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Interview on Breast Imaging
Germany / Prof. Christiane Kuhl

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Breast imaging in Germany

An interview with Prof. Dr. Christiane Kuhl, director of the Department of Diagnostic and Interventional Radiology at the University Hospital Aachen, Germany.

European Society of Radiology: *Breast imaging is widely known for its role in the detection of breast cancer. Could you please briefly outline the advantages and disadvantages of the various modalities used in this regard?*

Christiane Kuhl: Breast cancer is the most frequently occurring type of cancer in the female population and represents the most or second-most common cause of cancer death in women. Mammography is the baseline examination that we use to detect breast cancer within large screening programmes and is the basis of early breast cancer detection. It is the imaging method that has been used for the longest time; screening programmes have been conducted since the 1970s, therefore there are decades of experience and data. If mammography is used for early diagnosis, this translates into a survival benefit for women with breast cancer, estimate to be 22–35%; according to newer research, possibly even higher. Variations of estimations are likely because it takes a long follow-up period to see if people who have had mammography screening live longer than people who have not. The most important finding of mammographic screening trials, however, has been that early diagnosis of breast cancer – a disease previously held as 'primary systemic' by many – does indeed prevent progression to metastatic disease and death from breast cancer.

However, mammography has its limitations. It implies the use of projection radiography – a method that is hardly used for cancer detection in other fields of radiology. Such limitations persist in spite of impressive technical improvements that have been made, especially during the last ten years, such as full-field digital mammography (DM), and digital breast tomosynthesis (DBT). DBT provides images that are generated by conventional tomography – the same type of quasi-cross-sectional imaging that had been used before the advent of CT. Results of large screening trials are now available that suggest that DBT is not ground-breaking, but is simply a 'somewhat better mammogram'. It helps improve the rate of cancer detection and also helps reduce the number of false-positive diagnoses.

Most breast cancers arise from the cells that build the inner lining of milk ducts. In most cancers, there is a period during which the cancer cells stay inside the milk duct and fill up the milk duct lumen. This stage is called DCIS (ductal carcinoma in-situ) and is considered a precursor of actual breast cancer. Only when the cancer cells penetrate the milk duct wall and spread into the adjacent normal breast tissue are they considered 'actual', or invasive, breast cancer. Invasive cancer can gain access to lymphatic channels or blood vessels and then disseminate to the body. Diagnosing invasive cancer early is essential to avoid such spreading of cancer cells to other body organs to cause metastases; diagnosing a cancer in the DCIS stage means preventing such a development altogether. Some (about half) of the DCIS have useful features from a radiologists' perspective since they cause calcifications which can be readily seen on mammography. This is why we can use mammography to depict these precursors very well.

The main challenge with mammographic screening is the fact that the composition of the breast is very variable between women – and so is the accuracy that can be expected from a mammogram. If a breast is mainly composed of fat tissue, a mammogram is a powerful imaging method for early diagnosis because there will be a sharp contrast between the tumour (which will appear whitish) and the background (which will appear dark). However, if the breast contains normal fibroglandular breast tissue, this tissue will also be white on x-rays. In a dense breast, breast cancer can be obscured by the fibroglandular tissue since it has the same colour and density. Therefore, the sensitivity of mammography – that is, its power to find cancer – will be low in women with dense breast tissue,

and will be high in women with involuted (fatty) breasts. About half the cancers will go undetected by mammography if women have dense breast tissue. About half of women will have dense breast tissue, i.e. more fibroglandular tissue than fat tissue. This is one reason why other imaging methods are being explored.

