Our orientation regarding the ductal carcinoma in situ of the breast

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AIM: *The ductal carcinoma in situ is a malignant proliferation of mammary ductal epithelial cells without invasion beyond the basement membrane. The management of patients with DCIS is complex, controversial and has undergone changes over time.*
MATERIAL OF STUDY: *We treated 65 patients diagnosed with DCIS between 2002 and 2005. We surveyed women aged between 28 and 71 years (average age 51.4), the DCIS in 16 patients appeared as a palpable mass (about 2.2 cm) - group I and in 49 patients as microcalcifications detected on mammography - group II.*
RESULTS: *The most frequent histological type was found to be the comedocarcinoma. After 3 years of follow-up, we had 3 cases of recurrence (4.6%) in patients undergoing conservative surgery, with Van Nuys Prognostic Index between 3 and 4.*
DISCUSSION: *15-25% of cases of breast cancer are DCIS. Most of these are comedocarcinomas. Comedo form DCIS is an insidious cancer. Surgical treatment ranges from mastectomy to excision of the lesion, often the latter, followed by radiotherapy.*
CONCLUSION: *We prefer, with regard to surgical treatment, quadrantectomy with systematic control of the free margins. The search for the axillary sentinel node represents for us, too, the gold standard.*

KEY WORDS: Adjuvant radiotherapy, Conservative surgery, Ductal carcinoma in situ (DCIS)

Introduction

The ductal carcinoma in situ (DCIS) is a malignant proliferation of mammary ductal epithelial cells without invasion beyond the basement membrane. Before the spread of mammography screening, the percentage of diagnosed cases of DCIS amounted to 3-5%, most of which with palpable mass[1]. This diagnosis was strongly underestimated if we consider that, at present, several studies have shown that DCIS represents 15-25% of all cancers detected in large-scale mammography screening programs nationwide; we can say that about 1 out of 1300 mammography screenings leads to a diagnosis of DCIS[2,3]. Microcalcifications detected on mammography are the most common manifestation of DCIS[4]; so this diagnosis remains the most reliable, if often combined with ultrasound guided microbiopsy (Mammotome)[5]. Defining the extension of the tumor tissue is still the most contentious and difficult challenge of the instrumental methods, including the question of defining multicentrality or multifocality and contralateral lesions[6].
The management of patients with DCIS is complex, controversial and has undergone changes over time; in the

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past, mastectomy was the primary treatment, subsequently conservative surgery has become increasingly important as the surgical treatment of choice, although there is disagreement in literature[7-9]. Similarly, the sentinel node biopsy has replaced axillary dissection, although its role appears to be controversial, in view of the survival of patients with DCIS[10].

Patients and methods

In our study we treated 65 patients diagnosed with DCIS between 2002 and 2005, admitted to the Unit of General and Geriatric Surgery, Department of Gerontology, Geriatrics and Metabolic Diseases of the SUN (Second University of the Study of Naples).
We surveyed women aged between 28 and 71 years (average age 51.4), in 16 patients the DCIS presented as a palpable mass (about 2.2 cm) - group I and in 49 patients as microcalcifications detected on mammography - group II. In group I, fine needle citology was suspicious in 15 patients and not indicative in one patient; in group II, fine needle citology was performed in 18 patients (correct diagnosis in 16 cases), core biopsy in 14 patients (1 false negative) and ultrasound guided microbiopsy (Mammotome) in the remaining 17 patients (Table I). Excisional biopsy with a metallic marker or ROLL was performed in 42 patients to confirm the diagnosis.
Patients underwent the following surgical treatment:
– enlarged lumpectomy in 4 cases;
– quadrantectomy in 51 cases;
– mastectomy in 10 cases.
The mastectomy performed was of the simple type in 7 cases; in 2 patients out of these we used the skin-sparing technique and in one the nipple-sparing.
Furthermore, in 2 women, as a result of the detection of implicated margins after quadrantectomy, a subsequent mastectomy was needed. As regards the treatment of axillary lymph nodes, 53 cases underwent only the sentinel node biopsy, while the remaining 12 had axillary sampling.

Results

The most frequent histological type was found to be the comedocarcinoma (40 cases, 61.5%), followed by non-comedo (25 cases, 38.4%). However, we excluded from our work the DCIS with microinvasion.
The hormone receptors were positive in 48 cases, the positivity of c-erb was observed in 5 cases.
Adjuvant treatment was modulated taking into account several factors:
– TNM staging;
– histological type;
– free margins;
– hormone receptor positivity;
– c-erb positivity;
– chemotherapy (used only for a patient with sentinel node metastasis).
After 3 years of follow-up, there were 3 cases of recurrence (4.6%) in patients who underwent conservative surgery. In one patient surgery had been associated with adjuvant radiotherapy, while the other two patients had not received such treatment (Tables II).
In 2 cases recurrences were found in the same quadrant of the primary tumor, whereas in only one patient they appeared in a different quadrant of the breast affected by cancer (Table III).
The recurrence rate we obtained (4.6%) does not seem to differ from literature records, we also have a Van Nuys Prognostic Index between 3 and 4.
We noticed that the percentage of DCIS, compared to the total number of breast carcinomas, is below the average of international literature.
With regard to treatment with tamoxifen or aromatase inhibitors, all patients undergoing such hormone therapy were positive for hormone receptors. We preferred to administer tamoxifen and LH-RH inhibitors in patients in premenopause, while aromatase inhibitors were recommended to patients after the menopause.

