BREAST CANCER

When the World Throws You a Curve Ball: Lessons Learned in Breast Cancer Management

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Overview

In the care of patients with operable breast cancer, there has been a shift toward increasing use of neoadjuvant therapy. There are benefits to neoadjuvant therapy, such as monitoring for response, as well as an increased rate of breast conservation and reduction of potential morbidity associated with breast surgery, including axillary management. Among patients with highly proliferative tumors, such as HER2-positive or triple-negative breast cancer, those with residual disease are at higher risk of recurrence, which informs the recommended systemic therapy in the adjuvant setting. For instance, in patients with residual disease after neoadjuvant chemotherapy and HER2-targeted therapy, there is a role for adjuvant trastuzumab emtansine for those with residual disease at the time of surgery. The same holds true regarding the role of adjuvant capecitabine in patients with residual disease after neoadjuvant chemotherapy. With the added complexities of treating patients in the era of the COVID-19 outbreak, additional considerations are critical, including initiation of surgery within an appropriate time from completion of neoadjuvant therapy. National consensus guidelines on time to surgery must be developed to improve measurement and comparison across systems. In addition, there is emerging radiation treatment management research addressing a number of factors, including hypofractionation, role of proton beam therapy, safe omission of radiotherapy, and preoperative radiotherapy with or without drug combination. In this article, the multidisciplinary approach of treating patients with operable breast cancer is highlighted, with updates and future considerations described.

WHY SURGERY IS NOT ALWAYS FIRST: IDEAL INDICATIONS FOR PREOPERATIVE SYSTEMIC THERAPY

Neoadjuvant therapy refers to therapy administered before surgery. When evaluating a one-size-fits-all approach to neoadjuvant compared with adjuvant chemotherapy in randomized trials treating all breast cancer subtypes, there was no benefit in clinical outcomes based on the timing of chemotherapy.[1,2] However, with advances in systemic therapy, such as use of HER2-targeted therapies for HER2-positive breast cancer and evaluation of the prognostic significance of pathologic response by tumor subtype, it has been observed in various pooled analyses that patients with proliferative tumors, such as those with HER2-positive or triple-negative breast cancer, who achieve a pathologic complete response have a lower likelihood of recurrence compared with those with residual disease.[3,4] In addition, patients with HER2-positive or triple-negative breast cancer with residual disease after neoadjuvant therapy are candidates for adjuvant trastuzumab emtansine or capecitabine, respectively. Therefore, when reviewing the indications for neoadjuvant therapy, it is important to consider breast cancer subtype.

HER2-Positive Breast Cancer: The Importance of Neoadjuvant Therapy

HER2-targeted therapy has changed the landscape of treating patients with HER2-positive breast tumors. In patients with high-risk node-negative or node-positive breast cancer, dual HER2-targeted therapy with pertuzumab and trastuzumab in combination with chemotherapy leads to a higher pathologic complete response rate compared with single-agent HER2-targeted therapy with chemotherapy. Data from the neoadjuvant NeoSphere trial led to the accelerated, and eventually full, approval of pertuzumab in the neoadjuvant setting.[5,6] Importantly, in the KATHERINE trial, patients with residual disease after neoadjuvant chemotherapy and HER2-targeted therapy had an improvement in invasive disease-free survival if randomly assigned to receive trastuzumab emtansine as opposed to trastuzumab.[7] The KATHERINE trial led to the approval of trastuzumab emtansine in this setting. It is worth highlighting that patients with T1cN0 disease were eligible for the KATHERINE trial and that, in the forest plot, all subgroups of patients benefited from trastuzumab emtansine.

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PRACTICAL APPLICATIONS

- When considering neoadjuvant therapy, take into account the intent of the therapy, including therapy response monitoring and/or a less invasive surgical approach, such as breast conservation or axillary surgery management.
- Patients with HER2-positive breast cancer with residual disease after HER2 therapies and chemotherapy in the neoadjuvant setting benefit from adjuvant trastuzumab emtansine.
- Patients with triple-negative breast cancer with residual disease after chemotherapy in the neoadjuvant setting benefit from adjuvant capecitabine.
- National consensus guidelines on time to surgery must be developed to improve time to surgery measurement and comparison across systems.
- There are a number of emerging questions regarding radiation treatment, including hypofractionation, safe omission of radiotherapy in those at low risk of relapse, role of proton beam therapy in patients at higher risk of relapse, and preoperative radiotherapy with or without drug combination.

There are a number of ongoing studies in this space, including the CompassHER2 trial, which is enrolling patients with stage III or IIIA HER2-positive breast cancer and administering 12 weeks of a taxane plus trastuzumab and pertuzumab (NCT04266249). If patients achieve pathologic complete response, they complete trastuzumab and pertuzumab treatment. If patients have residual disease, they are eligible for the Alliance 11801 trial, in which patients are randomly assigned to receive trastuzumab emtansine alone or in combination with tucatinib (NCT04457596). In addition, the NSABP B-60 will randomly assign patients with HER2-positive residual disease after neoadjuvant therapy to receive trastuzumab deruxtecan or trastuzumab emtansine (NCT04622319). Given other notable drugs recently approved for the treatment of HER2-positive metastatic breast cancer, it is anticipated that the treatment of HER2-positive breast cancer will continue to evolve in the coming years.

