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ORIGINAL ARTICLE

Milestones in Breast Cancer Treatment

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■ **Abstract:** Modern treatment started in the 1880s with Halsted's mastectomy. The next milestone—a century later—was breast-conserving surgery, with equivalent survival but better esthetic outcomes than mastectomy. Sentinel node biopsy, introduced in the 1990s, was a milestone that permitted avoidance of axillary dissection if the sentinel node was disease-free. Chemotherapy was established for early breast cancer in the 1980s and its efficacy continues to improve; however side effects remain a concern, particularly since chemotherapy does not benefit most patients. External whole breast irradiation was introduced with conservative surgery, as it reduces recurrences. By the 2000s, 3-week regimens had been shown equivalent to standard 6-week regimens—easing pressure on patients and radiation centers. Intraoperative partial breast irradiation is potentially more beneficial as it permits complete local treatment in a single session; however, trials show that patients must be very carefully selected. From the 1990s irradiation technology was combined with imaging and computer technologies to produce equipment that directs radiation to more precisely defined target volumes, allowing increased dose to the target and markedly reduced dose to nearby tissues. Irradiation systems are evolving rapidly but are being implemented without data on long-term morbidity or efficacy, while costs rise steeply. The first targeted treatment was tamoxifen, a selective estrogen receptor inhibitor. Since its widespread use starting in the 1980s, tamoxifen has saved the lives or prolonged the survival of millions with estrogen-positive disease; it is cheap and has limited (but not negligible) side effects. The same cannot be said of newer targeted treatments like trastuzumab and pertuzumab, which, although effective against human epidermal growth factor receptor 2-positive cancer, come with important side effects and huge costs. Breast cancer mortality is declining in rich countries, but treatments have become more demanding and more expensive, so the outlook for the increasing numbers of women worldwide who develop the disease is uncertain. ■

Key Words: breast cancer, breast-conserving surgery, chemotherapy, external beam whole breast irradiation, intraoperative radiotherapy, radioguided occult lesion localization, sentinel node biopsy, tamoxifen, targeted therapies

Breast cancer was first described in ancient Egyptian medical papyri, in one case as a bulging condition of the breast that had no cure (1). Although rare, the disease remained well-known subsequently and was generally considered systemic, undoubtedly because it came to the attention of physicians at an advanced stage when systemic symptoms were present.

THE FIRST MILESTONE

Surgical techniques improved steadily during the 19th century and surgery became feasible for many conditions. It is fair to say that modern breast cancer treatment began in the 1880s, when Halsted developed a surgical approach based on the assumption that the disease was not always systemic. Halsted's mastectomy removed the breast, en bloc with the pectoralis muscles and axillary lymph nodes, along with a good deal of skin. The approach was often curative. It became the standard treatment for breast cancer and remained so for most of the 20th century. However Halsted's mastectomy tended to leave patients with long-term pain and disability, so some physicians experimented with less drastic approaches. For example, in the 1920s the Frankfurt gynecologist Max Hirsch treated a substantial series of patients with simple tumor resection followed by interstitial radiotherapy. Somewhat later, surgeons in the UK, Finland, France, and the USA experimented both with more limited and more radical versions of the Halsted mastectomy. By the 1970s, a modified mastectomy that did not include removal of underlying muscle was widely practiced, but there was a groundswell in favor of more conservative surgical approaches.

THE INTRODUCTION OF BREAST-CONSERVING SURGERY

The next milestone in breast cancer treatment was marked by the publication in 1981 of the results of a

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randomized trial that compared Halsted mastectomy with breast-conserving surgery (quadrantectomy) plus complete (3 Berg levels) axillary dissection plus full-dose radiotherapy to the residual breast (2). The trial, which recruited patients with tumor ≤2 cm, showed no difference in survival between the two groups. Importantly, quadrantectomy patients had superior esthetic outcomes. Subsequent trials (3,4) from the same group led by Veronesi in Milan, established quadrantectomy with complete axillary dissection followed by whole breast irradiation, as equivalent to Halsted mastectomy in terms of survival outcomes. The findings of the Milan trial were confirmed by long-term follow-up published in 2002 (5).