Another challenge is so-called overdiagnosis. Over-diagnosis means that not all cancers found with screening are the killers that we think they are. Some cancers that are found would never progress to become life threatening conditions for an individual. Overdiagnosis is the diagnosis of such conditions, i.e. findings that indeed correspond histologically to true cancers, but don't clinically behave like a cancer. A major reason for overdiagnosis is the fact that mammography is used to detect breast cancer mainly by detecting signs that are due to regressive changes. One could say that the slower a cancer grows, the better it will be picked up by mammography. In short: mammographic screening detects the 'friendlier half' of breast cancers. The flip side to this is that especially rapidly growing cancers – cancers that can really kill women – may not cause any detectable changes on mammography. They may mimic benign changes or even normal breast tissue. These cancers tend to remain undiagnosed by mammography, and then may pop up and become palpable a few months after a normal screening mammogram. This is then called an 'interval cancer'; a cancer that was found in the interval between mammographic screening rounds. Such interval cancers are the main driver of breast cancer mortality. With mammographic screening, between one-third to one-half of cancers diagnosed in screening participants will not be found by mammography, but will correspond to such 'interval cancers'. This may explain why, in spite of decades of mammographic screening, the actual problem is unchanged: breast cancer remains a major cause of cancer death in women. Accordingly, there is substantial need and ample room for improved breast cancer screening methods.

Ultrasound is the ideal companion of mammography because it works best in areas where mammography is weakest, that is in dense, fibroglandular tissue. In turn, ultrasound is less reliable in areas with fatty tissue, which is where mammography works best. Accordingly, ultrasound and mammography are complementary methods. Ultrasound, however, is not reliable in depicting DCIS or diagnosing cancers in fatty breasts, which is one reason why we do not use ultrasound alone for screening. Another reason is quality control. During an ultrasound examination, the breast is examined and a picture is only taken if the operator sees something suspicious; if the operator does not see something suspicious, or if he or she overlooks a cancer, then there is no documentation of this failure. The vast majority of images that are generated during an ultrasound examination remain undocumented. Another reason why ultrasound is not more frequently used is that the entire examination takes a lot of the radiologist's time, which is expensive. Last, in breast ultrasound, even with high resolution imaging, there is a relatively broad overlap between breast cancers and benign changes, leading to the fact that of all imaging methods, ultrasound is associated with the lowest positive predictive value.

Breast MRI is the most accurate imaging method for all types of breast cancer, be it precursor or invasive, primary or recurrent breast cancer, and is accurate irrespective of breast density. Compared with mammography, it doubles the sensitivity with which we can detect invasive cancer or DCIS. Moreover, breast MRI is especially good at finding biologically relevant, rapidly growing breast cancers that have the potential to kill women. As explained above, such cancers can be very difficult to find with mammography because they do not cause mammographically visible changes. MRI, however, depicts perfusion and protease activity; it is not only a diagnostic tool, but provides us with imaging biomarkers that reflect how aggressively a cancer behaves. One could say the faster and more aggressively a cancer grows, the better will it be visible on MRI.

Over the past few decades, MRI has been considered the gold standard for breast cancer imaging. However, it is also by far the most expensive imaging method, which guides its use for screening. In screening, the vast majority of women will be healthy, i.e they will not have breast cancer. At a given point in time, on the day of screening, only a small fraction of women will have breast cancer. However, only these ones, i.e. the ones who have cancer, can benefit from early diagnosis. Accordingly, the benefit of screening is low when referenced to the entire cohort undergoing screening – however large it will be for the individual who does have cancer and whose cancer is

found early. The more expensive an imaging method is, the less cost-effective will be the screening programme. Therefore, if MRI is used for screening, we try to 'enrich' the patient cohort by offering it only to women who have a high lifetime risk of developing breast cancer. Women who belong to this group either have many family members with the disease or other strong risk factors. The American Cancer Society recommends annual MRI examinations for women with a lifetime risk of 20% or greater. It should be well understood that the current reason to restrict the use of MRI for screening to high-risk women is mainly due to cost control reasons. Previously published results on women with variable lifetime risk levels, as well as our own results on screening MRI for women at average risk of breast cancer, show that the gradient between MRI and mammography, i.e. the difference in accuracy, is the same, independent of a woman's lifetime risk. This means that not only for women with high lifetime risk, but also for other woman, MRI is the best imaging method to ensure early diagnosis of breast cancer. For reasons explained above, this will be more important for women with dense breast tissue than for those with non-dense breasts.
In the long run, I think that the sensitivity profile of MRI – the fact that it is so good at finding aggressive cancers – is its most important advantage over mammography. In the year 2016, and in view of the debate about overdiagnosis, it's not about finding even more cancers, but about finding the right cancers early; the cancers with the potential to kill women. And this is what MRI can do.
However, in its current version, MRI is too expensive to be used on a broader scale. To tackle this problem, we published the concept of 'abbreviated breast MRI', or AB-MRI, in 2014. This is an MR examination that takes only a few minutes (less than four), and can be read by an experienced radiologist within a couple of seconds. We have shown that such AB-MRI can be used to screen larger cohorts of women, and yield a diagnostic accuracy that is similar to that achieved with the complex lengthy examination usually used for breast MRI. The ECOG/ACRIN 1141 study will investigate the utility of AB-MRI in a larger clinical trial. Once we have these results, we will likely use MRI for screening on a much broader scale, e.g. to compensate for the weaknesses of mammography in women with dense breast tissue.