Perioperative Management of Triple-Negative Breast Cancer

Triple-negative breast cancer accounts for 15% of all breast cancers and refers to breast cancers that lack expression of the estrogen receptor, progesterone receptor, and HER2. Compared with hormone receptor–positive and HER2-positive breast cancers, triple-negative breast tumors tend to act more aggressively, with a higher incidence of relapse within the first 3 years of diagnosis and a higher rate of 0.1ptdistant recurrence at first relapse.[8,9] Moreover, unlike hormone receptor–positive and HER2-positive breast cancers, where use of targeted therapy is standard of care to decrease risk of recurrence, there are no targeted therapies available for treatment of triple-negative breast cancer. Multiple studies have demonstrated improvement in outcomes in patients with triple-negative breast cancer who received perioperative chemotherapy compared with patients who did not.[1,10,11] Guidelines recommend patients with tumors larger than 1 cm (at least T1c) or with lymph node–positive disease irrespective of tumor size be offered chemotherapy.[12]

Neoadjuvant chemotherapy achieves the same long-term tumor control and survival as adjuvant therapy. However, neoadjuvant therapy is preferred, given the ability to downstage tumors, allowing for surgical minimization. Receipt of neoadjuvant chemotherapy is also prognostic, with patients who achieve pathologic complete response having a decreased risk of recurrence.[13,14] Moreover, in patients who receive neoadjuvant chemotherapy and have residual disease at time of surgery, additional adjuvant therapy can be used to decrease the risk of recurrence and improve overall survival. In the CREATE-X trial, patients with triple-negative breast cancer with residual disease in the breast and/or lymph node at time of surgery were randomly assigned to receive capecitabine or undergo observation. Patients with triple-negative breast cancer treated with adjuvant capecitabine had improved disease-free survival and overall survival compared with those who did not receive capecitabine.[15]

In terms of choice of neoadjuvant chemotherapy, a regimen containing an anthracycline and taxane is recommended based on clinical trials showing improved outcomes in women with triple-negative breast cancer treated with anthracycline and taxane–containing regimens compared with taxotere and cyclophosphamide without an anthracycline.[16] The use of carboplatin has been shown to improve rates of pathologic complete response.[17,18] However, there have been inconsistent data regarding the addition of carboplatin and improvement in clinical outcomes, given that these studies were not powered to look at outcome differences.[17,19] With associated increased rates of hematologic toxicity, the role of carboplatin remains controversial. The EA1131 trial (NCT02445391) was designed to address the role of platinums in the adjuvant setting. In March 2021, the independent data safety monitoring committee recommended that EA1131 be closed to accrual early because the trial was unlikely to show that a platinum drug was superior or noninferior to capecitabine, given the invasive disease-free survival events observed in both arms. Additionally, more grade 3 and 4 toxicities were observed in the platinum arm.

Despite the current management of triple-negative breast cancer, early recurrence rates remain high. New therapy modalities, including use of immunotherapy, have been explored. The I-SPY 2 study is an ongoing, open-label, adaptively randomized phase II multicenter trial of neoadjuvant chemotherapy for early-stage breast cancer in patients at high risk of recurrence (NCT01042379).[20,21] I-SPY 2 is a platform trial evaluating multiple investigational arms in parallel, each consisting of standard neoadjuvant chemotherapy plus an investigational agent. When added to standard neoadjuvant taxane and anthracycline–based chemotherapy, pembrolizumab more than doubled the estimated pathologic complete response rates for patients with triple-negative and hormone receptor–positive, HER2-negative breast cancer, indicating that checkpoint blockade was highly likely to succeed in a phase III trial.[22] Randomized trials where immunotherapy (pembrolizumab or atezolizumab) was combined with chemotherapy demonstrated improved pathologic complete response rates in patients who received immunotherapy. However, patients who received immunotherapy were also noted to have higher rates of serious adverse events, and long-term outcome data remain immature.[23-25] In February 2021, the Oncologic Drugs Advisory Committee of the U.S. Food and Drug Administration did not recommend approval of pembrolizumab in the surgical setting at this time, because data for event-free survival required additional maturity.[23,24] The S1418 trial is randomly assigning patients with triple-negative or low estrogen receptor–positive, HER2-negative breast cancer and residual disease after neoadjuvant chemotherapy to receive or not receive 1 year of pembrolizumab (NCT02954874).

Implications in Hormone Receptor–Positive/ HER2-Negative Disease and Data From the COVID-19 Era

The indications for preoperative therapy in hormone receptor–positive, HER2-negative breast cancer include large primary tumors and locally advanced disease, with the goal of improving surgical outcomes and controlling disease progression. Pathologic complete response (< 20%), a surrogate endpoint for improved disease-free survival and overall survival, with neoadjuvant chemotherapy is less likely to be achieved in hormone receptor–positive, HER2-negative disease compared with other breast cancer subtypes.[3,13,26,27] In a meta-analysis of 12 trials, the frequency of pathologic complete response in patients with hormone receptor–positive, HER2-negative tumors was greater in those with high- versus low- to intermediate-grade tumors (16% vs. 8%); however, improved survival outcomes were demonstrated in those who achieved pathologic complete response.[3]

In addition to disease burden and likelihood of treatment response, other factors such as menopausal status and medical fitness affect the recommendation for neoadjuvant chemotherapy. Among premenopausal women, superior clinical responses were seen with neoadjuvant chemotherapy compared with neoadjuvant endocrine therapy.[28] There are data in postmenopausal women demonstrating similar clinical responses and less toxicity with neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy, but the subpopulation to which they primarily apply is composed of those with strong hormone receptor expression and low proliferative index.[29-35] For medically fit, postmenopausal patients, the standard practice remains administration of neoadjuvant chemotherapy because of the wealth of data supporting long-term outcomes.[3] In those classified as poor chemotherapy candidates, neoadjuvant endocrine therapy can be considered as an upfront approach. However, if disease progression occurs, surgery should be pursued.