In the USA, Fisher and colleagues adopted a slightly more conservative approach. Their trial, published in 1985 (6) compared a more limited tumor resection (lumpectomy) with a mastectomy that included removal of the fascia overlying the muscles but not the muscles themselves. As in the Milan trials, patients with stage I-II breast cancer were eligible, but maximum tumor diameter could be 4 cm. Axillary dissection (at least Berg levels I and II) was generally more limited than in the Milan trials (all three Berg levels). Fisher found that distant disease-free survival and overall survival were no worse in the lumpectomy arm than mastectomy arm.

As a result of these studies, breast-conserving surgery became the preferred treatment for early breast cancer in 1990 (7) and the proportion of patients receiving mastectomy declined: in the USA from 77% in 1988 to 38% in 2004 (8). In the European countries of Italy, Belgium, Germany, and Switzerland, only 18.6% of women treated surgically for early-stage disease received mastectomy in 2010 (9).

SENTINEL NODE BIOPSY

The second major 20th century milestone in the surgical treatment of breast cancer was sentinel node biopsy (SNB). The SNB procedure involves injecting blue dye, radiotracer, or both close to the tumor. The dye/tracer moves in the lymph ducts to be taken up by the first node (or nodes) to receive lymph from the breast area containing the tumor. These sentinel nodes (SNs) are identified, removed and examined. The hypothesis is that the disease status of the SNs accurately predicts the status of the entire axilla. The SNs are identified either visually, or by scintigraphy and a gamma ray-detecting probe intraoperatively, and are removed and examined pathologically.

Axillary dissection had been a cornerstone of the conservative surgical approach to breast cancer, not simply because—in the 1970s and 1980s—many women still presented with overt axillary involvement but also because the pathologic state of the axilla provided essential staging information (10). Both the number of involved nodes and the level of axillary involvement were significant prognostic indicators (10). However, there had been interest in a more conservative approach the axilla at least since 1977, when 5-year results of the NSABP B04 trial (11) indicated that mastectomy patients not given axillary dissection were at no greater risk of distant disease or death than those given axillary dissection. The sequelae of axillary dissection were also a cause for concern: permanent lymphedema was common (12) and other side effects included pain, arm weakness, loss of arm movement, and limitation of hand movements (13).

The minimally invasive SNB procedure was shown, in the 1990s, to reliably predict axillary status (14,15). The first clinical trial on SNB in breast cancer was conducted at the European Institute of Oncology, Milan, and published in 2005 (16): 516 patients were randomized to either SNB plus immediate axillary dissection, or SNB with no further axillary treatment if the SN was negative. After over 5 years, there were no differences between the arms in terms of axillary recurrence, distant metastasis or survival, but arm pain was less, and arm mobility better, in patients who underwent SNB only. Ten-year results of this trial (17) supported the original findings, and reported slightly better overall survival in the SNB-only arm, with lower than expected cumulative incidence of axillary disease in the same arm (0.9%).

Even while this trial and others were being conducted, SNB was extensively adopted and soon after became the standard approach to the axilla in patients with a clinically clear axilla. The 2014 ASCO guidelines indicated that most early breast cancer patients should have SNB, so that if the SNs are negative, axillary dissection and its sequelae are avoided (18).

Even if the SNs are positive, recent trials show that axillary dissection is not always necessary. The IBCSG 23.01 trial, which recruited women with tumor up to 5 cm, showed that axillary dissection conferred no advantage if only micrometastases (foci up to 2 mm) were present in the SN (19). The earlier Z0011 trial (20) indicated that axillary dissection could be safely

omitted if the macrometastatic disease burden in the axilla was moderate (1–2 positive SNs). In 2013, the San Gallen Panel endorsed omission of axillary dissection in patients with 1–2 involved SNs undergoing breast-conserving surgery with whole breast irradiation, although the authors of Z0011 were reluctant to advocate omitting axillary dissection in premenopausal or estrogen receptor (ER)-negative patients; they also emphasized that most Z0011 patients received systemic treatment as well as whole breast irradiation (21).

