39 Clinical Implications of Breast Cancer

Dimitris-Andrew D. Tsiftsis

39.1 Introduction

In the USA, for 2015 estimated are 231,840 new cases of invasive breast cancer (BC) and 60,290 new cases of DCIS resulting in 40,290 deaths among women. The same year, about 2350 men were diagnosed with breast cancer and 440 men died from the disease. These figures make BC the leading malignancy in females with a 29% share and second in morbidity with 14% behind only lung cancer. The picture is similar in most Western and developed countries. Although the annual incidence of BC in the USA has a 2% decline between years 1999 and 2005, it is still increasing in developing countries. Encouraging though is the fact that since 1990 death rates decrease worldwide, reflecting the progress made in early diagnosis and treatment. More than 3.1 million US women with a history of breast cancer were alive on January 1, 2014. We live in an era where technological advancement in breast imaging and individualized treatments can and will take this achievement a step further.

Due to the elevated awareness of women in relation to BC and the resulting adoption of preventive strategies, we witness a decrease in the mean diameter of invasive cancers with less axillary involvement, more in situ carcinomas, and a steep increase in nonpalpable image-detected lesions. This poses more problems as to the more accurate BI-RADS classification, noninvasive tissue sampling, and less invasive staging. In addition to that, the spectacular advances in molecular biology have enabled us to classify BC to molecular subtypes according to gene expression profiles, to develop markers for targeted therapies and identify a population in genetic predisposition to cancer development. Combined with information from patient's family and past history, we can fairly accurately calculate her risk. In this setting, imaging oncology has a pivotal role to play in prevention protocols competing with chemoprevention and prophylactic surgery.

Critical to the employment of imaging modalities in breast oncology seems to be its rational and sensible use. Recently voices caution the overuse of high-cost imaging especially in stage IV patients [1]. This is attributed to many factors such as easy access to high-end technology, defensive practices, patients' demand, treatment predicament, etc. If this trend continues, it will not only cause to seriously ill patients unnecessary harassment and anxiety but will waste funds and effort much needed for other actions. To combat this, health-care providers must religiously adhere to evidence-based practice guidelines. In this context, new mammographic (Mm) techniques like photon-counting, contrast-

D.-A. D. Tsiftsis, M.D., Ph.D., F.A.C.S.
Hygeia Diagnostic and Therapeutic Center of Athens, Marousi, Greece

A. D. Gouliamos et al. (eds.), *Imaging in Clinical Oncology*, https://doi.org/10.1007/978-3-319-68873-2_39

enhanced, positron emission, tomosynthesis, and others such as breast-specific gamma imaging, enhanced MRI, etc., must be very carefully evaluated for their added diagnostic value as compared to cost and availability.

39.2 Clinical Implications

Breast cancer (BC) imaging has advanced by strides in the last few years reaching the stage of functional molecular imaging. The objectives though remain the same: detection of tumors at the earliest phase, reliable pre- and posttreatment staging, and correlation of image characteristics to prognosis.

39.3 Early Diagnosis and Preoperative Planning

It is well documented that early diagnosis of BC tenders less disfiguring treatments and thus improved quality of life. The crucial step to a woman's striving for early diagnosis is to have her risk assessed. For low to moderate risk, the accepted guideline is from age 40 to 70 digital mammography (dMm) every 2–3 years. In high-risk women, MRI of upgraded specifications to increase its specificity is introduced as a reliable screening, with better tumor yield even at a higher biopsy rate. MRI is also indicated in dense breasts and diffuse microcalcifications. It is imperative for centers using MRI to have available MRI-guided interventions like core biopsy and J-wire placement. In confirmed genetic predisposition, MRI breast screening protocols have to compete against prophylactic surgery that holds the leading role [2].

Another subject open to debate pertains to the routine use of MRI on all women with newly diagnosed BC preoperatively to detect multicentricity, contralateral disease, and the extent of the reference tumor. Meta-analysis has shown a raise of 16% in additional tumors detected at the cost of more radical surgery that does not translate into better survival or fewer re-excisions and recurrences. RCTs are needed to settle the argument, and until then this practice is not recommended [3].

39.4 Accurate Diagnosis of Breast Lesions

The cornerstone of the evaluation of a breast finding is the triple assessment. Central component of the triad is Mm, and the clinician is bound to take further action or not on the BI-RADS classification of the finding. The same applies to US and MRI.

