

Why Do Purely Intraductal Cancers Enhance on Breast MR Images?

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Ductal Carcinoma in Situ: X-ray Fluorescence Microscopy and Dynamic Contrast-enhanced MR Imaging Reveals Gadolinium Uptake within Neoplastic Mammary Ducts in a Murine Model¹

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**DCIS or intraductal cancer is considered a direct precursor of invasive breast cancer.
...However, as long as the lesion remains within the milk duct, it has no access to blood vessels or lymphatic channels, meaning it cannot metastasize through these routes.
curable with only local treatment .**

DCIS is a heterogeneous disease: High-grade DCIS lesions exhibit fast growth rates, high mitotic indexes, and after a relatively short intraductal period, these lesions will almost always progress to high-grade invasive cancer. ...

low-grade DCIS may be dormant over a long period of time and may never even leave the milk duct. If they do leave this duct, they will progress to low-grade invasive cancer.

The mammographic detection of DCIS is based on the depiction of microcalcifications.... probably caused by necrosis secondary to the hypoxia that occurs in the central parts of a DCIS lesion. DCIS lesions are fed by diffusion from extraductal vessels only; there is no sprouting of vessels inside the milk ducts. Thus, in ducts densely packed with DCIS, the diffusion distance may become too large. Therefore, hypoxia and calcified necrosis are **a frequent but not obligatory finding in patients with DCIS.**

DCIS was a rare and usually incidental diagnosis before the advent of mammographic screening.

With screening, well over 20% of cancers are now diagnosed as DCIS .
Accordingly, the success of mammography in the diagnosis of cancer in its preinvasive stage is unprecedented in the entire field of oncologic imaging.

However, a number of issues remain.

First, not infrequently, calcifications develop in only part of the DCIS, whereas the major part may remain mammographically occult ... inadequate resection margins ... additional unplanned surgery.

Second, ... increasing concerns that mammographic screening causes overdiagnosis (and ultimately overtreatment) of biologically inert DCIS.

Third ... underdiagnosis of DCIS with mammography ... mammography failed to depict prognostically relevant DCIS in a large number of women.

The Science

Over the past few years, ... MR imaging has a large role to play in the diagnosis of DCIS.

Still, the actual pathophysiologic correlate of contrast enhancement of DCIS lesions is completely unknown. There is no blood vessel infiltration into the milk ducts; however, increased capillary cuffing is observable around ducts containing high-grade DCIS.

What is it that makes DCIS lesions visible on MR images? Jansen and coworkers ([1](#)) used x-ray fluorescence microscopy to investigate the fate of gadolinium-containing contrast agents after intravenous injection in an animal model of DCIS (transgenic mouse model).

(a) murine DCIS lesions consistently exhibit enhancement on dynamic contrast material-enhanced MR images

(b) the contrast agent selectively accumulated within the milk ducts with DCIS. To verify that the contrast agent was indeed present **inside the extravascular-extracellular space of the milk ducts and not contained within the blood vessels**, they also performed x-ray fluorescence microscopy for iron to exclude the presence of red blood cells in the region of interest. The results of dynamic contrast-enhanced MR imaging and x-ray fluorescence microscopy were concordant in that there was no relevant gadolinium uptake in the normal mammary gland (normal milk ducts).

... there seems to be a **fundamental biologic or structural difference between normal ducts and ducts containing DCIS**, and it appears that dynamic contrast-enhanced MR imaging is able to depict this difference ... the difference may be due to the **increased permeability of the basement membrane of DCIS-containing duct**, allowing gadolinium chelates to penetrate the membrane and accumulate within the DCIS-filled milk ducts. The increased permeability is likely due to **increased protease activity** induced by the intraductal cancer cells. This protease activity **may be necessary to improve or maintain the nutrients and oxygen supply of a DCIS**; however, it may also constitute a **prerequisite or a first step for progression to invasive cancer**.

Accordingly.....enhancement on MR images could constitute a biomarker that helps in the prediction of the natural behavior of a DCIS lesion .

This is consistent with the observation that the sensitivity of MR imaging in the detection of DCIS increases with nuclear grading of DCIS which, in turn, correlates with the likelihood of DCIS progressing to invasive cancer.

... contrast enhancement in patients with DCIS requires the gadolinium chelate to diffuse from the intravascular interstitial space to the extravascular interstitial space and then... to the intraductal space. This is in perfect agreement with the clinical observation that the **enhancement kinetics of DCIS differ from those of invasive cancers**. DCIS enhancement rates will remain below the typical enhancement thresholds of invasive cancers; a washout signal time course in a DCIS is rare. This means that **current criteria related to enhancement kinetics are probably not useful in the diagnosis of DCIS and the current computer-aided detection software systems** calibrated to the enhancement pattern of invasive cancers **will consistently fail to highlight DCIS**.

The Practice

.... recent study **about half of all DCIS cases can be detected with both mammography and MR imaging because they exhibit both calcifications and contrast enhancement.**

However, as many as **half of the high-grade DCIS lesions remain mammographically occult because they do not exhibit calcifications ; however, they do exhibit enhancement on MR images .**

Whereas **a high-grade DCIS lesion without enhancement is rare (about 2% of cases), absence of enhancement is observed in about 20% of low-grade DCIS lesions.**

These lesions can be occult on MR images but may be **diagnosed with mammography because they may exhibit calcifications.**

... depiction of a DCIS lesion on an MR image should be expected to correlate with ... its readiness to invade. In contrast, the depiction of a DCIS lesion on a mammogram is based on calcifications. In other words, it is based on regressive changes associated with hypoxia and cell death. **DCIS lesions that exhibit calcifications on mammograms but no enhancement on MR images may be the lesions that do not prepare invasive growth** because their basement membrane integrity is intact and because they are not actively recruiting periductal blood vessels .

Accordingly, with all likelihood, DCIS lesions diagnosed at MR imaging will not be a source of overdiagnosis but will highlight DCIS lesions that indeed have the potential to progress to invasive cancer. Thus, on the basis of the results of the animal study performed by Jansen et al ([1](#)) and clinical observation ([4](#)), there is compelling evidence to suggest that the imaging phenotype of a DCIS lesion (its detectability at mammography and MR imaging, specifically the presence or absence of calcifications on mammograms and the presence and degree of their enhancement on MR images) conveys important biologic information that will be useful when guiding DCIS treatment.

Diagnosis and treatment of high-grade DCIS can be considered primary prevention of high-grade invasive cancer.

Thus, we have reason to assume that screening with MR imaging would offer a mortality benefit that is higher than that achieved with mammographic screening, not only because of the higher overall sensitivity offered by MR imaging but also because of its bias for selectively depicting prognostically relevant disease.