The future direction of the field, however, is in the development and incorporation of predictive tools to determine appropriate preoperative therapy. Factors such as survival, surgical optimization, and treatment toxicity will direct whether patients will benefit from neoadjuvant chemotherapy compared with neoadjuvant endocrine therapy. Several studies have investigated the role of gene expression profiling to guide preoperative therapy, but it has not been established as a standard of care.[36-39] However, in the setting of the COVID-19 pandemic, ASCO has recommended the use of gene expression profiling to assist in the evaluation of biologic risk and guide the preoperative approach.[40] The recent ASCO neoadjuvant guideline highlighted that no prospective trials have determined the clinical utility of genomic markers in deciding whether patients should receive neoadjuvant chemotherapy or selecting specific chemotherapy regimens.[12] Per this guideline, the clinical utility of genomic predictors such as the Oncotype Dx Recurrence Score has not been definitively determined in the context of neoadjuvant therapy.

During the COVID-19 pandemic, there has been a shift in practice patterns in the oncology community, with higher rates of upfront surgery, greater uptake of gene expression profiling, and increased use of neoadjuvant endocrine therapy to postpone surgery.[38-42] Because of the impact on care delivery and resources, the role of neoadjuvant therapy needs to be carefully considered and implemented in situations where the clinical benefits outweigh the risks of exposure to and development of COVID-19.[43-45] Therefore, ASCO created a new therapeutic guideline based on biologic risk classifications to address the management of hormone receptor–positive breast cancer.[40] Patients with low-risk biologic features (e.g., favorable pathology, low score on genomic profile, strong hormone receptor expression, low grade, lobular disease, and luminal A subtype [HER2 negative, low Ki-67]) are considered likely to

experience limited benefit from neoadjuvant chemotherapy compared with those with high-risk features (e.g., unfavorable pathology, high score on genomic profile, weak HR expression [estrogen receptor < 20%], high grade, and premenopausal).[46-48]

For patients with N1 or greater lymph node involvement, preoperative systemic therapy is recommended. Specifically, those with high-risk biologic features should pursue neoadjuvant chemotherapy, whereas those with low-risk biologic features should engage in an individualized discussion about the advantages and disadvantages of neoadjuvant chemotherapy compared with neoadjuvant endocrine therapy. The intent of neoadjuvant therapy should be considered, including increasing the likelihood of breast conservation and/or potentially reducing the axillary burden to improve the rate of postsurgical complications. Even beyond the circumstances of the COVID-19 pandemic, the management of operable, hormone receptor–positive breast cancer continues to shift toward a biologic risk–based approach as research in this area continues to grow.

SURGERY DELAY: WHO IS AT RISK, AND DOES IT AFFECT SURVIVAL?

The recognition of breast cancer as both a systemic and local disease has resulted in considerable deescalation in the management of the breast and axilla.[49] Nevertheless, breast surgery continues to be an integral treatment modality in the management of early-stage breast cancer with curative intent.[50] According to recent estimates from the American Cancer Society, approximately 95% of patients with stage I to II and 88% of patients with stage III breast cancer undergo surgical management.[51] Access to high-quality, high-value breast surgical care and timeliness of surgical management have been implicated in breast cancer outcomes, including surgical morbidity and disease-related mortality, respectively.[52,53] With the purposeful surgical delay imposed by the COVID-19 pandemic, the implications of delay in time to surgery with regard to disease-specific mortality are at the forefront of national discourse. Additionally, there is a robust national debate about the use of time to surgery as a metric for quality of care.[54-56] The objective of this section is to provide a summary of the literature on time to surgery and describe factors contributing to surgical delay.

Time to Surgery and Breast Cancer Survival

Surgery as the first treatment modality The time from biopsy-proven diagnosis to surgical management is a period of increased stress and anxiety for patients with breast cancer.[57,58] Unfortunately, an examination of trends in time to oncologic surgery suggests increasing wait times across multiple cancers, including breast cancer.[59] Studies of the impact of prolonged time to surgery on clinical outcomes, such as survival among patients receiving surgery as their first treatment modality, have been inconsistent. In the study by Bleicher et al[53] of the National Cancer Database and Surveillance, Epidemiology, and End Results-Medicare, a reduction in overall survival and disease-specific survival with each 60-day increase in time to surgery was reported. Notably, these findings were more pronounced in patients with stage I and II cancers. The review by Eaglehouse et al[60] of the U.S. Military Health Systems reported an even lower delay threshold of 36 days or more resulting in increasing mortality compared with shorter timeframes. These findings were confirmed by a recent meta-analysis showing a 6% to 8% increased risk of mortality for each 4-week delay in time to surgery.[61] Moreover, study estimates from the meta-analysis indicated that delays in breast surgical care for up to 12 weeks could result in 6,100 excess deaths in the United States.[61]

Although the results on surgical delay and survival are compelling, other studies have shown no association between delay in time to surgery (≥ 30 days) and overall or disease-specific survival.[62,63] The inconsistency in the data on time to surgery is further compounded by the lack of uniformly measured time intervals (e.g., time from symptoms to surgery, time from biopsy to surgery, or time from first surgical consultation to surgery) across studies and the absence of established national guidelines/benchmarks defining time to surgery. Nevertheless, timeliness of care is an important tenant of cancer care delivery, and consistent efforts should be made to ensure patients with breast cancer have the shortest possible wait time from diagnosis to surgery.[64]

Neoadjuvant systemic therapy and time to surgery For patients undergoing neoadjuvant therapy before surgery, the emerging literature on the relationship between time to surgery and survival is unclear. In their review of the National Cancer Database, Prakash et al[65] reported no association between time to surgery and overall survival among patients receiving neoadjuvant therapy. Conversely, Omarini et al[66] showed patients undergoing surgical management within 21 days of completion of neoadjuvant therapy had better overall survival and relapse-free survival. Additionally, recent data indicate targeting a surgery date within 6 weeks of chemotherapy completion may improve recurrence-free survival and disease-specific survival.[67] Taken together, these results suggest patients receiving neoadjuvant therapy may benefit from treatment within 3 to 6 weeks of completion of systemic therapy.

