The Future of Breast Cancer Diagnostics

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Epidemiology and Screening

Breast cancer is one of the most common causes of death. Every year, about 19,000 women die of breast cancer in Germany. True prevention is not possible as there exist no vaccines or other measures that can prevent the disease. Efforts to reduce mortality rates aim at improving either early detection or treatment once breast cancer has been diagnosed [1]. The objective of screening programs is to detect breast tumors as early as possible. Nearly all screening centers in Germany now use digital mammography [2–4] which has been shown to be the best imaging test for breast cancer detection [5]. Screening programs should meet the European quality guidelines to ensure optimal management of all women [3].

When analyzing the effects of screening, one often overlooks that not only improved diagnosis but also better therapeutic options have reduced mortality in women with breast cancer over the years [1, 6]. Despite extensive research, it is not clear how much either of these two factors has contributed to the reduction of breast cancer mortality but one may safely assume that the contribution of guideline-based treatment is at least 50%, while the introduction of screening programs has been found to result in an overall reduction of mortality of about 25–30%. About 25% of all tumors escape detection by mammography screening alone with the percentage skyrocketing in women with very dense glandular tissue [5].

Screening without Physicians?

Physician time is expensive. The healthcare expenditure of the compulsory health insurers was € 143.6 billion in Germany in 2005, about € 21 billion (15%) were direct physician costs (plus 10 billion for dentists) [7]. There is an increasing tendency in Germany and other industrial countries to delegate tasks

formerly performed by physicians to other medical staff (e.g. ‘Nurse Agnes’ program [8]). In mammography screening, there have been attempts to delegate certain tasks such as image interpretation [9]. Study results are disillusioning for radiologists: non-physicians were mostly found to be superior in terms of sensitivity, specificity, or accuracy compared with specialists in diagnosis. The extent to which such steps have actually been implemented is still minimal in most countries with mammography screening programs.

Physician costs are an issue not only in screening mammography but also in so-called ‘curative mammography’. Nearly all women undergoing follow-up mammography after breast cancer are additionally examined by ultrasound. It is highly likely that an additional ultrasound examination would improve breast cancer detection in the screening setting as well [10]. Cost is the limiting factor precluding general use of ultrasound. Automated breast ultrasound [11] is highly desirable from a medical perspective (objective and reproducible results, improved documentation) and for cost reasons. Two principal variants of automated ultrasound are currently under investigation – direct integration of ultrasound in mammography systems, which enables both automated ultrasound scanning and fusion of the image data, and stand-alone ultrasound systems for automated breast scanning by technicians [11, 12]. Image fusion is much more difficult with stand-alone systems which only allow simplified documentation of an ultrasound view of the entire breast. On the other hand, there is better coupling of the ultrasound transducer to the breast compared with integrated systems. In the latter, the breast is compressed as in conventional mammography and the ultrasound transducer is moved over the compression paddle. Since intervening air markedly degrades the quality of an ultrasound examination (because it causes total reflection), the periphery of the breast not in full contact with the compression paddle is not scanned. To overcome this limitation, it has been

proposed to perform combined mammography/ultrasound in the prone position with the breast in a water bath. This approach was found to be highly advantageous [13] but has not become established in clinical practice. However, the possible benefit of ultrasound in breast cancer screening might renew interest in this approach.

Diagnosis without Radiation?

