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REPRODUCTIVE HEALTH

A historic and scientific review of breast cancer: The next global healthcare challenge

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ABSTRACT

Breast cancer is fast becoming the leading cause of oncologic morbidity and mortality among women worldwide. Demographic changes in Asia, Southeast Asia, and South America will further accelerate this trend. Different specialties are involved in the treatment of breast cancer patients: gynecology, surgery, pathology, hematology/oncology, radiology, radiation oncology, and nuclear medicine. Optimal results are seen in countries providing standardized breast cancer care in certified breast centers. The present article provides an overview of current state-of-the-art treatment strategies and explains the contributions of different specialties to optimal and individualized care for breast cancer patients. Breast cancer will be one of the most important health issues facing physicians involved with women's health and a basic understanding of current treatment objectives will be essential medical knowledge for everyone taking care of female patients.

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1. Introduction

Breast cancer is the most common cancer among women, the number one cause of cancer mortality, and one of the leading causes of morbidity and mortality for women worldwide [1,2]. This represents a major change in morbidity and mortality specific to women; only 50 years ago, cervical cancer and morbidity associated with childbearing were the leading healthcare problems of women [3].

The main risk factor for breast cancer is age. Other significant risk factors are low parity and low rates of breastfeeding, which explains more than any other factor why breast cancer is the classical cancer of high-resource nations and continues to increase in almost all countries [4].

Breast cancer has always been a common disease of women. It is no coincidence that the surgical treatment of breast cancer was one of the first systemized surgical treatments during the first surgical revolution at the end of the 19th century. The scientific description and assessment of the radical mastectomy by Halstead remains—both in its groundbreaking association of science and surgery as well as with regard to its limitations as an overly radical local solution to a systemic disease—a fascinating example of how oncologic treatment started off barely 120 years ago [5].

Life expectancies in high-resource nations in Europe, North America, and Australia for women now reach 80-plus years. Life expectancies in China and India, representing almost 40% of the world's population,

have continued to increase at dramatic rates. The same can be said of Southeast Asia, postcommunist eastern Europe, and South America.

The world's population continues to increase in size, albeit at a decreasing rate. The single most important demographic factor determining future healthcare burdens will be age. For the gynecologist, this means an increase in diseases associated with age: problems of hormone deficiency, pelvic floor problems, and genital cancers such as endometrial and vulvar cancer. The incidence of ovarian cancer appears to be decreased by the use of oral contraceptives [6]. The one oncologic disease certain to increase is breast cancer: a disease affecting all ethnic groups in all prospering nations.

Breast cancer is an individual tragedy for those affected. It is a highly curable disease when detected early, and an inevitably mortal disease when discovered too late. Access to high-quality care leading to early diagnosis can mean the difference between life and death. Access to proper surgical and medical treatment can mean the difference between life and death [7].

Breast cancer is at the same time a major healthcare burden: screening programs are costly and difficult to organize, involving major logistic and quality control issues. Proper surgical treatment requires appropriate operating room facilities and highly qualified healthcare providers. More advanced treatment approaches involve local radiation, requiring facilities beyond the scope of most healthcare systems in low-income countries.

Adequate systemic treatment with chemotherapy or hormonal therapy is costly both in itself as well as with regard to the management of potentially severe adverse effects. All sophisticated breast cancer treatment requires the resources of advanced pathology, including

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immunohistochemistry and molecular pathologic analysis. New targeted therapies remain an evolving field where only one thing is certain: individual treatment costs are already threatening the best funded healthcare systems [8].

Breast cancer is a challenge for all countries: The present article will review how organizing and centralizing breast care around integrated breast centers can potentially provide optimal care to individual patients within different healthcare systems. On the other hand, lack of systematization and failure to focus resources will strain healthcare systems, particularly among emerging economies, to breaking point.

The article looks at screening, imaging, diagnosis, treatment stratification, surgical treatment options, systemic treatment and follow-up, and specifically addresses logistic and financial issues.

2. Screening and imaging

Early diagnosis is key to the successful treatment of breast cancer. T1 tumors measuring less than 2 cm in size have a 10-year survival of approximately 85%, while T3 tumors—essentially the result of delayed diagnosis—have a 10-year survival of less than 60% [9].

Four diagnostic procedures lead to the ultimate detection of breast cancer: (1) clinical examination; (2) mammography; (3) breast ultrasound; and (4) breast magnetic resonance imaging (MRI).