Factors Contributing to Surgical Delay

Social determinants of health In the Office of Disease Prevention and Health Promotion Healthy People 2020 initiative, social determinants of health are described as where people live, work, play, and worship.[68] Examples of social determinants of health include insurance, finances,

social networks, literacy, employment, transportation, and neighborhood.[69] Studies have implicated social determinants of health in stage of diagnosis, access to treatment, and survival.[70-72] For instance, uninsured or Medicaid-insured patients with breast cancer are more likely to present with advanced stages of breast cancer and have higher mortality than their privately insured counterparts.[73] In addition to presentation and treatment, social determinants of health have also been implicated in delay in time to surgery.[74] Low educational achievement, no insurance or government insurance (Medicaid or Medicare), and low socioeconomic status have been associated with delay in time to surgery.[65,75,76] Notably, the populations of patients described as experiencing surgical delay have traditionally faced barriers in accessing health care across the cancer continuum, from prevention through survivorship.

Race/ethnicity Black patients with breast cancer are more likely to have increased time to surgery compared with their White counterparts.[77] A recent evaluation of time to surgery among patients with stage I to III breast cancer in a national hospital-based registry showed 30% of non-Hispanic Black patients underwent surgery more than 60 days after diagnosis, compared with 18% of non-Hispanic White women.[78] Delay in time to surgery among Black women warrants additional investigation, because Black patients with breast cancer have a higher mortality rate compared with their White counterparts.[79] For surgeons in particular, racial disparities in time to surgery warrant additional knowledge and understanding. An evaluation of awareness among surgeons of racial and ethnic disparities showed only 36.6% of study participants thought racial and ethnic disparities existed.[80] Moreover, just 11.6% acknowledged racial and ethnic disparities existed in their clinics.[80]

The racial differences in time to surgery are most likely a complex interplay between social determinants of health, patient surgical preferences, and surgeon recommendations. To improve time to surgery for Black patients with breast cancer, more granular studies must be conducted to assess patient needs, institutional barriers, and physician attitudes.

Institutional factors contributing to surgical delay Institutional reasons for prolonged time to surgery are multifactorial and complex. For example, possible contributors to institutional delay include referral patterns, clinic time, operating room time, and surgeon availability.[81] Moreover, institutional processes such as patient triage, rereview of outside hospital pathology and images, and presentation of patients at multidisciplinary tumor boards can further contribute to surgical delay.[81,82] These issues are more pronounced at comprehensive cancer centers, academic cancer centers, and National Cancer Institute–designated cancer centers, which are more likely to receive referrals from outside facilities and as a result have increased time to surgery.[59,77,83] Notably, facility transfers can increase time to surgery by approximately 7 days.[84]

Surgery type and delay The decision to pursue mastectomy, breast-conservation surgery, or breast reconstruction depends on patients' personal value systems and cultural beliefs, surgeon recommendations, and availability of reconstructive surgeons. Patients undergoing mastectomy and reconstruction are more likely to experience longer time to surgery compared with patients undergoing breast conservation only.[81] Reasons for surgical delay based on surgery type are most likely secondary to institutional factors, such as surgeon availability (oncology and reconstructive), operating room time, and scheduling.

Purposeful Surgical Delay

As a result of the COVID-19 pandemic, the American Association for Breast Surgeons, Society of Surgical Oncology, and American College of Surgeons issued guidelines for delaying breast surgery for subsets of patients with breast cancer during the pandemic. Recommendations for delay were based on tumor subtype (e.g., hormone receptor positive, triple negative) and stage.[85] Patients with early-stage (stage I or II), hormone receptor–positive tumors received neoadjuvant endocrine therapy while awaiting surgical management.[44] Unfortunately, the long-term implications of purposeful surgical delay imposed by the pandemic are unclear. Although delay may not affect surgical options for the breast (mastectomy vs. breast conservation), the impact of receipt of neoadjuvant endocrine therapy on axillary management warrants additional investigation. Additionally, the effects of surgical delay on the patient population historically facing delay in time to surgery are currently unknown.

Future Directions

Timeliness of surgical care is an important component of breast cancer care delivery. Although the data on the implications of delay for survival seem inconclusive, the stress and anxiety imposed on patients by prolonged wait time are undeniable. Moreover, there are populations of patients, such as Black and low-income women, who warrant special attention secondary to consistent delay in surgical management. Health care systems and national organizations must work on the creation and implementation of uniform time to surgery guidelines to improve delivery of oncologic surgical care and allow uniform measurement and comparison of time to surgery across systems.

EMERGING EVIDENCE IN RADIATION TREATMENT MANAGEMENT IN BREAST CANCER

What Is the Problem Being Addressed?