While many physicians consider the risk of radiation exposure of a mammography to be negligible, women often experience the risk to be quite considerable. A double blind study for objectively estimating the risk of radiation exposure cannot be performed. Available risk estimates are based on the changes observed after the atomic bombings of Hiroshima and Nagasaki or the effects of X-ray screening programs for tuberculosis. It is doubtful that data from Japan with an approximately 10-fold lower incidence of breast cancer than for instance in the USA or Germany provides a reliable basis. Moreover, studies have shown that exposure to 'hard' radiation equivalent to cobalt-60, as it was released by the atomic bombings, causes fewer biological damage than the extremely 'soft' radiation used in mammography [14–16]. These studies found a 3–9 times higher risk compared with previous estimates. Mammography screening studies such as the Two-County Trial found a higher incidence of breast cancer in women who underwent breast cancer screening compared to controls without screening. However, this observation was primarily attributed to a large number of undetected breast cancers in the non-screening group and overdiagnosis in the screening group [17]. It is now generally assumed that the benefits of mammography by far outweigh its risks, but it is understandable that most women wish the radiation exposure to be as low as possible. That is why other tests not involving ionizing radiation are being developed such as impedance measurement [18, 19] which is based on the fact that the membranes of tumor cells have other electrical properties than normal cell membranes. The resulting difference in tissue conductivity/resistance can be measured. The aim of impedance measurement is to provide yes/no information, followed by other tests to establish a differential diagnosis. In the setting of breast cancer screening, a device for impedance measurement would be comparable to metal detectors used at airports: the device merely identifies metal on a person, while more sophisticated techniques are then needed to distinguish a belt buckle from a bomb for example. Similarly, impedance measurement would be performed in the screening setting by non-physician staff to identify women with an abnormality, who would then undergo further examination. Such a pretest should have an extremely high sensitivity; however, initial multicenter studies suggest that impedance measurement has a sensitivity comparable to that of conventional film-screen mammography. While impedance measurement may be a candidate for supplementing

mammography screening in certain situations or replacing it in healthy women, other tests not involving ionizing radiation such as laser mammography are only used as a supplement (add-on) to conventional mammography [20]. Laser mammography is comparable to computed tomography (CT) in that a laser source and a detector rotate around the breast. The laser absorption technique uses a laser wavelength that ensures maximum absorption by hemoglobin and aims at identifying neoangiogenesis in the breast. Initial results are promising but the additional benefit (when performed as an add-on to conventional mammography) appears to be lower than that of add-on ultrasound. The potential of laser mammography as a stand-alone diagnostic test remains to be determined and also depends on further technical developments. More recent experiments using intravenously administered dyes (for fluorescence absorption) to improve tumor delineation are promising.

In addition to these experimental techniques, established diagnostic modalities operating without radiation – ultrasound and magnetic resonance imaging (MRI) – are constantly improved for breast imaging. A large study by Kolb et al. [10] showed that additional ultrasound considerably improves sensitivity in the screening setting, most notably in women with dense glandular tissue where mammography has notorious limitations. The expected upsurge in false-positive findings and core biopsies with negative results failed to materialize though an increase was obvious. A further increase in sensitivity and/or specificity was found for state-of-the-art ultrasound techniques such as tissue harmonic imaging or 3D ultrasound [21–23]. The 'bird's-eye view' afforded by 3D ultrasound of the breast (with selected compression of the tumor) is considered to be the decisive advantage of 3D ultrasound. Spiculae are often nicely depicted and at times more clearly than with conventional ultrasound. Ultrasound contrast media have not yet become established in routine clinical use. It must also be borne in mind that initial experience with contrast-enhanced ultrasound in breast cancer was gained using strictly intravascular contrast media, which appears to be highly problematic for dynamic evaluation of contrast enhancement. More promising results have been obtained in recent studies. Further data will be needed to define whether there is a clinical role for contrast-enhanced ultrasound in breast imaging.

The only clinically established imaging modality that can be used with contrast media and does not involve ionizing radiation is MRI. The two most important indications for MRI of the breast are the differentiation of scar tissue from tumor recurrence and the evaluation of patients with normal mammography and ultrasound findings for cancer of unknown primary (CUP). At least in Germany, cost of MRI for these indications is covered by the compulsory health insurers. MRI of the breast is characterized by a very high overall sensitivity in tumor detection, and is often used for other indications as well. Many centers use MRI as the standard modality for pre-operative assessment, especially in patients with invasive lobu-

Fig. 1. Example tomosynthesis: original mammography (left), slice from tomosynthesis (right).
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Fig. 2. Example contrast-enhanced mammography (CEDM): original mammography (left), CEDM ring enhancement of tumor (right).

lar cancer or very dense breast tissue [24]. Studies have shown that MRI detects additional lesions in up to 30% of patients with invasive lobular breast cancer, resulting in a change of therapeutic management in many cases. While the high sensitivity of MRI in detecting invasive breast cancer is clearly acknowledged, many investigators think that mammography is necessary to detect ductal carcinoma in situ (DCIS). A controversy has been sparked by an article published by Kuhl et al. [25], and this debate received much attention outside the medical community. In their study, the authors found a high sensitivity for MRI in the detection of DCIS, which was statistically significantly superior to that of mammography for high-grade DCIS and also superior for low-grade DCIS without being significant. Two positions have emerged: one group considers