Category 3 is assigned to very few reports (2.34%), and the probability of malignancy remains low (0.81%). Short-term follow-up (FU) covers the patient sufficiently. In categories 4 and 5, a definite tissue diagnosis of the lesion is mandatory. In palpable lesions, this is accomplished either by FNA or core biopsy. The use of US helps to select the proper site of the mass to take the sample. In nonpalpable lesions, the sample has to be taken under the guidance of the imaging modality that has revealed the lesion. Core needle is used to secure a dissent specimen. Today we have automated stereotactic apparatus that can approach safely almost any part of the breast and cut specimens of a size that combines biopsy and cure. If sampling is unsuccessful or not feasible, a J-wire or a tracer is left in place for a guided open biopsy. The patient has the right to be fully informed and consulted of the nature of her finding and the treatment options available to her. Open surgical biopsy is not the first choice.

In cases where a patient has disease in her axilla with a negative Mm, MRI may reveal the index tumor in the breast and allow a sample of it. The surgical treatment of the axilla in patients with BC has become less extensive with the introduction of sentinel lymph node (SLN) biopsy. Further, clinical N1 nodes can be assessed preop by US and sampled by guided FNA. To locate the SLN during surgery, the patient usually has a radioisotope lymphoscintigraphy beforehand, and in theater the surgeon with a handheld probe spots the "hot" node. There are patients with unusual, complex, or delayed drainage and those with extra axillary drainage. In these cases, the use of SPECT/CT gives excellent results with 3D images and a clear map of the lymphatic route [4].

39.5 Evaluation of Response to Therapy

Accurately measuring the response to therapies of the index tumor or of the metastatic disease is a difficult but inescapable endeavor for many reasons. The size of the tumor does not correspond to the tumor cell volume. The criteria used (RECIST or WHO) have application limitations. Each treatment modality has different response time. Targeted treatment aims mainly at stabilizing and not decreasing the tumor burden. Different imaging studies have better yield in different organs. Technological evolution and the introduction of new methods are so rapid that the added value of each cannot be assessed in the long run. This reflects to the fact that there are not published guidelines.

For the evaluation of the primary breast tumor to induction chemotherapy, conventional means like clinical examination still hold strong. Mm and US are used widely correlating well with the pathology specimen. Modalities like quantified DW/PW MRI and dynamic PET cannot only measure response accurately but also tumor function and can predict if it will respond to given treatment. Another functional study is diffuse optical spectroscopy promising better prediction of response with early application in the treatment course.

For the evaluation of systemic disease, FDG-PET seems more accurate. Early results from trials using new imaging agents like amino acid analogs and choline fare even better [5]. As for the assessment of residual disease after breast-conserving surgery (BCS), MRI is the study of choice especially if the breast has been augmented with implants.

39.6 Preoperative Staging

A patient with confirmed BC needs clinical TNM staging and detailed review of her pathology report. For clinical stages I–IIB, additional imaging studies are not indicated unless directed by signs and symptoms. For stage IIIA or locally advanced disease when preoperative chemotherapy is scheduled chest CT, abdominal ± pelvic CT or MRI, bone scan, and FDG-PET/CT are recommended (NCCN, NICE, ESMO, BASO guidelines). In this clinical setting, RCTs are still trying to define which combination of imaging studies is best to detect metastatic disease being cost-effective at the same time and most importantly whether this additional information has any gain for the patient in terms of DFS or OS. Take into account that preop staging is the phase where a high proportion of patients undergo unnecessary, costly, high-end investigations to no avail.

39.7 Posttreatment Surveillance

Women after BCS may develop ipsilateral recurrence or a new metachronous primary in the operated or contralateral breast as well as systemic disease. Ipsilateral recurrence is known to affect survival. Women with a second tumor ≥2.0 cm are at greater risk of death compared to those with tumors ≤1.0 cm or no recurrence. So, early detection seems to be beneficial to the patient's outcome. Of the potentially treatable relapses, almost half are detected by Mm, 15% at clinical visits, and the rest by the patient. From the surveillance studies, Mm seems to have been adopted as the preferred method by the majority of clinicians (87%) and scientific bodies. Issued guidelines (ASCO, ESMO, NICE) differ in frequency, protocol, and duration. They agree on closer FU in the first 2–3 years. We must keep in mind that though relapses are indeed more often in the first 2–3 years, they never cease to appear and that metachronous tumors occur later. Mm is a widely available, reliable, time-honored study with a sensitivity of about 65% and a specificity of 85–97% [6]. A new array of technological improvements (tomosynthesis, spectral Mm, dye-enhanced, etc.) is expected to increase its performance. MRI fares better and is a useful tool in dubious cases. The length of FU should be 10 years for the average case. We do need though robust evidence from RCTs that would allow us to categorize patients according to their risk for relapse and tailor surveillance protocols to meet their needs.