Breast cancer is the most common cancer in women worldwide, with more than 2 million new cases per year, and

represents approximately 30% of the radiotherapy workload. In recent years, research has shown that breast cancer comprises several distinct molecular subtypes, with different patterns of clinical behavior. As such, systemic therapy is now tailored to these subtypes, whereas radiotherapy for breast cancer has continued with more of a one-size-fits-all approach, resulting in overtreatment of some patients. Many patients now have an excellent prognosis, but this does not mean that breast cancer management has been solved. It is imperative to maintain the excellent local control and survival outcomes already achieved, while avoiding overtreatment and minimizing physical, psychological, and economic adverse effects of breast irradiation.

Some patients develop metastatic disease despite current optimal management. Radiotherapy is a local therapy but can increase overall survival,[86,87] and research aimed at optimizing radiation treatment for very high-risk breast cancer may further improve survival outcomes. Proton beam therapy and the combination of radiotherapy with novel drugs are both promising avenues for potentially practice-changing research. This brief overview will highlight emerging radiation treatment management in key areas.

Five-Fraction Hypofractionation in Whole-Breast Irradiation

Radiation has been delivered to the breast traditionally as 25 daily 2-Gy fractions over 5 weeks. In the last 3 decades, research investigating moderate hypofractionation with daily fractions of 2.5 Gy to 3 Gy has demonstrated comparable 5-year rates of local recurrence and similar or better normal tissue effects with 3-week radiotherapy (in the Ontario Clinical Oncology Group[88,89] and U.K. START[90,91] trials). However, international adoption of this high-quality research has been slow, and 5-week radiotherapy is still practiced in some countries.

The U.K. FAST-Forward randomized trial[92] investigated five-fraction hypofractionation in whole-breast irradiation delivered over 1 week and was conducted in 97 U.K. hospitals among patients with early invasive breast carcinoma (pT1-3, pN0-1, M0) after surgery. Participants were randomly allocated on an equal basis to receive either 40 Gy in 15 fractions over 3 weeks (U.K. standard of care), 27 Gy in five fractions over 1 week, or 26 Gy in five fractions over 1 week. A total of 4,096 patients were recruited. At a median follow-up of 71.5 months, 5-year cumulative incidence of the primary endpoint of local relapse was 2.1% (95% CI, 1.4–3.1), 1.7% (95% CI, 1.2–2.6), and 1.4% (95% CI, 0.9–2.2) for the 40-, 27-, and 26-Gy groups, respectively. Prespecified noninferiority criteria for both investigational groups excluded an increase in ipsilateral breast tumor relapse of 1.6% or more; the upper confidence limits for the estimated differences at 5 years vs. 40 Gy were −0.3% (95% CI, −1.0%–0.9%) for 27 Gy and −0.7% (95% CI, −1.2%–0.3%) for 26 Gy.

Any moderate or marked clinician-assessed normal tissue effects at 5 years were 9.9%, 15.4%, and 11.9% in the 40-Gy, 27-Gy, and 26-Gy groups, respectively. The odds ratios versus 40 Gy across all clinician assessments over follow-up were 1.55 (95% CI, 1.32–1.83; $p < .0001$) for 27 Gy and 1.12 (95% CI, 0.94–1.34; $p = .20$) for 26 Gy. Both patient and photographic assessments showed higher risk of normal tissue effects for 27 Gy, but not for 26 Gy, compared with the control group.

In light of these data, a U.K. consensus meeting took place in October 2020 defining 26 Gy in five fractions over 1 week as a standard of care in whole-breast irradiation, chest wall irradiation, and partial breast irradiation. Although the pressure on resources caused by the COVID-19 pandemic may expedite this process internationally, one challenge remains: the tension between evidence-based medicine and inflexible reimbursement systems.[93]

Safe Omission of Radiotherapy for Patients at Very Low Risk of Relapse

Although radiotherapy is a highly effective treatment, the adverse effects, if incurred, can be permanent and distressing, impairing quality of life for some women. Five-year analysis of National Cancer Research Institute START trials showed that in approximately one-third of women, moderate or severe chronic adverse effects were reported (e.g., breast shrinkage, pain, tenderness, or hardness).[91] Even using intensity-modulated radiotherapy, 12% of patients have poor cosmesis at 5 years.[10] There are also much rarer but life-threatening risks such as cardiac toxicity and radiation-induced second malignancies. Avoidance of radiotherapy means that some patients avoid all potential adverse effects as well as the inconvenience of traveling for treatment.

Biomarkers of relapse risk have been validated in the setting of systemic therapy[94] and are an attractive prospect for similarly directing radiation treatment management strategy. Several ongoing biomarker-directed trials aim to identify a group of women in whom radiotherapy can be safely omitted after breast-conserving surgery. The IDEA (NCT02400190), LUMINA (NCT02400190), PRECISION (NCT01791829), and PRIMETIME[15] studies are all using a biomarker-directed prospective cohort design; in patients who fulfill genomic or immunohistochemical criteria to avoid radiotherapy, incidence of relapse is compared with a predetermined standard of acceptably low risk. The Danish Breast Cancer Cooperative Group Natural (NCT03646955) and EXPERT (NCT03646955) trials are also investigating this question but are using a noninferiority randomized controlled trial design, randomly assigning women thought

to be at low risk of local recurrence to receive or not receive radiotherapy (using traditional clinical and combined clinical and molecular criteria, respectively).

For patients for whom radiotherapy cannot be omitted completely, other aspects can be deescalated. Examples include use of partial-breast irradiation or omission of further axillary treatment (axillary dissection or radiotherapy) in patients presenting with positive lymph nodes that convert to negative after neoadjuvant chemotherapy (e.g., NSABP B51 [NCT01872975] and U.K. ATNEC [NCT04109079] trials).