Clinical examination is the most readily available mode of diagnosis. It is a simple form of early detection, capable of diagnosing tumors between 1 and 2 cm and bigger, depending on location and breast size. To this day, it remains the most common way breast tumors are first detected, normally by the affected women herself. Breast examination, however, assumes a fairly advanced understanding of what breast cancer is. The technical term is awareness—one of the key concepts in the fight against breast cancer [10].

Healthcare providers who are in regular contact with women need to be aware of breast disease as well as willing to examine women on a regular basis. The people who represent health care need to be recruited for breast cancer detection. Realistically, not all healthcare providers will qualify. Physicians and healthcare specialists, such as nurses or midwives, who are in regular contact with women qualify.

On the other hand, women themselves need to be aware of this disease threat. They need to be informed and willing to expose themselves to routine breast examinations.

Particularly in societies lacking advanced information technology and societies structured along patriarchal beliefs, as well as in societies with a high desire for female privacy, promoting the need for examining otherwise healthy breasts will require a considerable effort on the part of regional healthcare systems and providers [11].

With regard to early diagnosis and systematic screening, only mammography provides the key qualities: easy to perform, minimal technical set-up, easy to standardize, possible review, and possible direct comparison with previous mammographies. Because of this, almost all the available literature evaluating breast cancer screening modalities looks at mammography. Many countries with highly developed health systems have introduced systematic mammography screening for women, usually between 50 and 70 years of age in an effort to reduce breast cancer mortality, usually every two years. Because the available literature is heterogeneous, with a majority of publications supporting the ability of mammography to reduce mortality long term, acceptance among women has been variable and the systematic screening approach remains controversial. Many women are afraid of the procedure, which is often painful and cannot avoid some radiation exposure [12].

Breast ultrasound is an excellent tool in the management of breast disease. Most, but not all, breast cancers seen on mammography or MRI can also be visualized on ultrasound and subsequently biopsied using ultrasound-guided core biopsy techniques. Because the quality of breast ultrasound depends on a variety of variables, including breast

size, glandular tissue density, previous surgeries, or radiation and examiner experience, it has not been used as a large-scale screening tool [13].

The most expensive and logistically most demanding breast examination modality is MRI. With the best sensitivity but overall low specificity it is the favorite of many radiologists, who appreciate its accuracy, but do not have to deal with the clinical management of nonspecific and often benign findings that require extensive patient counseling. To rule out malignancy particularly in questionable cases and within breasts heavy on scar tissue, MRI remains second to none [14].

3. Diagnosis

Breast examination, mammography, breast ultrasound, and MRI only raise the suspicion of breast cancer. Ultimately, they find a lump, an area of microcalcification, a suspicious area on ultrasound, or a gadolinium-enhanced area on MRI. The next step is key to the diagnosis: histologic confirmation or exclusion of malignancy.

Some 80% – 90% of breast cancers can ultimately be identified on ultrasound, even if the primary diagnosis is made by one of the other imaging modalities.

Breast sonography allows direct, ultrasound-guided biopsy. Core biopsies allow an exact histologic diagnosis: invasive ductal or invasive lobular breast cancer, a first grading, as well as a determination of estrogen- and progesterone-receptor status and HER2 receptor status.

4. Treatment stratification

At this point, all relevant information to determine appropriate treatment is available: tumor location, tumor size, histology, and tumor-specific properties. Lymph node status can be assessed clinically, sonographically, and—if necessary—using cytology. Together with patient age and overall health status, a treatment course can be discussed.

Two major questions need to be answered:

- (1) If chemotherapy is needed, should it be delivered before surgery as a neoadjuvant therapy or after surgery as an adjuvant treatment?
- (2) Depending on the timing of chemotherapy and surgery, is breast conserving surgery possible or does the breast need to be removed totally (mastectomy)?

Adjuvant versus neoadjuvant therapy and breast conservation versus mastectomy remain the key decisions at the beginning of breast cancer treatment. For discussion at this point—within the available resources—are options for breast reconstruction should mastectomy be necessary.

As with prognosis, the earlier the diagnosis, the smaller the tumor, the lower the percentage of mastectomies, and the lower the number of costly breast reconstructive procedures. Again, early detection remains key both at an individual level as well as at a financial level.