TABLE I

	Group I	Group II
n. of patients	16	49
Needle citology	suspicious in 15 patients not indicative in 1 patient	18 patients (correct in 16 cases)
Core biopsy	/	14 patients (1 false negative)
Mammotome	/	17 patients

TABLE II

	Recurrence
Conserv. surgery + RT	1
Conserv. surgery	2
Total	3(4.6%)

TABLE III

	Location of recurrence
Quadrant of the primary tumor	2
Different quadrant of the same breast	1
Total	3

Discussion

15 to 25% of the cases of breast cancer are DCIS. Most of these are comedocarcinomas [4].

There are two morphological variants of DCIS: comedo and non-comedo. The comedo type is the most aggressive and presents, from an epidemiological and histopathological point of view, hormonal and reproductive risk factors similar to the infiltrating ductal carcinoma; whereas the non-comedo type presents a different behaviour[11]. This deserves some attention, as there has always been little importance given to DCIS risk factors, despite the presence of invasive carcinoma.

According to data provided by the National Institute of Health of the U.S., the non-comedo type comprises the most common histological subtype; its incidence has continued to grow until 2006. Conversely, the incidence rate of the comedo subtype is much lower. It had a peak in 1995, stabilized and then continued to decline until 2006. Currently, the incidence rate of the latter subtype is subject to change based on pathological reports and coding convenctions, as shown by the Surveillance, Epidemiology and End Results (SEER) records[12].

DCIS, however, especially the comedo type, is an insidious cancer.

Comedo DCIS and the invasive carcinoma share reproductive and hormonal risk factors such as age of the first pregnancy, lactation, age at menopause, multiple pregnancies, oral contraceptives for more than ten years. There is, instead, often negative correlation with the non-comedo type, which requires further studies[13].

Technological progress in the field of diagnostics and the increasingly organized mass screening programs, have led to the diagnosis of DCIS in 80-90% of the cases, with breast lesions not yet palpable[11,14]. Although mammography has 80% sensitivity and 30-70% specificity, the true extent of these lesions is underestimated in 46% of the cases. Often, however, it is not possible to locate the multifocality and it frequently happens that, when in doubt, the surgeon, performs a too broad excision to be sure to remove all neoplastic tissue. On this issue, many studies have shown that it is useful to add to mammography (and ultrasonography) a MRI of the breast in a next step, because it raises awareness and improves the negative predictive value[6,7]. It is thus possible to be more precise on the size and number of lesions and consequently on the presence or absence of multicentricity, multifocality and contralateral lesions[15-17]. It has been observed that MRI of the breast, applied in patients with suspected ductal disease with unilateral nipple discharge, may replace or supplement galactography (not always executable)[18]. In the preoperative evaluation for the extent of surgery, such diagnostic method is also useful in establishing the extensive intraductal components, which represent a significant risk factor for locoregional relapse[19,20]. Nevertheless it has some limits, presenting a low specificity and being always linked to each biopsy. In order to have a histological classification of the tumor, we can use both the excisional biopsy and the ROLL technique. While the former allows for the diagnosis of malignancy and invasiveness in 95% of the patients, but not for the tumor extension, the latter is more complete, that is, allows for the evaluation of the three parameters, and is characterized by a capacity to locate occult lesions in 90-97% of the cases[21]. This method, known as ROLL of 'Radioguided Occult Lesion Localization', provides for the introduction of a solution containing human albumin macroaggregates conjugated with radioactive technetium (99mTc) in a group of microcalcifications or small nodule clinically not palpable. Under the guidance of a probe for radioguided surgery, these lesions can be surgically removed in a targeted manner while maintaining the integrity of the breast. The day before surgery, a small amount of a colloidal albumen labeled with a radioisotope (Tc-99m) is injected by the radiologist at the center of an opacity (guidance) or a small group of microcalcifications (under stereotactic mammography). For verification, the patient is sent to nuclear medicine, where they are acquired scintigraphic images of the breast. The day of surgery, the surgeon with a special device (consisting of a gamma probe and a device that captures the signal of the radioisotope and translates it beeps) is able to identify and locate the lesion[22-24].

Surgical treatment ranges from mastectomy to excision of the lesion, often the latter, followed by radiotherapy[25].