Role of Proton Beam Therapy for Patients at Higher Risk of Relapse

Standard (photon) radiation delivered to internal mammary nodes in patients at high risk of breast cancer relapse improves disease-free survival.[95-97] However, even with the highest-quality photon radiotherapy, there is increased dose to heart and/or lungs when internal mammary nodes are added to breast/axillary nodal radiotherapy. This can result in rare but serious and potentially life-threatening major cardiac events many years later. In silico research on proton beam therapy suggests much better coverage of the breast and internal mammary nodes, with sparing of heart and lungs,[98] offering the exciting possibility of both better disease-free survival and less long-term toxicity.

Despite the promising dosimetric proton beam therapy studies, there is currently a paucity of high-quality clinical evidence to drive practice. In addition, there are concerns that the planned physical dose may differ from the actual biologic dose received, especially to the lungs. A number of ongoing studies seek to understand if proton beam therapy offers a real clinical advantage for patients, including the U.S. RADCOMP trial (NCT02603341) and the Danish Breast Cancer Cooperative Group randomized trial (NCT04291378). Both trials have a primary endpoint of major cardiac event at 10 years and are testing 5-week proton beam therapy. The Dutch proton beam therapy group has adopted a models-based approach rather than a randomized trial to triage patients with 2% or greater risk of radiation-induced late heart toxicity for breast proton beam therapy and is also using moderately hypofractionated 3-week proton beam therapy. U.K. investigators are developing a randomized trial (PARABLE) in which patients with breast cancer requiring radiotherapy with 2% or greater risk of radiation-induced late heart toxicity will be randomly assigned to receive 3-week proton beam therapy or standard 3-week radiotherapy. Coprimary outcome measures are mean heart dose as an early predictor of late major cardiac events[99] and patient-reported normal tissue toxicity in the breast at 2 years.

Preoperative Radiotherapy With or Without Drug Combination

Increasing breast-conservation rates improves cosmetic appearance and avoids reconstructive surgery. There has been considerable success in using chemotherapy to downstage biologically aggressive breast tumors to enable breast conservation. However, chemotherapy has less effect on lower-grade, strongly estrogen receptor–positive tumors. Therefore, patients with larger but biologically less aggressive tumors are more likely to undergo primary surgery, often with mastectomy (and reconstruction) or complex oncoplastic procedures. Intensity-modulated radiotherapy can target tumor while minimizing dose to nontarget tissue; when administered preoperatively followed by neoadjuvant endocrine therapy, this may increase chances of breast conservation with minimal adverse effects. Patients requiring mastectomy may also benefit from neoadjuvant radiotherapy; the U.K. PRADA trial (NCT02771938) is evaluating the feasibility, safety, and cosmetic outcomes of radiotherapy before mastectomy and immediate deep inferior epigastric perforator reconstruction. This sequencing avoids irradiation of healthy flap tissues, which may worsen cosmetic outcomes, as well as any delay to radiotherapy resulting from wound-healing issues.

The neoadjuvant setting also provides an ideal and unique opportunity for translational research investigating the direct effect of radiation on breast tumor.[27] This could improve the understanding of intrinsic tumor radiosensitivity and resistance and how the complex interactions between tumor and the immune system are influenced by radiation. Translational endpoints have been incorporated into ongoing and recently completed trials of neoadjuvant radiotherapy, such as the PAPBI trial, in which radiation-induced changes in gene expression were analyzed via paired pretreatment and surgical specimens.[100] The ongoing PRECISE study (NCT03359954) has the primary endpoint of change in tumor-infiltrating lymphocytes before and after neoadjuvant boost radiotherapy to estrogen receptor–positive, HER2-negative breast tumors and exploratory objectives investigating other components of immune response, cell death, and interactions between the two. Similar translational work in trials evaluating combinations of radiation and novel drugs, such as the European NeoCheckRay (NCT03875573) and U.S. CBCV (NCT03804944) and PANDoRA (NCT03872505) studies, could contribute additional insights. The greater understanding engendered by such work may enable optimization of radiation treatment strategy.

Summary

Radiotherapy is an important contributor to the treatment of breast cancer, and evolution of radiation treatment management over recent decades has improved outcomes for patients. Emerging approaches hold promise for tailoring strategy to the individual patient to widen the therapeutic

ratio, both by improving oncologic outcomes and by reducing long-term adverse effects.

CONCLUSION

The role of neoadjuvant therapy in the management of breast cancer is increasingly important. Caring for patients with operable breast cancer requires a multidisciplinary approach, with close collaboration among various disciplines, including pathology, radiology, surgical oncology, radiation oncology, and medical oncology. As our systemic therapies continue to improve, it is anticipated that various deescalation and escalation approaches will be evaluated, with adjuvant therapy approaches being based on response to neoadjuvant therapy.

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Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_320691.

REFERENCES

1. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol. 1998;16:2672-2685.
2. Bear HD, Anderson S, Brown A, et al; National Surgical Adjuvant Breast and Bowel Project Protocol B-27. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003;21:4165-4174.
3. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384:164-172.
4. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012;30:1796-1804.
5. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13:25-32.
6. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17:791-800.
7. von Minckwitz G, Huang C-S, Mano MS, et al; KATHERINE investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380:617-628.
8. Lin NU, Vanderplas A, Hughes ME, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer. 2012;118:5463-5472.
9. Smid M, Wang Y, Zhang Y, et al. Subtypes of breast cancer show preferential site of relapse. Cancer Res. 2008;68:3108-3114.
10. Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA. 2006;295:1658-1667.

