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THE ROLE OF MRI IN DIAGNOSIS AND PREOPERATIVE STAGING OF DCIS

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SUMMARY

The role of magnetic resonance imaging for breast ductal carcinoma in situ was analyzed for its use both for diagnostic and pre-surgical staging aspects. An important comparison with mammographic study was done. Features, views and actual limits of this technique were also analyzed.

Introduction

Ductal Carcinoma In Situ (DCIS) is one of the most common types of breast cancer lesions. The name 'ductal' is used because the lesion starts inside the milk duct, in the terminal ducto-lobular unit. 'Carcinoma' refers to all kinds of malignant epithelial tumors. 'In situ' is used because this lesion is non-invasive, meaning cell proliferation does not spread beyond the milk duct basal layer. According to several classifications, DCIS can be divided into different groups.

Pathologically, DCIS can be distinguished as:

- *Comedocarcinoma:* atypical cells that proliferate inside the duct, dilating and obstructing the lumen. Comedocarcinoma is characterized by an area of central necrosis with calcifications.
- *Non-comedocarcinoma:* necrosis is less evident and calcifications are less common. The non-comedo group includes several subtypes: papillary, micro-papillary, cribriform and solid (1).

From a biological perspective, based upon nuclei features and the presence or absence of necrosis, DCIS can be divided into high- and low-grades of differentiation (2,3). These classifications are important not only for the clinical prognosis but also for imaging.

The low-grade type of DCIS malignancy evolves into its invasive form very slowly (it can take up to 40 years). On mammography, low-grade DCIS malignancy appears granular with amorphous micro-calcifications, often involving more than one quadrant (figure 1). High-grade DCIS malignancy, on the other hand, evolves into its aggressive form in a short time. It appears as thin and branched pleomorphic calcifications on X-ray (figure 2). These kinds of lesions are more prone to recurrence and metastasis.

Diagnosis

Breast cancer is the most frequent cancer diagnosed among females. From 1998-2002 it represented 24.9% of all cancer diagnoses; ranking first as the cause of all cancer deaths among females with a 17.1% mortality rate.

In the Italian Network of Cancer Registries, there was a yearly average of 152.0 new cases of breast cancer per 100,000 females. It has been estimated that 36,634 new cases of female breast cancer are diagnosed in Italy every year. Regarding mortality, in 2002 there

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were 11,251 deaths reported due to female breast cancer (4,5). According to the American Cancer Society, more than 60,000 DCIS per year are diagnosed in the USA alone. DCIS accounts for about 20% of all female breast cancers. There are two main reasons why this number is so high and has been increasing over time.

1. People are living much longer lives.
2. Increased screening mammography (more cancers are being spotted earlier)

Although DCIS is a non-obligatory precursor of its invasive form, treatment is aggressive and cure rate is excellent with 10- and 20-year survival rates, respectively, of 98% and 95% (6).

Due to this optimal prognosis, correct and early DCIS diagnosis has become an important and fascinating challenge. 10% of DCIS are clinically detected by palpating a small lump during a physical examination. 90% of DCIS are detected during mammographic screening.

Typical DCIS mammographic features are:

- Micro-calcifications (75%): old cancer cells die off and pile up inside the ducts, which appear on mammography as tiny specks of calcium, better known as micro-calcification clusters.
- Gland distortion (10%).
- Change of gland density (5 %).

Mammographic techniques have a high sensitivity (>85%) but a very poor specificity (10-60%) (7,8). Mammography often underestimates DCIS extension and doesn't allow the visualization of multifocal areas: 25% of DCIS spread into 2 quadrants but are rarely multicentric (9).

If suspicious areas are identified on mammogram, the radiologist will likely recommend additional breast imaging (diagnostic mammogram which takes views at higher magnification from more angles, to get a closer look at micro-calcifications and to evaluate both breasts). If the area of concern needs further investigation, the next step could be an ultrasound, MRI or breast biopsy.

The role of breast MRI in DCIS detection

Breast MRI standard protocol includes:

- T2 Weighted Spin-Echo sequences before contrast medium.
- T1 Weighted Spin-Echo sequences after contrast medium, with subtraction repeated each minute for 5 times.
- MIP (Maximum Intensity Projection) reconstruction of the first minute after contrast injection.

Gadolinium contrast medium intravenous administration is necessary for an accurate dynamic study of the breast and to distinguish benign from malignant lesions. A neoplastic lesion undergoes neoangiogenetic processes, in particular, an increase in number, dimension and permeability of blood vessels around the lesion (figure 3).