If axillary dissection can be omitted in some patients with a positive SN, the question arises: what is the use of SNB? The ongoing SOUND trial was designed to address this. It is randomizing patients with a clinically negative axilla either to "SNB policy" (axillary dissection if the SN is positive), or to no surgical treatment of the axilla. To be eligible, patients must be candidates for breast-conserving surgery, have a lesion $\leq$2 cm, and a clinically negative axilla, ascertained by palpation, axillary ultrasound, or ultrasound-guided fine-needle aspiration if a single doubtful lymph node is identified on ultrasound (22).

A RAPID SUCCESSION OF MILESTONES

The progressively more conservative surgical approach to the axilla over the last 25 years must be seen in the context of other milestones in breast cancer treatment that occurred over the same period. For example, in developed countries, breast cancer was diagnosed at an increasingly earlier stage thanks to improved imaging modalities, now including digital mammography, ultrasound, MRI and PET-CT, combined with greater awareness of the disease (and its curability) by women and physicians. These changes meant that the axilla was rarely involved clinically and often uninvolved on axillary dissection.

There were also major improvements in radiotherapy and systemic therapies, driven, respectively, by advances in technology and better understanding of disease biology. This succession of milestones is described below; however, it is worth noting that these developments form part of a virtuous circle: they encourage women to undergo examinations able to diagnose disease at an increasingly early stage (23), permitting use of less aggressive and more targeted treatments. This virtuous circle is probably the main explanation for the encouraging reduction in breast cancer mortality seen in recent years in high-resource countries (24,25).

RADIOGUIDED OCCULT LESION LOCALIZATION

Widespread use of mammography and ultrasound resulted in a steady increase in the number of nonpalpable breast lesions diagnosed (26). Various techniques are used to localize nonpalpable lesions and guide their removal, including wire-guided localization, carbon localization, and radioguided occult lesion localization (ROLL) (27).

Radioguided occult lesion localization was developed in 1996 at the European Institute of Oncology. Radioactive tracer is injected into the center of the lesion under ultrasound or mammographic control. During surgery, a gamma ray probe is used to locate the lesion and guide its removal. ROLL has advantages over hooked wire and carbon tracking in occult lesion localization (28). For malignant lesions, ROLL is used together with SNB, a technique called SNOLL (29,30). In SNOLL, the patient receives two radiotracer injections: one directly into the lesion, and another subdermally or peritumorally. In the first case, the ^{99}Tc is bound to colloid macro-aggregates that are immobile and serve to locate the lesion. In the second case, the ^{99}Tc is bound to colloid micro-aggregates that move in the lymph ducts to accumulate in the SN.

SKIN-SPARING AND NIPPLE-SPARING MASTECTOMIES

Mastectomy is standard treatment for large or multicentric tumors, medium size tumors in a small breast, recurrences after conservative treatment, and diffuse intraepithelial neoplasia. In skin-sparing mastectomy the breast is completely removed but the overlying skin is preserved. This technique, which is oncologically safe (31–36), greatly facilitates immediate breast reconstruction leading to better cosmetic results; it also reduces costs compared to reconstruction performed later (36). However because the nipple is lacking, some patients are unhappy with the outcome. This can be overcome by a skin-sparing mastectomy that also conserves the nipple-areola complex (NAC) resulting in a more natural-looking reconstruction. NAC preservation implies preservation of a thin layer of retroareolar breast tissue to ensure adequate NAC blood supply, but this may increase the risk of

retroareolar recurrence. To reduce the risk, a tissue slice is taken from under the areola and examined intraoperatively. If it is cancer-free the NAC is preserved, otherwise it is removed. Limited data indicate that nipple-sparing mastectomy is as oncologically safe as skin-sparing mastectomy (36). Indications for the two mastectomies are similar.

EXTERNAL BEAM RADIOTHERAPY

External beam irradiation of the residual breast has always been an integral component of breast-conserving treatment. Early studies showed that omission of radiotherapy resulted in high local recurrence rates, but did not adversely affect survival (3). However, a large recent meta-analysis of trails (37) showed that radiotherapy also reduces breast cancer mortality. Until recently, standard treatment was 50 Gy with a 10 Gy boost to the tumor bed given by two opposed (tangential) beams over 5–7 weeks (conventional fractionation). Large-scale studies published in 2008 (38) and 2010 (39) make it clear that hypofractionated regimens—in which around 40 Gy is given over 3 weeks—are equivalent to conventionally fractionation in terms of cancer recurrence rates and late adverse effects. This is important because a 3-week course is convenient for the patient and relieves pressure on radiotherapy centers. Nevertheless, due to variations in breast contour, the distribution of radiation throughout the breast is inhomogeneous using two-tangential beams. Homogeneity is usually increased using wedges that attenuate the beam, with minimum attenuation along the chest wall and maximum attenuation in the sub-areolar region. However, the armpit and skin of the inframammary fold tend to receive more radiation than elsewhere, so skin effects in these areas are quite common. The heart (left breast irradiation) and lungs also receive radiation, sometimes giving rise to late toxicity (40).