ESR: *Early detection of breast cancer is the most important issue for reducing mortality, which is one reason for large-scale screening programmes. What kind of programmes are in place in your country and where do you see the advantages and possible disadvantages?*
CK: The German mammography screening programme has been in place since 2007. The programme is quite modern; it employs mainly digital mammography and enforces quality assurance guidelines set forth by the European Union.

ESR: *Do you know how many women take part (percentage) in screening programmes in Germany? Do patients have to pay for this?*
CK: Around 70% of women take part and they do not have to pay.

ESR: *The most common method for breast examination is mammography. When detecting a possible malignancy, which steps are taken next? Are other modalities used for confirmation?*
CK: Well, the first step is to talk to the patient. It is very important to explain that we try to find cancer very early and react to subtle signs, which in half the cases are not due to breast cancer. Therefore the first thing I tell women is not to be afraid. In the worst case, if it is indeed breast cancer, it is good to have found it early, so that with all likelihood, it can be successfully cured!
Depending on which type of finding was made on screening mammography, ultrasound is usually performed as the next step, to see whether the finding is suspicious on ultrasound, too, and if so, to do an ultrasound-guided needle biopsy. Of course, not all findings are caused by cancer; all imaging methods will cause so-called false positive diagnoses. Patients should know that radiologists don't walk on water. We strive to find breast cancer early, and this may mean that we react to findings that are subtle and may be benign, but this is only meant to avoid late diagnosis.
Sometimes it is argued that this is a good reason to discourage screening – women could be terrified by false positive diagnoses. However, most women I have talked to understand that through biopsy, without a hospital stay or anaesthesia, we are able to selectively collect tissue from a suspicious spot.

This is minimally invasive, there are no scars and we know for sure what it is and whether we have to act on it. This is usually understood by patients. Not offering screening would lead to false negative diagnoses – that is: missed cancers. Most women understand that this – a false negative diagnoses – is much more harmful and associated with much more dangerous effects than false-positive diagnoses.

ESR: *Diagnosing disease might be the best-known use of imaging, but how can imaging be employed in other stages of breast disease management?*
CK: Diagnosing disease early is only one way to use imaging. Once cancer is diagnosed, imaging is needed to map the extent of the tumour. The patient should have an MRI examination during this stage.
Most cancers are not palpable. Women seem to think that once the surgeon has opened the breast, he or she will see the cancer, but this is not true. Most cancers are not visible if the breast is opened and can't be felt because they are very small. If it is DCIS, it is almost never palpable. Therefore we map the disease extent to guide the surgeon with so called guidewires, which are placed under imaging guidance. These wires have a memory shape and will stay in place and the surgeon can use the wire like an Ariadne's thread to find the area of concern.
Moreover, through imaging, we can monitor the cancer's response to medical treatment. Systemic treatment (chemotherapy) used to be administered after surgery. Today women are increasingly treated by 'neoadjuvant' chemotherapy. This means that the sequence is switched: women first receive systemic treatment and only thereafter undergo surgery. The rationale is that invasive cancers kill by shedding cancer cells into the lymphatics and the blood stream. These cells can disseminate throughout the entire body and grow metastases, most often in bone, the liver, or lungs – but actually in any place. Such metastases will kill the patient. At the time of diagnosis, luckily, most women do not have such metastases – but most have circulating tumour cells in the blood stream that you cannot see. The problem is that if you cut away the cancer and don't see metastases, and then give chemotherapy, you don't know if the systemic treatment actually works. Therefore, the concept of neoadjuvant chemotherapy is to not remove cancer, but to give systemic treatment first, and watch what it does with the cancer in the breast, as a surrogate for the cancer cells we don't see. MRI is useful for monitoring the success of neoadjuvant chemotherapy because it helps us to find out early whether or not a cancer responds to treatment.