Breast MRI has evolved significantly in recent years acquiring a key role in detection and staging of ductal invasive cancer (DIC). MRI showed to have a great sensitivity (≈ 100%) and a relatively good specificity (65 – 80%) for DIC detection and staging (10). Conversely, breast MRI has showed a

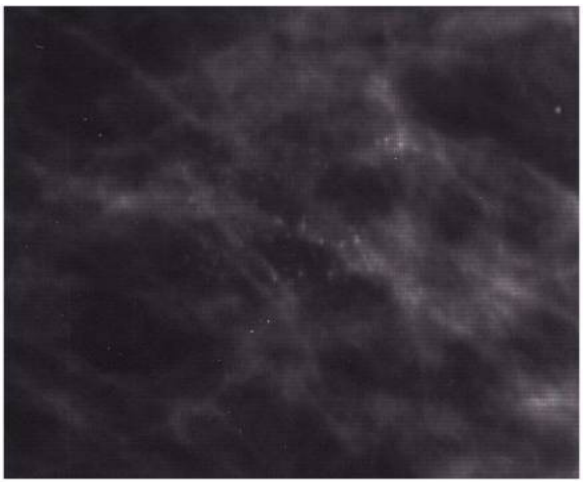

Figure 1: Digital mammography. Group of granular and amorphous micro-calcifications (low-grade malignancy DCIS)

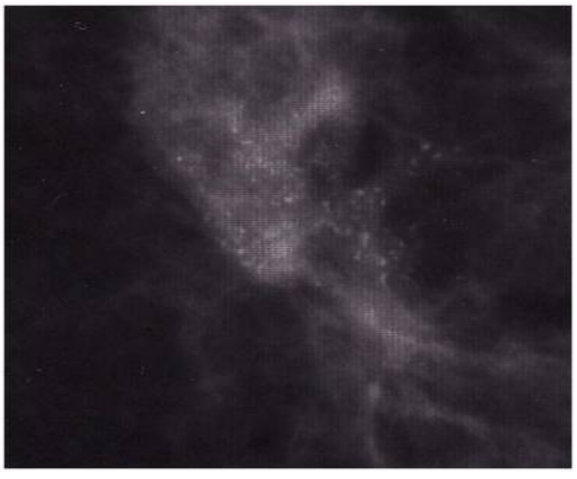

Figure 2: Digital mammography. Group of branched and thin micro-calcifications (high-grade malignancy DCIS).

good sensitivity (88-95%), but only a moderate specificity (30-85%) for invasive lobular carcinoma diagnosis (11). Unfortunately, the current literature reports that MRI sensitivity for DCIS is much more variable (33 – 100%) (12) with an average of 70 – 80% (13,14). This spectrum of differences with MRI sensitivity reflects multiple factors, including differences in magnetic field strength, imaging parameters, imaging interpretation, and most importantly, histologic variability of benign and malignant lesions (15). Lower DCIS sensitivity could be explained by the heterogeneity with which DCIS can present: histological grade of differentiation, tumoral neoangiogenesis grade, diameter of the lesion, imaging technique and interpretation (16).

An important study (Viehweg et. al. 2000) showed that 96% of DCIS present a central area of contrast enhancement on MRI, but only in 50% of cases is this enhancement typically leading to DCIS detection. MRI identification of DCIS is challenging due to the heterogeneity of DCIS histology.

From a morphological point of view, DCIS can have 3 typical enhancement patterns:

- Focal (figure 4)
- Linear/Ductal (figure 5)
- Segmental (figure 6)

Fortunately, in the last decade several studies have demonstrated that signal intensity-time curves are useful for analyzing enhancement kinetics of the lesions (17,18).

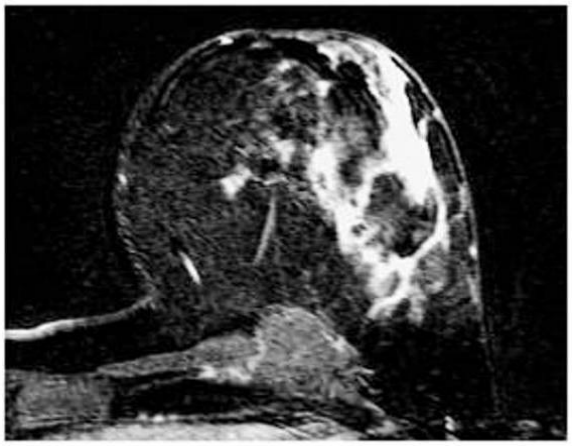

Figure 3: Breast MRI. Contrast medium spreads and accumulates mainly in neoangiogenetic foci. Thanks to this feature, a more precise assessment of DCIS extension is possibile.

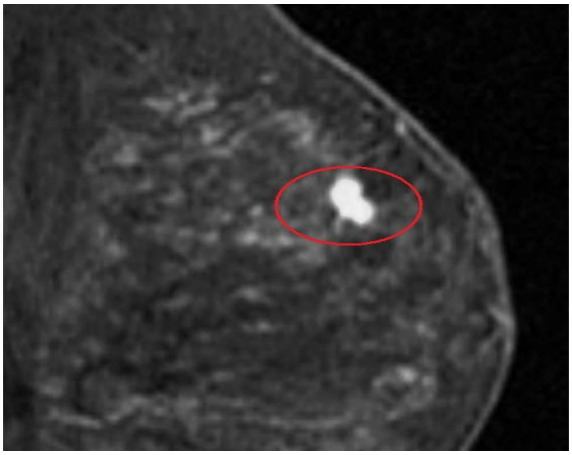

Figure 4: Breast MRI. *Focal* contrast enhancement pattern of a DCIS lesion.