While the hypofractionation trials were being conducted, irradiation technology was combined with imaging and computer technologies to produce advanced radiation delivery modalities such as three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), and others. These rapidly evolving techniques made it possible to direct the radiation to ever more precisely defined clinical target volumes, markedly reducing the dose to nearby tissues and making it possible to safely increase the dose to the target volume (41). The newer 3DCRT and IMRT modalities are image-guided (e.g., by CT or MRI) so that the exact position of the volume to be irradiated is determined during the treatment itself (when movement—e.g. breathing—can be compensated for). With IMRT, the intensity of radiation across the treatment volume can also be controlled.

Small randomized studies on early breast cancer patients indicate that these new radiotherapy modalities reduce acute toxicity (42,43). However, they are being widely implemented without evidence-based knowledge of their long-term morbidity or efficacy (44). Furthermore, IMRT is more than double the cost of conventional radiotherapy in part because of increased physician and radiologist workload to generate treatment plans (44). Thus it remains to be seen whether 3DCRT, IMRT, and other similar techniques (e.g., tomotherapy) constitute a genuine milestone in breast cancer treatment.

INTRAOPERATIVE RADIOTHERAPY

Up to 85% local recurrences after conservative treatment develop in the scar area (45,46), even though occult cancer foci are distributed throughout the breast in a large proportion of mastectomy specimens removed for small breast cancer (46). These findings suggest that in many patients, only the tumor bed needs to be irradiated. Furthermore, if this partial breast irradiation could be given in single session, and was noninferior to conventionally fractionated whole breast irradiation, it would substantially ease the difficulties of women who have to contend with long waiting lists for radiotherapy or who live distant from a radiotherapy center. Such treatment would also be simpler and less expensive than conventional whole breast irradiation. For these reasons, the European Institute of Oncology developed an intraoperative radiotherapy (IORT) technique that can deliver full-dose irradiation (21 Gy) over a few minutes during surgery. The method employs a mobile linear accelerator that delivers an electron beam via an arm to which is attached a sterile cylindrical applicator. After cancer removal, the surgeon detaches the residual breast from the underlying fascia and inserts an aluminum-lead disk between the fascia and the gland to protect deep structures. The breast is temporarily reconstructed and the skin retracted out of the way. The energy of the electron beam (variable from 3 to 12 MeV) is selected based on gland thickness as measured by a needle.

The cylindrical applicator is then applied directly to the breast by the surgeon. All personnel leave the room for the short duration of irradiation. Subsequently, the surgeon removes the shielding disks and completes breast reconstruction (47).

The trial (48) to validate this Intraoperative Radiation Therapy (IORT) technique recruited 1,305 women aged 48–75 years with early breast cancer and tumor up to 2.5 cm, randomized either to external beam whole breast irradiation or IORT with electrons. After a median of 5.8 years, significantly more patients in the IORT arm had ipsilateral disease recurrence (hazard ratio 9.3, 95% CI 3.3–26.3). There was no difference in survival between the arms, but significantly fewer skin side effects in the IORT group ($p < 0.001$). Factors associated with ipsilateral recurrence in the IORT group were tumor size, grade, and molecular subtype: all determined at histologic examination after IORT. The authors suggested that patients whose cancers had less favorable characteristics might still receive IORT, but should receive an additional short course of whole breast radiotherapy after pathologic examination.