MRI to be an expensive but much better screening method than mammography, others criticize the methodology of the study by Kuhl et al. [25]. The study population investigated by Kuhl et al. [25] is not typical of a screening population as there was a high proportion of women with symptoms or a markedly increased risk of breast cancer. While Kuhl et al.'s [25] results clearly show that DCIS can be diagnosed using MRI as long as the images are interpreted by an experienced radiologist, the less wide availability of MRI and higher costs preclude the widespread use for general screening outside a high-risk population such as women with a family history of breast cancer.

Mammography without 'Summation Effects'?

The general quality of mammography is often questioned. An argument frequently advanced by critics is that mammography misses many tumors in dense glandular tissue. Nevertheless, one must be aware that screening mammography is currently the only quality-assured and evidence-based method for the early detection of breast cancer, which has been shown to decrease mortality rates in large randomized studies. Admittedly, the major drawback of mammography alone is that tumors 'hide' in dense glandular tissue due to the fact that mammography is a two-dimensional technique degraded by overlying or underlying dense glandular tissue. The sensitivity of mammography alone is therefore markedly reduced in women with dense glandular tissue. Therefore, improvements of the method are desirable. The so-called DMIST study, which included nearly 50,000 women who underwent both film-screen mammography and digital mammography, showed that the latter fares better in dense glandular tissue [5]. Digital mammography has become widely available over the last 10 years and is used by the vast majority of German mammography screening centers. Storage screen systems and direct digital mammography devices can be distinguished. The former are a fairly inexpensive option for digital upgrading of conventional film-screen systems, merely requiring purchase of phosphorous cassettes and a suitable readout device. Future developments of storage screen systems concern phase-contrast mammography and selenium-based systems.

Direct digital mammography including tomosynthesis uses either the slot scan technique or flat panel technique. Tomosynthesis is widely believed to be a promising new diagnostic tool (fig. 1). Tomosynthesis of the breast using a flat panel system was first described by Niklason et al. [26] in 1997. While conventional tomography, a widely used radiologic technique in the past and still in use today, is characterized by the X-ray source and film simultaneously moving in opposite directions, only the X-ray source moves in flat panel tomosynthesis and the detector is stationary. In this way, many views (11–25) are generated showing the object from different perspectives. Algorithms (simple shift and add algorithms, or back projection

algorithms which are now most common) are used to compute single slices from the source data.

Contrast-enhanced mammography [27] also enables visualization of tumors without inference from superimposed structures (fig. 2). Different techniques are used for the visualization of contrast media. Initial experience is available for flat panel systems using the dual-energy technique and so-called temporal subtraction mammography. The dual-energy technique exploits the k-edge of iodine which is about 33.2 keV. When two images are obtained, one directly above and the other directly below the k-edge, there will be a leap in the absorption of X-rays by an iodine-based contrast medium, while other structures show only little change in contrast. The image resulting from subtraction of the two images will therefore nearly exclusively show the iodine enhancement. However, the patient may move between acquisition of the two images with blurring of the subtraction image, making it more difficult to identify smaller tumors. Slot scan systems provide a more elegant solution. The technique exploits the fact that photon-counting slot-scan detectors can separate the contributions of high-energy and low-energy photons to the image. In this way,

it is possible to generate two different images from a single scan – one on the basis of high-energy photons and one on the basis of low-energy photons. Subtraction of the two images will also yield a dual-energy image of the contrast medium. This method eliminates motion artifacts, and separation between high-energy and low-energy photons is more accurate, which should result in improved visualization of contrast medium. Initial phantom experiments using this system suggest that tumors as small as 3 mm can be detected with average contrast enhancement.

If a precontrast image and a series of postcontrast images are obtained using the flat panel system, the temporal course of contrast enhancement can be visualized on a series of subtraction images, similar to MRI. Artifacts occur if the patient moves between acquisitions. The ‘hard’ X-ray beam beyond the k-edge, which is necessary to visualize iodine, is very difficult to generate with conventional digital mammography systems. Despite these limitations, however, temporal subtraction is the most widely studied alternative approach, and some very promising results have been reported.

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