39.8 DCIS

As a result of breast screening, the incidence of DCIS has increased disproportionately to other tumors. Age-adjusted incidence rate is 32.5 per 100,000 women. The average size is 1.0–1.5 cm, 50% is high grade, and the usual histologic type is "non-comedo." In 2005, the estimated prevalence in the US was 500,000 cases. This number is expected to double by 2020. The 10-year survival rate is 96–98%. A substantial proportion will remain in situ and will never progress to invasive. It is easily concluded that a tumor of fairly good prognosis is very often treated aggressively to a great psychological and physical cost for the woman.

MRI is more often employed in today's pretreatment to evaluate the local extent, multicentricity, and contralateral disease. Comparison to dMm gives inconsistent results. Therefore, if there could ever be an imaging study that combined with the findings of the core biopsy could safely distinguish patients in need only of FU, it would had provided women and the health-care system with a miraculous service.

39.9 Screening Mammography

Breast cancer mass screening was introduced in the 1980s to diagnose and treat breast cancer at a stage not yet clinically apparent, in the belief that early detection would reduce mortality. It was greeted with enthusiasm and raised expectation to all engaged parties, i.e., state, women, and scientists. But with the lengthening of follow-up time and the in-depth analysis of the results, the pendulum swung to denial. Objections related to high recall rates, unnecessary interventions and treatment, increased incidence of small tumors (<2 cm) without corresponding decrease of large (>2 cm) ones, and high numbers needed to screen to prevent one death which is another name for cost. There are other ambiguities as to the age to start screening, the frequency, the cutoff age, etc.

In the effort to decide where to stand in breast screening, one must take into consideration the following facts:

- Mass screening is sustained by state funds, is a political issue as to the allocation of health-care resources, and does not relate to the individual woman who seeks advice from her doctor about her breast cancer prevention. For a woman to participate in a screening program, the decision lays solely on her after being thoroughly informed of the pros and cons. Advice to the individual woman is the responsibility of her doctor after estimating her risk.
- It is prudent to exclude DCIS from any program evaluation since its biological behavior cannot be predicted. At present, there are no morphological or imaging features able to distinguish benign from malignant predisposition.
- Recall rates depend mainly on the quality of the image and less on the interpretation of the findings. Nowadays the wide use of the available low-cost modern technology (digital tomosynthesis) is expected to reduce recall rates substantially.
- Estimating overdiagnosis relies on statistical methods that use assumptions and extrapolations. The results may vary widely depending on the quality and the robustness of the data used [7].
- The ideal approach to estimate overdiagnosis would be a randomized controlled trial perfectly randomized for all risk factors in one screened and one nonscreened arm following them for 40 years.

We know only too well that depending on the molecular signature of the tumor, one can advance rapidly, while another can remain indolent for years. This does not mean that it does not exist or that it will disappear at some point. It simply means that today we don't have the tools to predict accurately the biologic behavior of a tumor by its imaging and molecular features. The same issue as with DCIS. It is not an overdiagnosis problem; it is a prognosis one. To ease the argument, we can accept that an efficiently beneficial screening program may have on average a recall rate for an additional US or extra images of 5–10%, should start at 40 years with annual visits,

and may have a 1–2% chance for a needle biopsy and a probability of 10–15% of treatment of an indolent tumor. It is up to a thoroughly informed woman to participate or not to the program.

One thing we must not forget though is that all, proponents and opponents, agree that screening saves lives. To what extent remains to be determined.

References

1. Yabroff KR, Warren JL (2012) High-cost imaging in elderly patients with stage IV cancer: challenges for research, policy, and practice. J Natl Cancer Inst 104:1113–1114
2. Kurian AW, Sigal BM, Plevritis SK (2010) Survival analysis of cancer risk reduction strategies for BRCA ½ mutation carriers. J Clin Oncol 28:222–231
3. Houssami N, Hayes DF (2009) Review of preoperative magnetic resonance imaging (MRI) in breast cancer. CA Cancer J Clin 59:290–302
4. Vidal-Sicart S, Olmos RV (2012) Sentinel node mapping for breast cancer: current situation. J Oncol 2012:361341
5. Zhu A, Lee D, Shim H (2011) Metabolic positron emission tomography imaging in cancer detection and therapy response. Semin Oncol 38:55–69
6. Robertson C, Arcot Ragupathy SK, Boachie C et al (2011) The clinical effectiveness and cost-effectiveness of different surveillance mammography regiments after the treatment for primary breast cancer. Health Technol Assess 15:1–322
7. Jørgensen KJ, Gøtzsche PC, Kalager M, Zahl PH (2017) Breast cancer screening in Denmark: a cohort study of tumor size and overdiagnosis. Ann Intern Med 166(5):313–323. [Epub ahead of print]