It will be the preclinical study of the patient (diagnostic tests in the first place and if possible, palpation) to guide the surgeon. The availability of a cytological or histological exam will be diriment. Local recurrence can be assessed by the "Van Nuys Prognostic Index", which is useful to optimally address the management of a patient with DCIS[26]. At this point we can say that the width and positivity of the excision margins are two important predictors of local recurrence after breast-conserving surgery for DCIS[27].

In any case, if a simple lumpectomy is performed, the risk of recurrence increases, although the carcinoma histological grade is 1 or 2 (according to the modified Bloom and Richardson histological grade) and the tissue of excision margins is healthy, since, even in tumors <2.5 cm, microinfiltrations may occur (2-3% of cases)[28,29]. Invasiveness increases in high-grade dysplasia, comedo forms, extensive intraductal components, widespread lesions and in the presence of palpable mass[30,31].

It is noteworthy how conservative surgery, if combined with the ROLL technique, shows a rate of local recurrence and survival superimposable to that of traditional mastectomy (cure in 90% vs 89% and 99.5% vs 90% of the cases respectively) although indicated in 87% of the cases [32,34].

The main risk factors for recurrence are:

1. grade;
2. size;
3. positivity of excision margins[35].

These three risk factors combine to achieve an index of prognosis and divide into three groups the patients with DCIS undergoing conservative surgery. In the first group, characterized by small tumors and low grade, the relapse rate is lower and radiotherapy does not seem to have a therapeutic effect; in the second group, tumor size changes (<3 cm) with low grade, 20% of the patients have relapses and it seems that radiotherapy reduces the recurrence risk; in the third, a tumor larger than 3 cm and high grade, 50% of the patients have relapses despite radiotherapy[36,37].
Numerous studies claim that the positive cases for lymph node metastases in the axilla cover a limited range, from 0 to 7%. Therefore, we consider complete dissection excessive, in spite of the uncertainties that persist in international guidelines[38,39]. Given, however, that one fifth of the cases has infiltration past the basement membrane, it is advisable to always apply the search technique for the sentinel node (T <3cm, N0), especially in the presence of palpable mass and calcifications[40]. Recently, some authors argue, however, that the sentinel node technique can not be a standard procedure for all cases of DCIS[41,42].

Conclusion

The ductal carcinoma presents a certain complexity as to diagnosis and treatment. The extent, histopathological classification (five subtypes of which the most common is the comedocarcinoma), surgical resection, adjuvant radio-therapy and hormonal therapy are key aspects. Currently, the most frequent modality of presentation is represented by non-palpable breast lesions at diagnosis. Mammography has 80-90% sensitivity and 30-70% specificity; MRI, as a complement to mammography and ultrasound, has high sensitivity (94-100%) and identifies or excludes multifocality, multicentricity and the presence of contralateral lesions [6].
The surgical management of DCIS ranges from mastectomy to local excision; in our experience we prefer quadrantectomy with systematic control of the free margins. The search for the axillary sentinel node represents for us the gold standard; we apply lymphadenectomy or sampling only in a small percentage of cases. Adjuvant radiotherapy has been suggested as a treatment to patients who have a high-grade comedo DCIS. Patients with positive hormone receptors received hormonal treatment.
In conclusion, the treatment of DCIS is complex; both the risk of exceding surgical and/or adjuvant treatment and that of incomplete exeresis seem to be possible[43]. Defining the molecular factors necessary for progression to invasive cancer or the development of a malignant phenotype will be in the future keys to a better identification of the various types of DCIS.

Riassunto

OBIETTIVO: Il carcinoma duttale in situ è una proliferazione maligna delle cellule epiteliali duttali mammarie senza invasione oltre i confini della membrana basale. La gestione dei pazienti con DCIS è complessa, dibattuta ed ha subito modificazioni nel tempo.
MATERIALI E METODI: Abbiamo trattato 65 pazienti con diagnosi di DCIS tra l'anno 2002 e 2005. Abbiamo preso in esame donne di età compresa tra i 28 e i 71 anni (età media 51,4); il DCIS si presentava in 16 pazienti come una massa palpabile (di circa 2,2 cm), gruppo I, e in 49 pazienti come microcalcificazioni rilevate alla mammografia, gruppo II.
RISULTATI: Il più frequente istotipo è risultato essere il comedocarcinoma.
Dopo circa 3 anni di follow up, abbiamo avuto 3 casi di recidive (4,6%) nelle pazienti sottoposte ad intervento chirurgico conservativo, con un Van Nuys Prognostic Index compreso tra 3 e 4.
DISCUSSIONE: Il 15-25% dei casi di carcinoma mammario sono DCIS. La gran parte di questi sono comedocarcinomi. Il DCIS, in forma comedo, è un tumore subdolo. La terapia chirurgica va dalla mastectomia all'escissione della lesione, spesso, quest'ultima, seguita dalla radioterapia.
CONCLUSIONI: Nella nostra esperienza preferiamo la quadrantectomia con metodico controllo dei margini liberi. La ricerca del linfonodo sentinella ascellare rappresenta anche per noi il gold standard.

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