Imaging in oncology: the role of MRI today and tomorrow

The packed audience at the Bracco-sponsored scientific symposium on MRI in oncology at this year’s ECR congress were treated to top-of-the-line presentations given by clinicians renowned in their field and who described the current status and future potential of MR imaging in prostate, breast and pancreas cancer respectively. A feature common to all presentations was the demonstration of the important role played by Contrast-Enhanced MR imaging in the different pathologies.

Highly efficient MR Contrast media in clinical practice

As an introduction to the session Prof Martí Bonmatí gave a short presentation describing how higher relaxivity contrast media are advantageous in improving diagnosis and clinical outcome. Simply put, contrast media increases contrast resolution, thereby improving the detection of lesions and their characterisation, classification and grading. In addition the approach allows quantitative voxel-based biological data to be extracted, permitting analysis of perfusion, angiogenesis, permeability, flow, cell number and viability. With MR contrast media the signal intensity enhancement achieved varies with the dose administered, the rate at which the contrast agent is administered, the MR sequence parameters selected and, importantly, the relaxivity of the agent which in turn is related to its biological distribution and physicochemical properties. The chemical nature of the chelating molecule affects the biodistribution, pharmacokinetic properties and relaxation rates.

There are two main groups of gadolinium-based contrast agents, namely those with high relaxivity e.g. the Multihance product from Bracco with a relaxivity at 1.5T of approximately 6.2 L/mmol.s⁻¹ and another group with a lower relaxivity at 1.5T of approximately 3.9 - 4.6 L/mmol.s⁻¹.

At higher field strength, relaxivities progressively decrease, e.g. at 3T the relaxivity of the Multihance product is approximately 5.4 L/mmol.s⁻¹.

Contrast media with similar relaxivities and administered at similar doses, give similar enhancement. From the quantitative point of view it is important to recognise that there is a bolus dispersion, i.e. a dilution during the first pass through the lungs and the heart. Bolus dispersion leads to a normalization of the bolus shape for an equivalent total dose. Relaxivity remains however the most important factor. In oncology, CE-MR imaging can be used for many different tasks. This can lead to evaluation of tumor variability, but also to the characterisation of many different tumor features of such as structural, metabolic, physiological, cellular, biophysical and molecular features.

MRI in prostate cancer management: an evolving role

The starting point of Prof Oto's presentation was the dramatic changes in the quality of prostate MR imaging over the years. Comparison of the first MRI image of the prostate taken in 1982 with those routinely obtainable today shows a striking improvement in image quality. Such improvement is due not just to evolution in technology, but also in the whole prostate "landscape", particularly as far as PSA screening is concerned.

As regards technology there has been significant improvement in scanner technology (e.g. 1.5T to 3.0T), in coils (endorectal and phased array coils) and also in functional sequences e.g. Diffusion Weighted Imaging (DWI) and dynamic contrast-enhanced imaging (DCE). Currently multiparametric MRI (mpMRI) — a combination of T2W, ADC mapping and DCE — is the optimal approach to imaging the prostate, and has a PPV of 98 %. There are however still some pitfalls with mpMRI, namely in transition zone cancer and prostate toxicity. Additionally, even though T2W and ADC mapping are the mainstay of prostate imaging there is a subset of prostate cancer (PCa) which is only visible with DCE. For this DCE should always be retained in the armory of available techniques.

In addition to technological evolution the overall "landscape" of PCa has changed over the last decade, as a direct consequence of the introduction of PSA screening. A consequence is that radiologists see an increasing number of patients of younger age and succeed in diagnosing prostate cancer at an earlier stage.

However, there have been two major problems associated with this trend, namely inefficient diagnosis and overtreatment. MRI can help with both these problems.

A further significant change in the field over the last three decades or so is that of evolving indications of the MRI technique. Initially, MRI was primarily used for detection, localization and local staging of PCa. Over the last decade, many new indications for the technique have arisen, such as risk stratification, delineation of lesions, targeted biopsies, follow-up and triage for active surveillance (an important emerging area),
with PCA has two options: either whole gland therapy or active surve-
nance. Focal therapy is a middle ground solution balancing onco-
logic efficiency and safety and has the goal of eradicating the target and in so doing sparing the at-risk organs (rectum or bladder) and keeps the treatment options — either focal or whole gland therapy — open. There are several approaches to focal therapy, e.g. cryotherapy, high intensity focused ultrasound, electroporation, photodynamic therapy, radiotherapy and MRI-guided laser ablation. This latter approach has generated encouraging phase one results; phase two studies are being initiated.