IORT TO GIVE BOOST

Randomized trials have shown that a tumor bed boost after whole breast radiotherapy produces a small but significant benefit (49–51). However, it may not be easy to accurately define the tumor bed when irradiation is given post surgery, particularly if the breast was reconstructed, marker clips were not placed, or imaging evidence (scar or seroma cavity) of tumor location is unavailable. IORT can overcome these problems since, as noted above, direct exposure of the tumor bed during the operation overcomes localization inaccuracy and allows irradiation of a well-defined breast volume. Giving the boost in a single intraoperative session only modestly increases operating time (by 15–20 minutes) and reduces the time for external treatment, with consequent cost savings and greater patient convenience. Highly encouraging long-term results were obtained from a pooled analysis of 1,109 unselected any risk patients given a boost with IORT with electrons, followed by external beam whole breast irradiation of 50–54 Gy (1.7–2 Gy per sitting) in the supine position with 3D-CT-planning (52). After a median of over 70 months (range 0.8–239) there were only 16 breast recurrences, giving a local control rate of 99.2%. By multivariate analysis, only grade 3 tumor significantly predicted local recurrence. Although nearly half the study patients were over 60 years of age (in whom the absolute benefit of boost is low), IORT with electrons provided local control rates similar to or better than other boost techniques (52).

The convenience of an IORT with electrons boost would be enhanced if the succeeding whole breast irradiation course could be shortened (hypofractionated). Preliminary data on 12 Gy IORT with electrons followed 3–4 weeks later by external beam radiotherapy to the whole breast in 13 fractions over 2.5 weeks for total dose of 37 Gy have been encouraging, with acceptable acute/intermediate toxicity. Eligible patients were premenopausal, below 48 years, with cT1-T2, cN0-1 disease, scheduled for breast-conserving surgery (53). A nonrandomized trial (54) is further investigating hypofractionated whole breast irradiation following intraoperative boost.

HORMONE THERAPY

Hormonal manipulation, for example by total oophorectomy, had been known since the 19th century to produce temporary breast cancer remission. In 1971, the first clinical study with tamoxifen—originally developed as a contraceptive—showed that it induced temporary remissions in late breast cancer (55). Although the drug was subsequently promoted as a treatment for late stage disease, it was eventually (1980) tried as an adjunct to chemotherapy in patients with early breast cancer and found to improve survival (56). Pharmacological studies (57) showed that tamoxifen metabolites antagonize the ER in breast tissues, but are an ER agonist in endometrium and other tissues. Thus, tamoxifen administration blocks the effect of estrogen in breast cells (and ER-positive cancer cells) preventing them from dividing, but stimulates the endometrium. The large meta-analysis of tamoxifen trials published in 1998 (58) showed that tamoxifen significantly reduced recurrences and mortality in pre- and postmenopausal women with ER-positive cancers; and that the longer the administration (up to 5 years) the greater the effect (up to 47% reduction in recurrence, and up to 26% reduction in mortality, compared to patients not receiving tamoxifen). The incidence of endometrial cancer approximately doubled in trials of 1 or 2 years of tamoxifen and approximately quadrupled in trials of 5 years. The

absolute decrease in contralateral breast cancer was about twice as large as the absolute increase in incidence of endometrial cancer.

The 2014 ASCO guidelines (59), which evaluated more recent trials, recommended tamoxifen for 10 years in most women with ER-positive disease. The guidelines (59) noted that, in addition to modest survival gains, tamoxifen for 10 years was associated with lower risks of breast cancer recurrence and contralateral breast cancer than 5-year treatment. The known side effects of tamoxifen (increased incidence of endometrial cancer, uterine cancer and deep vein thrombosis) were confirmed, but benefits were considered to outweigh harms. However results of the SOFT and TEXT trials (60), published after the guidelines, showed that in premenopausal women with hormone receptor-positive early breast cancer, adjuvant treatment with exemestane (aromatase inhibitor) plus ovarian suppression was associated with significantly fewer recurrences than tamoxifen plus ovarian suppression for 5 years. Grade 3 or 4 adverse events were 30.6% for exemestane-ovarian suppression patients, and 29.4% for patients given tamoxifen-ovarian suppression.

Long-term tamoxifen for women with ER-positive disease is clearly a major milestone in breast cancer treatment. In 2003 (61), it was estimated that over 400,000 women were alive as a result of tamoxifen, and that millions more had enjoyed extended disease-free intervals. The toxicity profile of the drug is considered acceptable, and although raloxifene—a more recently developed selective ER modulator—is associated with fewer thromboembolic events and endometrial cancer than tamoxifen, it appears as a less potent inhibitor of breast cancer (62).