ESR: *What should patients keep in mind before undergoing an imaging exam? Do patients undergoing radiological exams generally experience any discomfort?*
CK: Of course, there is some discomfort during a mammogram, as the breast is squeezed between two compression plates. This does not do harm to the breast, but it is uncomfortable or sometimes even painful. Yet the better a breast is compressed, the less radiation dose is needed to do a mammogram, and the better the resulting image quality of the mammogram will be. Ultrasound is completely painless, but associated with a high rate of false-positive findings that may then require needle biopsy. MRI is noisy and involves being confined in a relatively narrow space and having an injection of contrast agent.

ESR: *How do radiologists' interpretations help in reaching a diagnosis? What kind of safeguards help to avoid mistakes in image interpretation and ensure consistency?*
CK: Radiologists are the ones that establish the diagnosis. Most patients do not even know that this is the case – they seem to believe that the doctor who reads the radiology reports to them is also an expert in diagnostic imaging. But this is not the case. This is also why I believe that radiologists should step out of the dark and assume their share of responsibility in patient care. Since they are the experts, they should explain the imaging findings to patients directly. This will not be doable, nor desirable or necessary, for each and every imaging study. But there are many situations where this would be good clinical practice and useful for patients.
Regarding quality assurance: for the field of breast imaging, expertise and quality assurance help avoid mistakes to an extent that breast imaging sets the pace for the rest of radiology. The reason is

simple: in breast imaging a radiologist is constantly challenged. Radiologists' interpretations are confirmed or proven wrong by the biopsy that will follow each and every time a radiologist calls something suspicious. In other fields of radiology, radiologists can describe vague findings that no one can ever prove right or wrong – and still survive.

ESR: *When detecting a malignancy, how is the patient usually informed and by whom?*
CK: I am not sure about mammography screening programmes, but at least in diagnostic imaging outside screening programmes in Germany, it's the radiologists who talk to women directly about the breast cancer diagnosis and biopsy findings. It is radiologists who talk to women, decide to biopsy, perform the biopsy, and discuss the biopsy with the pathologist and the patient. We may even be the referring physicians for our breast surgeons.

ESR: *Some imaging technology, such as x-ray and CT, uses ionising radiation. How do the risks associated with radiation exposure compare with the benefits? How can patient safety be ensured when using these modalities?*
CK: Simple: the likelihood of being diagnosed with breast cancer is 10–12% in western countries today. If mammography is used on a regular basis, the risk is increased. This is called an attributable risk, due to the use of ionising radiation in mammography. However, this is a small risk compared to the risk of developing breast cancer. If a mammogram is added every two years, the attributable risk increases the lifetime risk from about 12% to about 12.0001%. So the relative risk is negligible and no reason to replace mammography. A reason to replace mammography would be that it is not the best test for breast cancer that we have right now.

ESR: *How aware are patients of the risks of radiation exposure? How do you address the issue with them?*
CK: Surprisingly, with regard to their breasts, patients are very picky. It is difficult to convince women to undergo mammograms, but easy to convince them undergo chest CT, although the organ dose is that of 20 mammograms. For some reason, at least in Germany, women are very aware of radiation risks, but somehow don't get the bigger picture: yes, radiation is a health risk, but the actual radiation dose that is delivered to the breast through a diagnostic mammogram is negligible compared to the regular risk of developing breast cancer. The other fact I find surprising is that women are careless when it comes to CT imaging and I wish women would more frequently ask if a CT is really necessary.

