Review

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Paradigm Shift From Halstedian Radical Mastectomy to Personalized Medicine

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ABSTRACT

Breast cancer management changed from radical mastectomy to precision medicine in a period longer than a century. The aims of these changes were to refrain from overdiagnoses and overtreatments as well as their harmful side effects and extra costs. Breast cancer is a heterogeneous disease and characterized by many morphological, clinical and molecular features. We now increasingly realise that a one-size-fits-all strategy does not apply to all breast cancer patients. Personalized medicine may be used for breast cancer screening, diagnosis and treatment. Individualized screening can decrease the number of unnecessary mammograms, additional radiologic studies, breast biopsies and false positivity rates. However, additional 15 to 20 years are necessary to reach the results of prospective randomized trials comparing low-risk and normal-risk women. We also should wait for outcomes of risk-based screening trials. The rates of overtreatment in patients with early-stage breast cancer have reached 40% in many studies. Personalized treatment has succeeded in reducing it substantially by using tumour genetic profiling and tumour receptors in early breast cancer patients. However, it has its limits and it is impossible to generalize it to all patients. New biomarkers and molecular classifications have also led to the development of novel therapies and treatment strategies. And, they can contribute to a more personalized management of breast cancer patients.

Keywords: Breast cancer, individualized medicine, over diagnosis, over treatment, molecular subtype, genetic profiling

Introduction

The paradigm shift in breast cancer biology has changed the management of breast cancer from radical mastectomy to precision medicine. In the late 19th century, William Steward Halsted thought that breast cancer was a local-regional disease, and he proposed radical mastectomy, which became the standard surgical treatment of breast cancer for nearly 100 years (1). Halsted succeeded in decreasing the locoregional recurrence rate to 6% at 5 years in contrast to his European counterparts, whose local recurrence rates ranged from 50 to 80% (2). Despite the decrease in local recurrence rate, radical mastectomy did not improve survival rate in comparison to lesser surgical procedures.

Bernard Fisher's alternative paradigm championed an emergence of breast cancer as a systemic disease in 1970s (3-4). He considered that breast cancer was a systemic disease at the outset as a consequence of cells entering lymphatics, but also into the blood via communications. According to this hypothesis, systemic treatment became a substantial part of breast cancer management, and multidisciplinary approaches were required for a more effective treatment. Prospective randomized clinical studies of the 1970s and 1980s (NSABP B04, NSABP B06, MILAN I study, etc.) supported Fisher's hypothesis - variations in the extent of local therapy such as simple mastectomy, quadrantectomy or wide tumour excision plus whole-breast radiation therapy yielded no significant differences in survival outcomes (5-7). Both Halstedian and Fisherian Hypotheses recommended one treatment protocol (radical mastectomy or systemic treatment±radiation therapy) to all patients with breast cancer (one size fits all). Since these two old hypotheses did not separate low-risk patients from high-risk patients, overtreatment was a major problem for patients with low-risk breast cancer. Today, we accept the intermediate paradigm that is combination of Halstedian and Fisherian hypotheses. Rising breast cancer awareness and mammographic screening have increased early-stage breast cancer and ductal carcinoma in situ rates. Almost half of these patients have good prognostic factors and do not require systemic treatment and/or radiation therapy. Patients diagnosed via screening mammography have better prognostic factors than symptomatic breast cancer patients. Systemic treatment and radiation therapy have very harmful side effects despite of their life saving benefits (8). They are also expensive and impose an economic burden on the health care system (9).

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Personalized Screening

Randomized controlled trials (RCTs) have shown that mammographic screening can reduce breast cancer mortality by 25-30% after 7-12 years from entry into the trials (10). Nevertheless, since 2000, concerns have been raised about the validity of these trials because of harms of mammography screening and supposed 'flaws' in randomization and ascertainment of cause of death(11). Implementation of the same mammography screening guidelines to all women with low-risk breast cancer have caused overdiagnosis (1%-10%), false negativity (0.9% to 6.5%), false positivity, unnecessary biopsies, and additional diagnostic tests (12-13).

According to a systematic review by U.S. Preventive Services Task Force, 556 mammography, 55 additional radiologic studies, and 5 biopsies are necessary to diagnose 1 case of invasive breast cancer in women aged between 40 and 49 (14, 15). The new American College of Radiology and American College of Surgeons guidelines recommend that all women begin annual mammography screening at no later than 40 years old and supplementary screening with breast MRI be considered for women with a lifetime breast cancer risk of 15-20% or higher (14-16). Various risk prediction models have been developed to inform patients about their individual risk (17). The Gail, BRCAPro, Claus, and Jonker models underestimate risk, whereas the Tyrer-Cuzick (IBIS) and BOADICEA models produce higher, more accurate estimates. Personalized screening is difficult today due to the lack of long-term (15 to 20 years), prospective, randomized clinical trials comparing screening of low-risk women to women participating in the present screening guidelines. On the other hand, a new ongoing randomized controlled trial of annual vs. personalized screening [WISDOM (The Women Informed to Screen Depending On Measures of risk)] will study the efficacy, safety, and acceptability of risk-based screening (18). As WISDOM is one of the first trials on risk-based personalized screening, these data will be crucial in evaluating whether precision screening will improve the effectiveness of breast cancer screening, particularly whether it leads to screening algorithms that identify cancers for which treatment extends a woman's life.