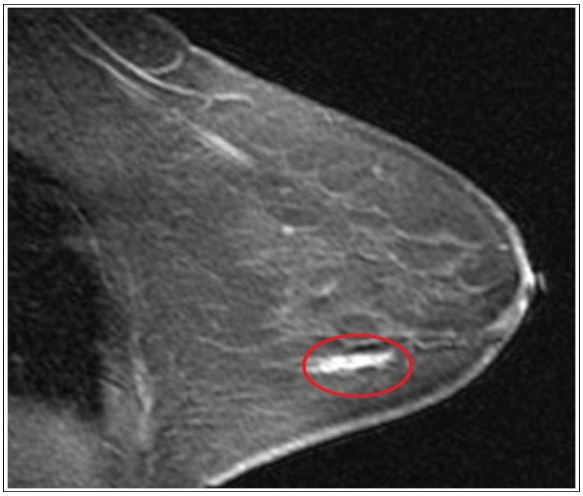

Figure 5: Breast MRI. *Linear/ductal* contrast enhancement pattern of a DCIS lesion.

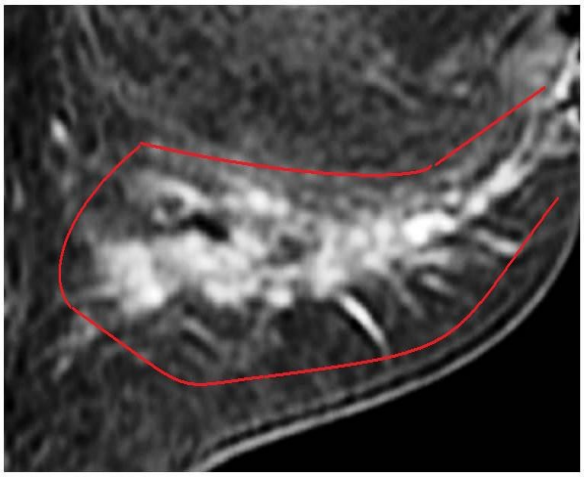

Figure 6: Breast MRI. *Segmental* contrast enhancement pattern of a DCIS lesion.

Breast MRI In preoperative staging

For breast cancer preoperative staging, MRI is more effective than mammography regarding detection of residual disease foci (MRI sensitivity 97% vs. mammography sensitivity 81%. MRI specificity 58% vs. mammography specificity 43%).

Another positive feature of MRI compared to conventional imaging is the identification of invasive components associated with the in situ lesions (MRI sensitivity 86% vs. mammography sensitivity 14%. MRI specificity 82% vs. mammography specificity 97%).

Furthermore, MRI provides more chances to localize multicentric and multifocal lesions having a higher sensitivity compared to mammography (94% vs. 38%) and a similar specificity (89% vs. 91%) (19).

Extensive intraductal components (EIC) are easily detected by MRI. These components can be expressed with several patterns: linear area of contrast enhancement with ductal distribution, contrast enhancement foci surrounding lesion or star-shaped contrast enhancement lesions.

The correlation between MRI and DCIS pathology lesion size is quite good even though it's lower than with invasive cancer (20).

Esserman et. al., in 2006, lead a study demonstrating how MRI overestimates a significant number of DCIS; mainly, the so-called complex disease where neoplastic areas and free areas are alternated.

A possible explanation for overestimation could be the parenchymal contrast enhancement on the background due to benign proliferation (adenosis, fibrocystic changes), presence of high risk lesions (atypical ductal hyperplasia, in situ lobular carcinoma), or fibrous and granulated tissue (liponecrosis areas) (21).

Conclusions

Although MRI is a useful imaging modality for invasive cancer, its role in preoperative planning for DCIS has not yet been established. Data focused specifically on the role of MRI for preoperative planning in newly diagnosed women with DCIS are scarce.

Breast MRI has a good sensitivity (80% for DCIS diagnosis) since it is able to detect lesions that don't show micro-calcifications on mammography. MRI is also the best diagnostic tool to evaluate multifocal and/or multicentric DCIS and DCIS lesion size, particularly, the EIC (extensive intraductal component).

However, breast MRI has a high number of false positives (specificity ≈ 70%) of DCIS detection. An ultrasound is necessary to reduce false positives by taking a second-look, and a biopsy is necessary for an accurate preoperative staging (22). Another breast MRI issue in DCIS preoperative staging is the moderate correlation between MRI and pathology lesion size with a possible overestimation that could lead to wider excision.

The objective of this review is to establish whether or not MRI is beneficial in preoperative planning for women with DCIS. Three main studies focused on this topic (Itakura et. al. 2011; Kropcho et. al. 2012; Davis et. al. 2012) and all of them demonstrated that patients with DCIS, who had preoperative MRI were more likely to undergo mastectomy and sentinel lymph node biopsy (SLNB) than those patients without preoperative MRI (23, 24, 25). No benefits in surgical outcome favoring the preoperative MRI group with respect to negative margins, margin size and number of re-excisions have been found. Until the benefits of preoperative MRI for patients with DCIS are prospectively evaluated (in terms of re-excisions), senologists should limit MRI use to patients, such as women with multifocality, multicentricity, or with a strong family history, who may have more benefit from this type of examination.

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