5. Surgical treatment options

Surgery for breast cancer has undergone tremendous change over the past 20 years. Radical mastectomy as introduced by Halstead was modified but remained the standard of care until well into the 1980s. It still remains standard therapy in many countries where healthcare systems lack a specialized focus for breast disease.

In the early 1970s, two outstanding physicians, Umberto Veronesi, Italy, and Bernhard Fisher, USA, developed the concept of breast conserving surgery, advocating that the removal of the malignant tumor, combined with local radiation provide the same cure rates as mastectomy. This revolutionary concept was introduced against tremendous opposition. Its ultimate success has greatly improved the lives and the fate of hundreds of thousands of women worldwide, if not millions [15,16].

Breast conserving surgery has become a challenging area of surgery with the introduction of oncoplastic surgery. It requires an intimate knowledge of what is and what is not possible. It requires and understanding of the breast as a physiologic and aesthetic entity that is composed of two different parts: the skin and the glandular tissue, which need to be treated almost separately, only to be reconnected within a new breast shape at the end of the procedure.

Only specialist breast surgeons will develop the necessary competence to provide acceptable breast conserving solutions for up to 70% of patients with small tumors and only few countries will offer this kind of specialization within their health systems. Surgeons performing abdominal surgery, cholecystectomies, and—possibly—mastectomies will have neither the time nor the interest to focus on this “small” but aesthetically challenging area of surgery [17].

In countries without a strong specialization for breast and breast conserving surgery, mastectomy—often performed by a nonspecialized general surgeon—and, if possible, reconstruction—often performed by a nonspecialized plastic surgeon—are the best alternatives, leading to a fragmentation of care and making treatment decisions unnecessarily complicated for patients. The higher the skill of the surgeon and the smaller the tumor, the lower the mastectomy rate.

What kind of mastectomy is performed determines what kind of reconstruction is necessary or possible. The most advanced versions of mastectomy are skin-sparing mastectomy or nipple-sparing mastectomy, allowing direct reconstruction with artificial implants. These surgical techniques were developed in the 1990s. Again, a specific kind of training is required: An insufficient resection, leaving behind too much subcutaneous tissue, will also leave behind too much breast tissue, while a too radical resection will lead to excessive thinning of the skin and subsequent necrosis.

Autologous reconstruction techniques are either vascularized skin/muscle flaps (latissimus dorsi flap, TRAM flap), or free flaps (DIEP, superior gluteal flap) and allow either the reconstruction after skin-sparing mastectomy or the plastic reconstruction after loss of the breast skin as part of a traditional mastectomy.

An integral albeit changing aspect of breast cancer surgery is the management of the axilla. Traditionally, axillary dissection along anatomic levels defined by the pectoralis minor muscle was an important part of adequate staging and thought to be an important part of curative surgery. In recent years, large prospective studies have raised doubts about the therapeutic benefits of axillary resection now only considered diagnostic. The introduction of the sentinel lymph node was one of the major advances to reduce nontherapeutic morbidity. As our diagnostic insights into the prognostic aspects of molecular profiling improve, therapeutic decisions rely less and less on knowledge of the status of the axillary lymph nodes. Future treatment concepts might be able to do without any kind of axillary exploration [18].

6. Systemic treatment

Chemotherapy for oncologic disease was first introduced as a therapeutic measure during the 1950s to treat nonsolid tumor entities such as leukemia. The treatment of solid tumors was much less successful, particularly in advanced disease. During the 1970s, using breast cancer as a model, the concept of adjuvant therapy was developed and remains one of the cornerstones of breast cancer treatment—although the exact mechanism of action remains unexplained. One of the oncologic mysteries of breast cancer is why a locally cured disease has the potential to recur systemically after one, two, or—sometimes and even more intriguingly—after 10 or more years as metastatic and incurable breast cancer. A question that remains to be answered is where exactly in the human body do these breast cells with oncologic potential “hide,” how do they survive, and why do they ultimately metastasize? [19].

The big molecular biologic mystery can be clearly defined: cells metastasizing from the primary tumor should have a high oncologic potential; therefore, it makes no sense that these cells somehow

transform to “dormant” cells hiding somewhere within the body only to reappear much later as incurable disease [20].