CHEMOTHERAPY

Combination cytotoxic agents to treat metastatic breast cancer were first applied in the late 1960s (63). Bernard Fisher (63) and Gianni Bonadonna (64) started combination chemotherapy in the adjuvant setting in the early 1970s. Five-year findings of the Bonadonna trial, which employed cyclophosphamide, methotrexate and fluorouracil (CMF), were that relapse-free and overall survival were significantly better in the CMF group than those who received mastectomy only. Acute toxic effects could be "distressing" (65) but occurred in a minority of patients and were reversible. After 10 years, the chemotherapy was not associated with increased incidence of second cancers (65).

There had been considerable opposition to chemotherapy at the beginning of the 1970s, as many physicians considered that the agents then available were too toxic (64). These concerns were not allayed as new adjuvant and neo-adjuvant chemotherapy regimens for breast cancer were developed and tested in the 1980s and 1990s, and became an important part of the treatment of the disease (66). By this time, oncologists were placing much greater emphasis on patient quality of life and were aware that most patients given chemotherapy experienced side effects including nausea, hair loss, pain, weight loss or gain, fatigue, and myelosuppression. Dose-dependent cardiotoxicity was also a problem with anthracycline-based regimens (67). A meta-analysis of trials that began before 1990 found that, for early breast cancer patients given polychemotherapy, the absolute improvement in 10-year survival was 7–11% for those diagnosed before age 50, and 2–3% for those 50–69 years at diagnosis (68). These improvements, though significant, were only modest. For example, according to (68), survival was 77.6% at 10 years for node-negative patients under 50 years given chemotherapy and 71.9% for node-negative patients not given chemotherapy. This implies that 21 patients needed to be treated with cytotoxic drugs to save a single life. A similar calculation shows that nearly 10 patients needed to be treated prevent a recurrence in node-negative patients under 50 years. The number needed to treat was generally greater in older patients. Thus, most patients given these agents received no benefit from them.

CLASSIFICATION OF BREAST CANCER INTO SUBTYPES

Perhaps better patient selection would reduce the number needed to be given chemotherapy to benefit a single patient. Tumor size and extent of axillary involvement are established prognostic factors used to select patients for chemotherapy. However, after standardization for age and time from randomization, the above-mentioned meta-analysis (68) found that proportional reductions in risk were similar for women with node-negative and node-positive disease. Furthermore, the benefits of polychemotherapy appeared to be largely independent of menopausal status, ER status, and whether tamoxifen was given.

In recent years, patient stratification has become more sophisticated, as several subtypes of breast cancer have been recognized, requiring different treatments (69). The classification is based on gene expression profiles, but since these are still expensive, surrogate histopathological characteristics are used to define subtypes as follows: (69)

- Luminal A: ER positive, human epidermal growth factor receptor 2 (HER2) negative, Ki-67 low and PgR high
- Luminal B (HER2 negative): ER positive, HER2 negative, and *either* Ki67 high *or* PgR low
- Luminal B-like (HER2 positive): ER positive, HER2 overexpressed or amplified, any Ki67, any PgR
- HER2 positive: HER2 overexpressed or amplified, ER and PgR absent
- Triple negative: ER and PgR absent, HER2 negative.

It is expected that this classification will eventually be superseded by analysis of the entire genome of the breast cancer (70). However, since targeted therapeutic agents are largely unavailable and understanding of many of the abnormalities identified by gene analysis is limited, the current "surrogate" classification is the most applicable at the present time. It is ironic, however, that for most subtypes (HER2-positive luminal B-like; HER2 positive and triple negative) cytotoxic chemotherapy is recommended; and while hormone therapy alone is sufficient for HER2-negative luminal B and luminal A disease, it is recommended for both subtypes if other factors are unfavorable.