Regarding the future, there are several areas where progress is needed. One of these is standardization, both for image acquisition and reporting, e.g. via the PI-RADS system. Validation is also needed, e.g. in multicentric clinical trials so that the true benefits of MRI involvement can be evaluated. Cost-effectiveness of MRI must also be demonstrated.

Despite the future need to address these issues, currently there is no doubt that MRI can address the shortcomings of diagnosis and treatment of PCa. Targeted biopsies, follow-up, risk stratification and focal therapy are emerging MRI indications. However organized research is needed for validating and establishing the role of MRI.

All in all this is an exciting field, and one in which urologists are heavily involved. It is important for radiologists to be aware and actively involved as well.

Breast Cancer Screening: who, when and how?

Following on from the previous presentation on prostate cancer, there are several features in breast cancer screening which have similarities in prostate cancer: most importantly the conclusion that breast cancer is a heterogeneous disease with a broad spectrum of cancers that differ with regard to their biologic importance. Radiologists should respond to the increasing clinical need of avoiding overdiagnosis of prognostically irrelevant disease as well as under-diagnosis of prognostically important cancers, and improving treatment stratification. The one thing that has been proven by the mammographic screening trials conducted in the 1970s is that early diagnosis of breast cancer — i.e. diagnosis of breast cancer that is confined to the breast — does translate into improved survival. Age-standardized mortality rates of breast cancer show a significant decrease in mortality from breast cancer over the past decades – an effect that is at least in part contributable to early diagnosis through mammographic screening. In the light of these encouraging trends, the question can be put: why is there a need to look for additional breast cancer screening methods? One answer to this is overdiagnosis. Precise estimations of the number of over-diagnosed cases vary; recent estimations are that about 10% of breast cancer cases are “overdiagnosed”. Whatever the precise level of over-diagnosis, the fact remains that mammography is particularly sensitive for the detection of slowly-growing cancers. There is an inherent, technologically based bias in mammography for the detection of architectural distortions, spiculations and calcifications, i.e. pathophysiological processes (e.g. hypoxia, necrosis, fibrosis) that reflect regressive changes. The same characteristics apply to breast tomosynthesis (DBT). It is well established that mammographically visible lesions enjoy a better prognosis than lesions that were mammographically occult, i.e. were diagnosed as interval cancers – an effect known

![MRI in Prostate cancer](image)

**FIGURE 1.** There are several areas where MRI has a potential role in the management of PCa. 1. In patients with elevated PSA, even before TRUS guided biopsy. 2. MRI has recently been approved by the European Association of Urology for the examination of negative biopsy. 3. Once the patient has been diagnosed with PCA, he faces a wide range of treatment possibilities. MRI can provide a lot of information to help make such a decision more evidence-based. 4. In patients undergoing active surveillance, one third will need radical prostatectomy. MRI can help in identifying such patients. 5. For patients undergoing focal therapy, it is of course desirable to know where the lesion is. 6. Likewise in cases of biochemical recurrence, i.e. where PSA levels rise after treatment it is important to know where the cancer is. MRI can help in this.

decisions for focal therapy as well as detection of any recurrence of the cancer.

MRI has a significant potential in several stages of the management of PCa, although, as yet, none of these applications have been established as being a method of standard clinical care.

As Figure 1 shows, MRI can provide valuable information in the management of PCa. The challenge is to use this information to generate improved outcomes. Certainly MRI-guided biopsy is becoming more and more widespread. There are three subsets of this, namely 1) straightforward MRI biopsy (in bore); 2) cognitive registration where the urologist uses the MRI information to mentally guide the ultrasound biopsy process and 3) MR-US fusion, where the MRI images are sent to the urologist’s ultrasound instrument and fused together on the work station to enable the biopsy to be taken precisely on target.

This latter MRI-US fusion approach involving collaboration between radiologist and urologists is becoming more and more common. Overall the cancer detection rate with the approach is lower than that of TRUS-guided biopsy, but more clinically significant PCa is detected, with fewer cores. Importantly the MRI-US fusion guided biopsy detects clinically significant PCa missed by TRUS-guided biopsy.

Regarding the role of MRI in active surveillance, there are cases of apparently low risk PCa being shown on MRI follow-up to have developed in fact into aggressive high risk cancer requiring radical prostatectomy.

As far as focal therapy is concerned, currently a man diagnosed with PCA has two options: either whole gland therapy or active surveillance. Focal therapy is a middle ground solution balancing oncologic efficacy and safety and has the goal of eradicating the target and in so doing sparing the at-risk organs (rectum or bladder) and keeps the treatment options — either focal or whole gland therapy — open. There are several approaches to focal therapy, e.g. cryotherapy, high intensity focussed ultrasound, electroporation, photodynamic...
as “length time” bias. Overdiagnosis is just an extreme form of length time bias.