The theory of micrometastatic tumor cells that have left the primary breast tumor and spread into the body led to the therapeutic concept of adjuvant chemotherapy. After appropriate local treatment, almost all breast cancer patients are clinically free of disease. Depending on prognostic factors such as tumor size, lymph node status, hormone receptor status, HER2 receptor status, and grading, a certain percentage of these initially cured patients will have a systemic treatment failure over the course of 5–10 years. These treatment failure rates vary between 5% up to 50% depending on the factors mentioned previously.

Large prospective studies were able to show a measurable decrease in long-term systemic failure and mortality between 10% and 20% in patients treated with adjuvant chemotherapy; although up until now, it has been impossible to determine exactly which patient will benefit, leading to overtreatment of thousands of patients worldwide and an interesting hunt for genetic tumor profiles benefiting from chemotherapy and profiles already cured by local therapy.

Over the years, different chemotherapeutic regimens have developed, beginning with the CMF regimen (cyclophosphamide, methotrexate, and 5-fluorouracil) and leading to today's standard of epirubicin and cyclophosphamide, followed by paclitaxel (EC-paclitaxel) [21].

A multitude of other therapeutic agents have been tested, mostly in the metastatic but also in the adjuvant phase, including docetaxel, capecitabine, vincristine, gemcitabine, eribulin, pegylated liposomal doxorubicin, and so on.

The other major oncologic breakthrough specific for the treatment of breast cancer was the introduction of targeted therapy using antiestrogens such as tamoxifen and fulvestrant and, later, aromatase inhibitors. The effect of oophorectomy on the disease progression of metastatic breast cancer was already established in the 1890s.

With over 60% of patients positive for estrogen and progesterone receptors, adjuvant treatment with antihormonal medication has proven as successful as adjuvant chemotherapy [22].

During the first decade of the 21st century, an additional targeted therapy introduced another revolution for those 15% of breast cancer patients positive for the HER2 receptor. With the treatment option trastuzumab, recently increased with further substances such as lapatinib, pertuzumab, and TDM1, treatment of HER2-positive breast cancer has become an entire chapter in the textbook [23].

In most countries, the systemic treatment of breast cancer remains in the hands of medical oncologists. Again, while basic breast chemotherapy is not difficult, the multiple treatment options available in neo-adjuvant, adjuvant, and metastatic situations require a specialization similar to the treatment of the different leukemias. It is unlikely that the same doctor will be an expert in the treatment of leukemias and an expert in the treatment of breast cancer.

These systemic breast cancer treatment plans need to be closely coordinated with the surgical and radiation oncology measures. Outside specialized breast cancer centers, patients will be mostly on their own to find the best appropriate individual care, as treatment propositions will depend too much on the specialist they first encounter.

7. Radiation oncology

Breast radiation is an integral part of breast conserving surgery. The extent and necessity of radiation in an elderly population are undergoing considerable changes. Evaluation of the indications for breast radiation is particularly interesting in low-income countries. On the one hand, breast conservation is key to educating women how to detect breast cancer early, so that the breast—a major esthetic symbol—does not need to be removed. Breast conservation gives breast cancer treatment a “human” face. On the other hand, more than any other part of breast cancer treatment, breast radiation requires modern, state-of-the-art, high-cost facilities to avoid considerable adverse effects. While

centralization is the logical answer, in many countries, travel options are limited if not impossible.

8. Follow-up

In advanced health systems, 80% – 85% of breast cancer patients will be cured. Owing to long-term relapse, follow-up becomes a major issue as patients with previous breast cancer are at high risk of developing subsequent breast cancers, i.e. in the contralateral breast. At the same time, breast cancer survivors are breast cancer advocates. They show how this increasingly common disease can be cured. Raising awareness of breast cancer within different cultures is the main challenge, particularly in emerging economies with developing healthcare systems. Management of breast cancer survivors will play an integral part.

9. Summary

The way breast cancer is diagnosed and treated has undergone tremendous changes over the past two decades. In health systems with a long tradition of breast cancer care, this process has inevitably led to the creation of breast cancer centers, where the different specialties involved—gynecology, pathology, radiology, surgery, plastic surgery, radiation oncology, nuclear medicine, and medical oncology—come together for the benefit of the patient. In an increasing number of countries, the lead physician has been the gynecologist as the doctor with the most contact with otherwise healthy women. Breast cancer represents a major financial burden that will only increase in years to come as the proportion of elderly women increases. New treatment concepts need to consider all of these aspects.

Conflict of interest

The author has no conflicts of interest.

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