define the real extent of the DCIS, frequently underestimated by mammography, though it has not shown an increase of negative margins ratio of surgical pieces in cases of conservative treatment. Is important to keep in mind that despite having a high sensitivity, it has a poor specificity, overestimating the size of up to 25% of cases of DCIS and provoking over diagnosis [12].

As we said, the definitive diagnosis is given by the pathological study (PS) obtained from a suspicious lesion usually found casually in an imaging study. The PS report should include the histological type, architecture or morphological patterns, the nuclear grade, presence or absence of necrosis, estrogen and progesterone receptors positivity, presence of affected or free margins, and the distance from the nearest margin [13].

PS for DCIS presents a diagnostic challenge, due to the difficulty to classify DCIS and to differentiateit from other entities such as microinvasive carcinoma, usual or atypia ductal hyperplasia, and Lobular Carcinoma in situ (LCis). In microinvasive carcinoma there are points where the carcinoma crosses the basal membrane more than 1mm. PS that reports as DCIS with microinvasion the microinvasive carcinoma can be confusing. It is important to differentiate them, since the therapeutic approach changes.

3.Treatment

The main goal of treatment is to avoid the potential evolution of DCIS to invasive carcinoma. The different existing therapeutic options range from surgery to radiotherapy and adjuvant hormonal therapies.

3.1. Surgery

Surgery is usually the first therapeutic approach. Is important to consider the surgery technique planed to perform according on the biological behavior of the DCIS (intracanalicular progression) and evaluateall tests performed (mammography, MRI, ultrasound). Depending on the characteristics of multifocality, multicentricity, bilateralityand anthropometric data of patient's breast (size and cup), we will assess whether it is feasible to perform anoncoplastic-conservative surgery, usually segmentectomy, or simple mastectomy due to DCIS extension, often nipple-skin-sparing with immediate reconstruction.

It is very important the orientation of the surgical piece at the time of surgical resection, to guide the pathologist correctly. PS will have to confirm and correlate the pathological findings with those obtained by imaging techniques and above all, precisely inform the distance of resection margins. We will use stitches, inks, diagrams and even refer the surgical piece to radiodiagnosis so that they mark with needles / harpoons the area of greatest representation of the lesion.

Surgery often provides definitive diagnosis (discarting infiltration of the stroma). But despite demonstrating on PS that the basal membrane remains unaffeced, we know that exists a risk of recurrence in cases of conservative surgery and even if a

mastectomy has been performed.

The main prognostic and recurrence risk factors of DCIS are: patient age, tumor size, resection margins, nuclear grade, presence of comedonecrosis and estrogen receptors and progesterone. Those factors allow subdividing DCIS into low-grade (older patients 50 years, low or intermediate nuclear grade, tumor size less than 2.5cm, resection margin> 3mm) and high grade (under 50 years, resection margins <3mm, high nuclear grade, tumor size> 2.5cm), according local recurrence risk[14]. In conservative surgeries up to 50% of cases recurrence will occur as DCI [15-16].

Although there are still controversies regarding the definition of negative margin in DCIS, we consider adequate a margin of resection greater or equal to 2mm. Margins greater than 2mm do not significantly minimize the risk of recurrence compared to 2mm margins.

The use of a 2 mm margin as a standard for an adequate margin in the DCIS posteriorly treated with breast radiotherapy (RT) is correlated with a reduction in local recurrence rates, a decrease in re-excision rates and associates improvement of cosmetic results and reduction of medical costs [17].

In case of patients presenting margins fewer than 2 mm, although the recommendation is surgical re-excision, the need for additional surgery must be agreed in the multidisciplinary committee [18]. If the re-excision is performed and positive margins persist, the possibility of mastectomy will be assessed.

In order to adequately assess the behavior to be followed, it is therefore necessary that the PS report indicates whether the margin affected is by proximity or by contact, if it is focal or extensive, the length of affectation presented, and in what location (anterior, posterior margin or lateral) of the surgical piece. According this information and the prognosis factors previously described, the Committee will be able to decide whether or not to conduct reexcision [19].

If a surgical treatment of the DCIS with adequate margins can be performed, survival rates of 96-100% can be reached at 5 years [20]. The recurrence risk in cases of conservative management plus radiotherapy (RT) seems to be equal to that of patients receiving mastectomy not undergoing RT [21].

Regarding sentinel node in DCIS, due to its in situ condition, it presents an almost negligible risk of lymph node involvement. If conservative surgery performed, the technique of Selective Sentinel Node Biopsy (SSNB) is not advised [22]. When a mastectomy is performed, the lymphatic drainage of the breast is permanently altered, making it impossible in the case of a subsequent diagnosis of DCI and the correct realization of a SSNB. That is why it is the main indication of SSNB in DCIS. We must also consider SSNB in those situations presenting high risk of stromal infiltration as clinically palpable lesions, of high radiological suspicion (nodular patterns, extensive lesions...) or by characteristics of the initial biopsy (high-grade lesions, presence of comedonecrosis), although is not routinely indicated.

Radiotherapy:

In different randomized trials it was shown that the association of RT with conservative surgery reduced the absolute risk of local recurrence to 10 years by 15.2%, regardless of age, tumor size and margin status [23]. No benefit was demonstrated regardingmortality. RT reduced the rate of local recurrence of DCIS and infiltrating ductal carcinoma [24].