IMMUNOTHERAPIES

The first successful immunotherapeutic agent for breast cancer was trastuzumab—a humanized monoclonal antibody against HER2, which is overexpressed on the cell membrane in about 20% of early breast cancers. HER2 has no known ligand and complex interactions between different HER family members, involving dimerization, are required for mitogenic signaling. Overexpression of HER2 favors the production of activated homo- and heterodimers, and is associated with poorer disease prognosis (71). Extensive studies in the 1990s and early 2000s established trastuzumab (added to chemotherapy) as first-line treatment for metastatic cancers—and subsequently early breast cancers—that highly overexpress HER2 (72). Although trastuzumab is generally well-tolerated, heart toxicity is a problem particularly if anthracyclines are also given (73). Trials to determine the optimum duration of treatment were partly motivated by the desire to reduce cardiotoxicity: they showed that the standard duration of trastuzumab should be 1 year in patients with HER2-positive disease (73,74).

The humanized monoclonal antibody pertuzumab, which inhibits HER2 dimerization, was approved by the FDA in 2012 as first-line treatment for HER2-positive metastatic breast cancer in combination with trastuzumab and docetaxel. Approval stemmed from the phase III CLEOPATRA trial (75), which found that addition of pertuzumab to trastuzumab and docetaxel improved progression-free survival by about 6 months. There also appeared to be a considerable survival benefit associated with pertuzumab. Definitive CLEOPATRA data, presented at the ESMO congress in September 2014 (76) appear to confirm an astonishing 15.7 month increase in median overall survival in the pertuzumab arm, even though progression-free survival only improved by 6 months. Pertuzumab tolerability was considered acceptable, but side effects were common, with rates of diarrhea, mucosal inflammation, febrile neutropenia, and dry skin rash higher in the pertuzumab arm. Furthermore, like trastuzumab, pertuzumab is prohibitively expensive—close to 6,000 USD for a month's supply (77).

CONCLUDING REMARKS

The modern era of breast cancer treatment began in the 1880s with Halstead's mastectomy. The next milestones were breast-conserving surgery and SNB in the 1980s and 1990s that reduced the aggression of surgery with no penalty on survival, and were applicable to most women with early breast cancer. It is unsettling, however, that as the proportion of women receiving breast-conserving surgery increased in the USA (76.5% in 1988; 38.0% in 2004; $p < 0.001$), the proportion receiving breast-conserving surgery without radiotherapy also increased (8).

It is also noteworthy that, after a nationwide decline in the proportion of US women receiving mastectomy up to 2004 (8) some major US institutions documented a significant increase in the proportion of their patients receiving mastectomies from the early 1990s to mid 2000s (78,79). The reasons for this upsurge are unclear, but may be related to the increasing use of preoperative MRI which can reveal more

extensive disease than mammography or ultrasound (78,79).

Radiotherapy for breast cancer has improved steadily since it was introduced as an adjuvant to breast-conserving surgery in the late 1970s. Modern imaging-guided computer-assisted radiotherapy equipment can define and hit the target volume more precisely and avoid healthy tissue more than ever before. The downside is a large increase in costs, in the context of no data on long-term efficacy or side effects. IORT, which can be completed in minutes and essentially targets only the tumor bed, promises to be a milestone as it allows completion of definitive local therapy in a single session. However the technique is not applicable to all patients, and very careful patient selection is essential.

There has been an accelerating improvement in the effectiveness of chemotherapy for breast cancer since it was introduced in the 1970s. Side effects remain a concern however, and the newer "molecular" classification seems to be directing more, not less patients, to cytotoxic therapies. Targeted therapies like trastuzumab and pertuzumab are not associated with fewer side effects.

To conclude, both therapeutic and diagnostic approaches to breast cancer have changed radically since the 1990s, and the pace of change shows no signs of signs of slackening. Overall these changes have been effective since, according to GLOBOCAN estimates for 2012 (26), female breast cancer mortality has been declining in the resource-rich countries since at least the mid-1990s, notwithstanding increasing incidence worldwide. However, while the momentum of the "less invasive" surgical revolution that began in the 1970s has been maintained, breast cancer treatments overall have become more, not less, demanding for the patient. They have also become massively more expensive: this is a tragedy for the nearly 20% of US women who do not have health insurance, and a problem for European governments struggling to fund their national health services. In many countries of the rest of the world, breast cancer incidence is increasing and it remains to be seen how those countries will meet the demands of their female citizens for adequate breast cancer diagnosis and treatment.

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