ESR: *How much interaction do you usually have with your patients? Could this be improved and, if yes, how?*
CK: We talk to patients and their families and their family doctors a lot. Patients come to see me, and talk to me, either because they want to have a screening examination, or in case they have had questionable imaging findings in an outside institution, or because they need a biopsy, or in the follow-up after breast cancer, or to help treat hepatic metastases e.g. by radio-embolisation. We explain our findings, we explain the implications, what options they have, the risks involved in a biopsy or a treatment, and so on. You have to address the concerns of the family, avoid fear and anxieties. I am convinced that our task as doctors is not only to provide good medical care – but to be reassuring to help her cope: be approachable, supportive, and caring.

ESR: *How do you think breast imaging will evolve over the next decade and how will this change patient care? How involved are radiologists in these developments and what other physicians are involved in the process?*
CK: Not in the next decade, but possibly within the next 20 years or so, I believe that population-wide mammographic screening programmes will be replaced by so called 'liquid biopsy' programmes – high-tech methods that use simple blood tests to search for very subtle traces of cancer cells in the blood stream. This will help us to screen large cohorts of women, and identify the few who are at-risk

of having cancer. These pre-selected women will then undergo contemporary, powerful imaging tests such as MRI, or even PET-MRI, to confirm or refute the suspected disease.
Another field that will be evolving is interventional radiology. As a radiologist you not only diagnose cancer, but we also treat disease. For many years, radiologists have been using imaging such as fluoroscopy, MRI or CT to navigate probes or catheters through the human body to carefully and selectively treat only the diseased area. This is called interventional radiology and it provides minimally-invasive treatment of cancer. So far, interventional radiologists have mainly treated metastasis of cancer. However, we can also treat the cancer locally. With the increased potency of systemic treatments and targeted therapies, the importance of local surgery will decrease. I think that surgery will in the future be seen as adjuvant therapy; something that is done in addition to the systemic treatment. When surgery becomes adjuvant, there will be a place for local ablation of these tumours.
Another aspect that favours local therapy is its possible effect on the immune system. There is increasing evidence to suggest that local therapy that does not remove the tumour, but kills it in place, opens up the door for immune-therapy. A dead tumour that is not removed serves as an antigen for the body's immune system. Simply speaking, the dead breast cancer cells in the breast serve as a vaccine against cancer, and help the body fight tumour cells that may circulate in the blood stream, and thus prevent metastasis. Such systemic effects of local treatment are currently being investigated. If these observations are confirmed by clinical trials, radiologists will use cryotherapy or IRE to treat cancer in the breast.

Prof. Dr. med. Christiane Kuhl is currently director of the Department of Diagnostic and Interventional Radiology at the University Hospital Aachen. She is an internationally recognised expert in the field of cancer imaging and image-guided treatment of cancer ('interventional oncology'). She has authored or co-authored well over 1,000 papers and conference abstracts, including several highly-cited landmark papers on the use of MR imaging for cancer diagnosis. She served as Principal Investigator in several large multi-institutional clinical studies. She underwent medical training and board certification and fellowship training for radiology and neuroradiology at Bonn University Medical School. In 2004, she was appointed to the position of Full Professor of Radiology and Endowed Chair on Oncologic Imaging and Interventional Oncology – the first and only professorship dedicated to this field in Germany. From 2009 onward, she served as vice president *(Prorektor)* of Bonn University. In 2010, she was appointed the position of Chairman of the Department of Diagnostic and Interventional Radiology at the RWTH Aachen. She has received numerous awards such as the European Magnetic Resonance Award, the Gold Medal of the ISMRM (International Society of Magnetic Resonance in Medicine), the 'Holthusen Ring' (highest award of the German Radiological Society), and several 'Best of ASCO' awards. She has been a Visiting Professor at many international institutions, and held numerous named lectures at international conferences. She has served as member of the Working Group on Breast MRI of the United States Health Service's Office on Women's Health Commission on Standards and Accreditation, and on the BI-RADS-Committee of the American College of Radiology (ACR). She is Honorary Fellow of the Royal College of Radiologists, and member of a number of international societies such as the Radiological Society of North America (RSNA), the American Society of Clinical Oncology (ASCO), the American College of Radiology (ACR), the European and US Societies of Breast Imaging (EUSOBI, SBI), and the Cardiovascular and Interventional Radiological Society of Europe (CIRSE). She is certified by DEGIR as interventional radiologist for the entire field of interventional radiology, and licensed to train interventional radiologists.