11. Steenbruggen TG, van Werkhoven E, van Ramshorst MS, et al. Adjuvant chemotherapy in small node-negative triple-negative breast cancer. Eur J Cancer. 2020;135:66-74.
12. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. J Clin Oncol. Epub 2021 Jan 28.
13. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol. 2008;26:778-785.
14. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19:27-39.
15. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147-2159.
16. Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in early breast cancer: the ABC trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). J Clin Oncol. 2017;35:2647-2655.
17. Poggio F, Bruzzone M, Ceppi M, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol. 2018;29:1497-1508.
18. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol. 2018;19:497-509.
19. Petrelli F, Coinu A, Borgonovo K, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;144:223-232.
20. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004;351:2817-2826.
21. Rugo HS, Olopade OI, DeMichele A, et al; I-SPY 2 investigators. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. N Engl J Med. 2016;375:23-34.
22. Nanda R, Liu MC, Yau C, et al. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. JAMA Oncol. 2020;6:676-684.
23. Schmid P, Dent R, O'Shaughnessy J. Pembrolizumab for early triple-negative breast cancer. Reply. N Engl J Med. 2020;382:e108.
24. Schmid P, Salgado R, Park YH, et al. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann Oncol. 2020;31:569-581.
25. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020;396:1090-1100.
26. Chollet P, Amat S, Cure H, et al. Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer. Br J Cancer. 2002;86:1041-1046.
27. Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. JAMA Oncol. 2016;2:1477-1486.
28. Kim HJ, Noh WC, Lee ES, et al. Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy in pre-menopausal patients with oestrogen receptor-positive and HER2-negative, lymph node-positive breast cancer. Breast Cancer Res. 2020;22:54.
29. Smith IE, Dowsett M, Ebbs SR, et al; IMPACT Trialists Group. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol. 2005;23:5108-5116.
30. Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the P024 trial. Breast Cancer Res Treat. 2007;105(suppl 1):33-43.
31. Fontein DB, Charehbili A, Nortier JW, et al. Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients—a phase II trial. Eur J Cancer. 2014;50:2190-2200.
32. Alba E, Calvo L, Albanell J, et al; GEICAM. Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. Ann Oncol. 2012;23:3069-3074.
33. Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer. 2007;110:244-254.
34. Palmieri C, Cleator S, Kilburn LS, et al. NEOCENT: a randomised feasibility and translational study comparing neoadjuvant endocrine therapy with chemotherapy in ER-rich postmenopausal primary breast cancer. Breast Cancer Res Treat. 2014;148:581-590.
35. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol. 2001;19:3808-3816.
36. Bear HD, Wan W, Robidoux A, et al. Using the 21-gene assay from core needle biopsies to choose neoadjuvant therapy for breast cancer: A multicenter trial. J Surg Oncol. 2017;115:917-923.
37. Pease AM, Riba LA, Gruner RA, et al. Oncotype DX® recurrence score as a predictor of response to neoadjuvant chemotherapy. Ann Surg Oncol. 2019;26:366-371.
38. Ueno T, Saji S, Masuda N, et al. Changes in recurrence score by neoadjuvant endocrine therapy of breast cancer and their prognostic implication. ESMO Open. 2019;4:e000476.
39. Akashi-Tanaka S, Shimizu C, Ando M, et al. 21-gene expression profile assay on core needle biopsies predicts responses to neoadjuvant endocrine therapy in breast cancer patients. Breast. 2009;18:171-174.