Surprisingly enough, given the current debate and focus on overdiagnosis, i.e. the tendency of mammographic screening to pick up prognostically irrelevant disease there is another issue that one could call “underdiagnosis”, i.e. the fact that mammography screening has a limited sensitivity for prognostically relevant disease. This has been known for some time from the results of several trials, e.g. the DMIST trial of several years ago, where the average sensitivity for both techniques was around 36%. Likewise, cancer epidemiology studies show that, despite many years trials of mammography screening, breast cancer continues to be the most important cause of cancer death in women. The fact that many women continue to die of breast cancer is in itself a rebuttal of the idea that overdiagnosis is the only, or even the major, issue associated with mammographic screening.

In summary, mammography screening has two apparent shortcomings, namely overdiagnosis of prognostically irrelevant cancer as well as underdiagnosis of prognostically important disease. This is the rationale behind the search for, and evaluation of new screening methods which may provide better performance, namely avoiding both over- and under-diagnosis. There are several such candidate screening technologies:

Candidate breast cancer screening modalities

Five technologies have the potential to fill such a role, namely Digital breast tomosynthesis (DBT); contrast enhanced digital mammography; hand-held ultrasound (HHUS); automated ultrasound (ABUS); and MRI. Of these, data of their use in screening applications are available for DBT, HHUS and MRI.

- Screening Digital Breast tomosynthesis (DBT).

There are several large clinical studies available (the most recent being Friedewald SM et al JAMA. 2014;311:2499) which show that when DBT is used in conjunction with full field digital mammography, on average an additional 1.25 cancer cases out of 1000 patients can be detected, i.e. a significant increase compared to screening mammography alone.

- Hand-held ultrasound (HHUS).

A large clinical trial (Berg WA et al JAMA. 2008; 299: 2151) compared screening with ultrasound plus mammography versus mammography alone. It was found that the addition of ultrasound increased the number of detected cancer cases by 4.1 out of a 1000 patients, so a considerable increase on mammography alone. However the average time need for the radiologist to complete a bi-lateral screening ultrasound examination was 21 min. The same group extended their ultrasound trial to include a single MRI screening (Berg WA et al JAMA 2012; 307; 1394). They found that the inclusion of a single MRI screening round increased the number of detected cancers to 14.6 per 1000 patients, i.e. a huge increase compared to ultrasound combined with mammographic screening.

- MRI

There have been several trials of MRI in breast cancer, e.g. the EVA trial (Kuhl C J Clin Oncol. 2010; 28: 1450) from which one of the striking conclusions was the very high sensitivity of the technique in detecting breast cancer [Figure 2]. This high sensitivity has been confirmed in several other trials, although a few have reported slightly lower sensitivities. These latter results have been explained by a relatively low detection of DCIS cases, which has significantly “improved over time with experience” Warner E et al Breast J. 2011; 17: 9. What comes out of all these trials is that the rate of interval cancer is extremely low.

Moreover, MRI has a technology-inherent bias to preferably detect biologically important disease. All pathophysiological processes that are required for carcinogenesis, cellular proliferation, invasion, and metastatic growth, such as angiogenic activity and local protease activity, lead to strong and early enhancement of breast cancer on MRI. Accordingly, MRI is a biomarker for prognostically important disease, especially DCIS.

One criticism of MRI for screening for breast cancer is that it is expensive, all the more so since only a small percentage of women examined will be found to have breast cancer. For this reason, many studies of MRI in breast screening have an enriched cohort, including women who have a high risk of developing cancer. A deeper analysis of the costs of breast MRI shows that MRI could become a true screening modality if the acquisition time could be reduced, the radiologist’s reading time reduced and if there were expert MRI radiologists available to read the images. This is the principle behind the abbreviated (AB MRI) protocol approach [Figure 3] which uses a reduced time protocol with acquisition times of 3 min vs 17 min for a full diagnostic protocol (Kuhl CK J Clin Oncol. 2014; 32: 2304).

This approach, using an MRI table time of about 3 min and an expert radiologist reading time of about 2 sec, was shown to be able to give an additional cancer yield of 18.3 per 1000 women who had been previously screened using a full diagnostic protocol.

The AB MRI approach appears to fulfill the criteria of the desirable radiological role of imaging methods with a maximum sensitivity for prognostically relevant disease and a low sensitivity for prognostically unimportant disease.

