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Evolution of breast imaging: Beyond mammography

Regarding the early diagnosis of breast cancer, population based mammographic screening has been shown to help reduce breast cancer mortality. Mammographic screening, reduced post-menopausal hormone intake and the development of new, targeted therapies all contributed to the reduction of breast cancer mortality that has been observed in the last couple of years. Still – breast cancer is one of the most frequent cancers overall, and it continues to be the leading cause of cancer death in women, indicating that there is room – and need! – for improvement.

Magnetic resonance imaging (MRI) of the breast has been introduced a decade ago. Over recent years, it has become increasingly evident that breast MRI is by far the most powerful breast imaging technique that is currently available. Across all different clinical and screening scenarios, MRI has been shown to be superior to mammography – be it for diagnosing primary or recurrent, invasive or intraductal, familial or sporadic breast cancer, irrespective of a woman's breast density. And yet is the technique only slowly adopted in clinical practice. Arguments against the use of breast MRI include costs, frequency of false positive diagnoses, lack of evidence by randomized controlled clinical trials, and, last, fear of overtreatment. In this lecture, these concerns are reviewed, discussed and weighted against the advantages of screening and diagnostic applications of breast MRI.

The point is made that on the long run, the main advantage of breast MRI over mammography will not be its higher overall sensitivity for breast cancer – but its tendency to identify biologically active disease. In other words: In view of the heated discussion around overdiagnosis and overtreatment of cancer in general and breast cancer specifically, the future question with regards to breast cancer screening methods will no longer be: “How many breast cancers do we detect by a screening method?” but “What type of breast cancers do we detect?”. The following pathophysiological considerations fuel this statement:

It is well established that breast cancers that are diagnosed through mammographic screening have a better prognosis than those detected by clinical examination: Mammography tends to detect slowly growing cancers, a well known effect referred to as “length time bias”, of which overdiagnosis is an extreme form. On the other hand, it is well established that breast cancers detected through MRI screening exhibit adverse biological profiles. Accordingly, whereas mammographic screening has a bias for detecting slowly growing cancers, MRI screening has a bias for detecting rapidly growing cancers.

The reason for this difference lies in the different pathophysiological basis of breast cancer detection in mammography and MRI:

Mammography detects breast cancers by revealing structural changes that go along with *impeded* neoplastic growth (calcifications due to necrosis, architectural distortions due to local fibrosis which is secondary to hypoxia). Accordingly, breast cancer detection in mammography is mainly based on the depiction of regressive changes associated with slowed growth. This is different for DCE breast MRI, where cancer is detected due to local contrast enhancement. Enhancement of a DCIS or of an invasive cancer depends on a locally increased vessel density, an increased vessel permeability and – in the case of DCIS – an increased

permeability of the ductal basal membrane. Accordingly, breast cancer detection in MRI is based on pathophysiological changes that are indicative of cancer proliferation, infiltrative growth and metastasis. In fact, the more angiogenesis or protease activity a cancer or DCIS exhibit, the higher the likelihood that it will be detected by MRI. Accordingly, detection of a DCIS or of an invasive cancer in MRI is biased towards cancers that are successful in maintaining an adequate supply of oxygen and nutrients and thus in maintaining metabolic homeostasis and metastatic potential. In addition, local contrast enhancement is an in-vivo biomarker for DCIS protease activity, because an increased ductal basal membrane permeability is required to allow a gadolinium chelate to accumulate within the milk ducts. It is well established that protease activity is an essential initial step in the process of invasive growth of DCIS, and of metastatic growth of invasive cancer.

Accordingly, we propose that overdiagnosis of prognostically irrelevant, biologically inert cancer (with all its important medical and socio-economical implications) is closely related to the very basis of mammographic breast cancer detection, and can hence be considered a modality-inherent, unavoidable side effect of mammographic screening.

In contrast, overdiagnosis may not be an inevitable consequence of MRI screening. We propose that in spite of the higher overall sensitivity of MRI and in spite of the higher cancer detection rates that have been published with MRI screening, *over*diagnosis could even be *reduced* if MRI *alone* was used for breast cancer screening. This will probably be especially true for the diagnosis of DCIS.