Recently, a prospective trial regarding hypofractioned RT schemes in DCIS has been published, including 1608 patients randomized to complete irradiation of the breast in a hypofractionated scheme (42.5 Gy in 16 fractions) versus normofractionated scheme (50 Gy in 25 fractions), with a 3-year follow-u. A statistically similar cosmesis was achieved between both groups ($p \geq 0.18$) [25].

The indication of overpressure (boost) on tumor bed in conservative surgery would be applied to cases with presence of residual lesion or insufficient margin especially in those cases in which surgical reexcision is not possible. Regarding RT in patients who have undergone mastectomy, it is not routinely indicated, but it can be assessed in cases of large margins affected [16].

There is a randomized trial including low-grade DCIS according prognostic factors, which compares after conservative surgery, performance of breast RT versus observation. Up to a 7.1-year follow-up, is evidenced a 0.9% local recurrence rate in the RT group versus 6.7% in the observation group [14]. Another randomized trial reaching 12-year follow-up showed a local recurrence rate of 14.4% in the RT group versus 24.6% in the observation group [26]. To date, clinical-pathological characteristics cannot reliably identify low-risk DCIS that benefit from conservative surgery and observation without increasing the risk of recurrence.

Regarding Partial Breast Irradiation (PBI), in 2017 the update of the PBI consensus of the American Society for Radiation Oncology (ASTRO) was published and the new recommendation includes patients with DCIS as suitable for PBI. In 2018, preliminary results were presented in San Antonio Breast Cancer Symposium: RAPID trial that randomized 2135 patients to perform full breast RT versus PBIand follow-up of 8.6 years, 18% of the patients included presented pure DCIS; Local recurrence rates were 2.8% versus 3% for PBI, which reflected that the PBI was not inferior to the complete irradiation of the breast, but did show an increase in late toxicity on PBI group. Also has been presented the preliminary results of NSABP B-39 / RTOG-0413 trial that randomized 4216 patients to perform full breast RT versus PBI, with a median follow-up of 10.2 years, 24% of the patients included presented pure DCIS, the local recurrence rates were 4.1% versus 4.8% for IPM. The PBI in this trial did not convene the criteria of equivalence to the complete irradiation of the breast in the risk of local recurrence.

3.2. Hormone Therapy:

Finally, the benefits of offering adjuvant therapies, such as hormone therapy, chemotherapy and targeted anti-HER2 therapies have been studied. Only hormone therapy is in use, as it has been shown to reduce the risk of recurrence in the form of DCIS and IDC without significant associated morbidity [27]. Chemotherapy, on the other hand, does not have a role in DCIS given the low risk of distant metastases. Regarding anti-HER2 therapies, there is insufficient evidence to recommend its use up to date [28].

The indication of adjuvant systemic hormone therapy includes those patients with DCIS who demonstrate positive hormonal receptors, to whom a bilateral mastectomy has not been performed, and who discussing risks and benefits accept the treatment individually. We must explain that current data shows that the risk of relapse is significantly reduced, but has not been shown to improve overall survival[29]. The usual duration of treatment is 5 years. The risk-benefit in patients who have received bilateral mastectomy is not considered adequate to recommend treatment, neither in patients who do not have positive hormonal receptors in immunohistochemistry.

Tamoxifen (TMX) is a common part in the management of DCIS that expresses hormonal receptors, which accounts for up to 75% of cases. In 2014, a Cochrane meta-analysis confirmed the benefit of tamoxifen (TMX) in the prevention of breast events (both ipsilateral and contralateral) [27]. TMX is the only drug approved by the FDA (Food & Drug Administration) for adjuvant treatment of DCIS that overexpresses hormonal receptors in young women and that do not have associated comorbidities[30]. Studies using aromatase inhibitors such as anastrazole have also shown despite not yet being approved, its benefit, even improving TMX results in postmenopausal patients subgroup [29]. Nowadays there is no evidence or indication of neoadjuvant treatment for either of the two families of hormonal therapy in DCIS.

In 2019, a randomized trial has been published, which includes 500 patients suffering DCIS that undergone conservative surgery. It randomizes TMX 5mg / day for 3 years versus placebo. Reached 5.1-year follow-up, they report 14 neoplastic events in TMX-group and 28 in placebo-group. TMX appears to decrease contralateral breast events by 75%. They conclude that reducing the dose of TMX is possible to decrease recurrence in DCIS with limited toxicity, which may provide a new treatment option in these patients [31].

4. MAIN POINTS

1. The primary therapeutic approach to DCIS is surgery.

2. The highest rate of recurrence reduction is obtained combining surgery (if conservative, with correct margins) and radiotherapy of the entire gland.

3. The 50% of recurrences will be as infiltrating ductal carcinoma.

4. Margins are considered adequate if they are greater than or equal to 2 mm.

5. Adjuvant hormonal therapy is advised in cases of DCIS expressing positive hormonal receptors. Currently tamoxifen is the only endocrine treatment approved by FDA, the maximum recommended duration is 5 years.

6. Sentinel node technique should be added to DCIS surgery in selected patients and not systematically (cases of mastectomy or high risk of infiltrating carcinoma).

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