Personalized Surgery

Breast-conserving surgery rate has increased in recent decades due to the early detection of small sized breast tumours. And, most breast surgeons do not perform axillary lymph node dissection even in the presence of 1 or two positive sentinel lymph node(s) due to the results of ACOSOG Z0011 trial (19). New consensus conferences on surgical margins in patients with invasive and ductal carcinoma in situ (DCIS) recommend no-ink on tumour for invasive, and 2 mm for DCIS as clear surgical margin (20-21). This new margin status has been increasing the breast conserving surgery rate and decreasing re-excision(s), thereby resulting in poor cosmetic results. New systemic treatment drugs and whole breast radiation with a boost also help decrease local recurrence rates and increase overall survival rates.

The term 'oncoplastic surgery' has been used very frequently in last decade (22). Increasing disease free survival rates drew attention to the cosmetic results of breast conserving surgery. Compared with standard quadrantectomy or lumpectomy, oncoplastic surgery (ONC) achieves more accurate tumour resection and free resection margins with better cosmesis (23). Oncoplastic surgery may be personalized for patients with breast cancer by allowing partial mastectomy with good cosmesis, and can decrease total mastectomy or subcutaneous mastectomy with prosthetic reconstruction in many patients without increasing local recurrence, and has fewer complications than mastectomies.

Personalized Systemic Treatment

New developments on molecular biology techniques such as microarrays, next-generation sequencing, and whole exome sequencing, etc. allow scientists to better understand tumour biology and identify biomarkers involved in multiple signalling pathways that can improve general clinical practice contributing to a personalized prognostic and predictive approach to management (24). A precision medicine consists of effective treatment by targeting genomic abnormalities that drive tumour biology. Molecular profiling of tumours has also helped individualize the diagnosis and treatment of breast cancer (25). According to these studies, breast cancer is a complex, and heterogeneous disease. Intra-tumoural heterogeneity shows individualized features. There are several assays studying tumour genetic profiling, such as Oncotype DX® (Genomic Health, Inc., Redwood City, CA), MammaPrint® (Agendia, Amsterdam, The Netherlands), Prosigna® (PAM50; NanoString Technologies Inc, Seattle WA), EndoPredict® (Myriad Genetics Inc, Salt Lake City, UT) and the Genomic Grade Index (GGI), which identify gene signatures to predict response to therapy by using RT-PCR or microarray technology (26). The Oncotype DX Breast Recurrence Score Assay was analytically and subsequently clinically validated as a prognosticator and a predictor of chemotherapy benefit in ER+ early breast cancer according to the biomarker validation guidelines (27-28). MammaPrint uses a microarray technology to assess the expression of 70 genes, The MINDACT [The Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy is a prospective trial using Mammaprint, and its results constitute level 1A evidence for the prognostic role of MammaPrint (data derived from fresh frozen tissue samples)](29). In the MINDACT trial, approximately 46% of women with breast cancer who are at high clinical risk might not require chemotherapy. The Prediction Analysis of Microarrays (Prosigna®, PAM50) is a 50-gene set that was originally developed for the classification of intrinsic breast cancer subtypes based on the initial work by Perou, Sorlie and colleagues (30). EndoPredict is a gene expression signature that predicts the likelihood of distant recurrence in ER+ and HER2-negative early breast cancer patients treated with adjuvant endocrine therapy. The results demonstrated a concordance rate of 100% in risk group classification (high/low) for the 10 tumours assessed, and the EP scores did not differ by a score unit of more than 1.0 from a pre-defined reference (31). The Genomic Grade Index (GGI) was previously developed, evaluated on frozen tissue, and shown to be prognostic in early breast cancer (32).

Personalized Radiation Therapy

Adjuvant radiotherapy is a standard treatment for patients with breast conserving surgery, and it is also recommended for many patients with mastectomy regardless of their molecular subtypes. However, locoregional recurrence rate differs by molecular subtypes, and triple negative and HER2-enriched subtypes have a higher risk of loco-regional recurrence despite radiotherapy (33). While there is an absolute need for greater precision in prescribing radiotherapy in patients with breast cancer, Speers and his colleagues formulated a molecular signature of radiation response from in vitro studies, and they found that there was no relationship between radiosensitivity and molecular subtype (34). Radiotherapy needs to be tailorable to tumour biology ranging from no treatment to partial breast irradiation and loco-regional irradiation, even including the internal mammary chain (35). However, there is still a long road ahead before we can truly tailor the post-operative management for patients with early breast cancer. Nonetheless, it looks feasible in the coming decades.

Conclusion

In order to avoid overdiagnosis and overtreatment of patients with early breast cancer, screening, diagnosis, surgery, and other treatments should be individualized. The concept of individualized medicine is very promising. On the other hand, intra-tumour heterogeneity, lack of large coordinated research programs and clinical trials, cost of molecular diagnostic assays, toxicities and partial inhibition of the signalling pathways of molecular targeting agents are limitations on personalized medicine. Nevertheless, it is promising for the future.

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