**FIGURE 2.** MRI has the highest sensitivity for the detection of breast cancer. The combination of other modalities such as mammography (Mx) or ultrasound (US) with MRI does not significantly increase the sensitivity of MRI alone.
The role of MRI in the diagnosis and early detection of pancreatitis: current situation and future perspectives

Pancreatic neoplasms, can be classified into solid and cystic categories.

For solid pancreatic neoplasms, CT is the modality of choice, with MRI being a problem-solving technique. In contrast, for cystic pancreatic neoplasms, MRI is the method of choice and CT a problem-solving technique.

There are several pathologies in the solid pancreatic tumor category:

- **Pancreatic Adenocarcinoma**

  This is one of the most common of all pancreatic neoplasms, representing 75-80% of all cases. The very poor prognosis (5y survival < 5%) is due not only to the very aggressive nature of the cancer but also to the problem of late diagnosis. The carcinoma is desmoplastic in nature with the amount of fibrous tissue being the reason behind the frequently used description of the pathology as "the scar that never heals". The fibrous tissue can be detected in ultrasound analysis and CT shows hypodensity due to the desmoplastic reaction. On MRI the fibrous tissue gives low signal both on T1 weighted images and T2 weighted images. With contrast enhanced imaging, since pancreatic adenocarcinoma is hypovascular, there is delayed wash-out.

- **Pancreatic Neuroendocrine tumors (NETs).**

  These represent <2% of all pancreatic neoplasms. In contrast to pancreatic adenocarcinoma, 75% of pancreatic NET patients survive 2yrs after diagnosis. From the clinical point of view, the tumors can be non-functioning (83% of cases) or functioning (17%) These latter have a better prognosis. On T1-weighted MR imaging the majority of NETs are hypointense while on T2 weighted images. With contrast enhanced imaging, since pancreatic adenocarcinoma is hypovascular, there is delayed wash-out.

- **Mucinous cystic neoplasms (MCNs).**

  MCNs are a different entity and are mostly located in the body/tail of the pancreas. Nearly all patients are females with a mean age of onset 45 years. On pathology, MCNs have an appearance of ovarian stroma. One theory to explain this is that in embryonic development, the ovaries are very close to the tail pancreas. From the biological point of 5.5% of MCNs are carcinoma in situ, 12% are invasive carcinomas, 10.5 % are borderline and 72% are adenomas.

- **Serous cystadenoma (SCA)**

  In contrast to IPMNs which are characterized by recurring episodes of acute pancreatitis, SCAs, are mainly asymptomatic and are mainly non-communicating. There is equal male/female predominance and the mean age of onset is 70 years of age. The malignancy rate is 0 %. The macroscopic appearance of SCA is “honeycomb” and on pathology, the epithelial cells are glycogen -rich which is the hallmark of SC, which can occur anywhere in the pancreas (52% of cases in the pancreatic head, and 48% in the body/tail).

- **Intraductal papillary mucinous neoplasms (IPMNs)**

  With a mean age of onset of 60 years and an equal predominance between men and women, IPMNs arise in the pancreatic duct system. The symptoms are intermittent occurrences of pancreatitis caused by the blockage of the pancreatic duct system and the development of upstream pressure. In IPMNs the progression of adenoma to carcinoma depends principally on the location of the lesion. When there is involvement of the main pancreatic duct the chance of progression to malignancy is about 70% whereas if the site is in the side ducts, the risk of progression is 25%. Another risk factor for adenoma-carcinoma progression is age: the more elderly the patient, the more likely a transformation to a malignant stage. Some estimates of the time taken for such a transformation is approximately ten years, but the precise time is still unknown.

A close follow-up of the patient is required to monitor for signs of malignant transformation. Signs are the size of the main pancreatic duct but more importantly the presence of mural nodules (Figure 5). On MRI, these latter must enhance, reflecting new vascularization. Since they are small in size it is important in contrast-enhanced imaging to use an agent of high relaxation.

- **Intraductal papillary mucinous neoplasm (IPMN); a cystic pancreatic neoplasm.** Pancreatic neoplasms can be categorised as solid or cystic. In the latter category MRI is the imaging modality of choice. For differential diagnosis, the acronym FLAG is useful, where F= frequency of the pathology, L=Location of lesions; A= the Age of patient and G= the Gender of the patient.

  **Figure 4.** Example of Intraductal papillary mucinous neoplasm (IPMN), a cystic pancreatic neoplasm. Pancreatic neoplasms can be categorised as solid or cystic. In the latter category MRI is the imaging modality of choice. For differential diagnosis, the acronym FLAG is useful, where F= frequency of the pathology, L=Location of lesions; A= the Age of patient and G= the Gender of the patient.