40. Sheng JY, Santa-Maria CA, Mangini N, et al. Management of breast cancer during the COVID-19 pandemic: a stage- and subtype-specific approach. JCO Oncol Pract. 2020;16:665-674.
41. Gasparri ML, Gentilini OD, Lueftner D, et al. Changes in breast cancer management during the corona virus disease 19 pandemic: An international survey of the European Breast Cancer Research Association of Surgical Trialists (EUBREAST). Breast. 2020;52:110-115.
42. Cavalcante FP, Novita GG, Millen EC, et al. Management of early breast cancer during the COVID-19 pandemic in Brazil. Breast Cancer Res Treat. 2020; 184:637-647.
43. Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group. Oncologist. 2020;25:e936-e945.
44. Dietz JR, Moran MS, Isakoff SJ, et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. Breast Cancer Res Treat. 2020;181:487-497.
45. Registry study describes COVID-19 mortality and hospitalization in patients with breast cancer. Oncologist. 2021;26(suppl 2):S17-s18.
46. Iwata H, Masuda N, Yamamoto Y, et al. Validation of the 21-gene test as a predictor of clinical response to neoadjuvant hormonal therapy for ER+, HER2-negative breast cancer: the TransNEOS study. Breast Cancer Res Treat. 2019;173:123-133.
47. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018;379:111-121.
48. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat. 2017;165:573-583.
49. Mamounas EP. NSABP breast cancer clinical trials: recent results and future directions. Clin Med Res. 2003;1:309-326.
50. National Comprehensive Cancer Network. NCCN Guidelines: Breast Cancer. Version 3.2021. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419. Accessed April 23, 2021.
51. America Cancer Society. Breast Cancer Facts & Figures 2019-2020. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Accessed April 23, 2021.
52. Wang T, Baskin AS, Dossett LA. Deimplementation of the Choosing Wisely recommendations for low-value breast cancer surgery: a systematic review. JAMA Surg. 2020;155:759.
53. Bleicher RJ, Ruth K, Sigurdson ER, et al. Time to surgery and breast cancer survival in the United States. JAMA Oncol. 2016;2:330-339.
54. Kaufman CS, Shockney L, Rabinowitz B, et al; Quality Initiative Committee. National Quality Measures for Breast Centers (NQMBC): a robust quality tool: breast center quality measures. Ann Surg Oncol. 2010;17:377-385.
55. Landercasper J, Bailey L, Buras R, et al. The American Society of Breast Surgeons and quality payment programs: ranking, defining, and benchmarking more than 1 million patient quality measure encounters. Ann Surg Oncol. 2017;24:3093-3106.
56. Del Turco MR, Ponti A, Bick U, et al. Quality indicators in breast cancer care. Eur J Cancer. 2010;46:2344-2356.
57. Drageset S, Lindstrøm TC, Underlid K. Coping with breast cancer: between diagnosis and surgery. J Adv Nurs. 2010;66:149-158.
58. Drageset S, Lindstrøm TC, Giske T, et al. Being in suspense: women's experiences awaiting breast cancer surgery. J Adv Nurs. 2011;67:1941-1951.
59. Bilimoria KY, Ko CY, Tomlinson JS, et al. Wait times for cancer surgery in the United States: trends and predictors of delays. Ann Surg. 2011;253:779-785.
60. Eaglehouse YL, Georg MW, Shriver CD, et al. Time-to-surgery and overall survival after breast cancer diagnosis in a universal health system. Breast Cancer Res Treat. 2019;178:441-450.
61. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087.
62. Mariella M, Kimbrough CW, McMasters KM, et al. Longer time intervals from diagnosis to surgical treatment in breast cancer: associated factors and survival impact. Am Surg. 2018;84:63-70.
63. Brazda A, Estroff J, Euhus D, et al. Delays in time to treatment and survival impact in breast cancer. Ann Surg Oncol. 2010;17(suppl 3):291-296.
64. Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academies Press; 2001.
65. Prakash I, Thomas SM, Greenup RA, et al. Time to surgery among women treated with neoadjuvant systemic therapy and upfront surgery for breast cancer. Breast Cancer Res Treat. 2021;186:535-550.
66. Omarini C, Guaitoli G, Noventa S, et al. Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients. Eur J Surg Oncol. 2017; 43:613-618.
67. Sutton TL, Schlitt A, Gardiner SK, et al. Time to surgery following neoadjuvant chemotherapy for breast cancer impacts residual cancer burden, recurrence, and survival. J Surg Oncol. 2020;122:1761-1769.
68. Office of Disease Prevention and Health Promotion. Healthy People 2020: social determinants of health. https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health. Accessed April 23, 2021.
69. Artiga S, Hinton E. Beyond Health Care: The Role of Social Determinants in Promoting Health and Health Equity. San Francisco, CA: Kaiser Family Foundation; 2018.
70. Obeng-Gyasi S, O'Neill A, Zhao F, et al. Impact of insurance and neighborhood socioeconomic status on clinical outcomes in therapeutic clinical trials for breast cancer. Cancer Med. 2021;10:45-52.
71. Ayanian JZ, Kohler BA, Abe T, et al. The relation between health insurance coverage and clinical outcomes among women with breast cancer. N Engl J Med. 1993;329:326-331.

72. Byers TE, Wolf HJ, Bauer KR, et al; Patterns of Care Study Group. The impact of socioeconomic status on survival after cancer in the United States: findings from the National Program of Cancer Registries Patterns of Care Study. Cancer. 2008;113:582-591.

73. Shi R, Taylor H, McLarty J, et al. Effects of payer status on breast cancer survival: a retrospective study. BMC Cancer. 2015;15:211.

74. George P, Chandwani S, Gabel M, et al. Diagnosis and surgical delays in African American and White women with early-stage breast cancer. J Womens Health (Larchmt). 2015;24:209-217.

75. Polverini AC, Nelson RA, Marcinkowski E, et al. Time to treatment: measuring quality breast cancer care. Ann Surg Oncol. 2016;23:3392-3402.

76. Smith EC, Ziogas A, Anton-Culver H. Delay in surgical treatment and survival after breast cancer diagnosis in young women by race/ethnicity. JAMA Surg. 2013; 148:516-523.

77. Fedewa SA, Edge SB, Stewart AK, et al. Race and ethnicity are associated with delays in breast cancer treatment (2003-2006). J Health Care Poor Underserved. 2011;22:128-141.

78. Jackson DK, Li Y, Eskander MF, et al. Racial disparities in low-value surgical care and time to surgery in high-volume hospitals. J Surg Oncol. 2021; 123:676-686.

79. DeSantis CE, Miller KD, Goding Sauer A, et al. Cancer statistics for African Americans, 2019. CA Cancer J Clin. 2019;69:211-233.

80. Britton BV, Nagarajan N, Zogg CK, et al. US surgeons' perceptions of racial/ethnic disparities in health care: a cross-sectional study. JAMA Surg. 2016; 151:582-584.

81. Golshan M, Losk K, Kadish S, et al. Understanding process-of-care delays in surgical treatment of breast cancer at a comprehensive cancer center. Breast Cancer Res Treat. 2014;148:125-133.

82. Loftus L, Laronga C, Coyne K, et al. Race of the clock: reducing delay to curative breast cancer surgery. J Natl Compr Canc Netw. 2014;12(suppl 1):S13-S15.

83. Liederbach E, Sisco M, Wang C, et al. Wait times for breast surgical operations, 2003-2011: a report from the National Cancer Data Base. Ann Surg Oncol. 2015; 22:899-907.

84. Bleicher RJ, Chang C, Wang CE, et al. Treatment delays from transfers of care and their impact on breast cancer quality measures. Breast Cancer Res Treat. 2019;173:603-617.

85. Society of Surgical Oncology. Resource for management options of breast cancer during COVID-19. https://www.surgonc.org/wp-content/uploads/2020/03/Breast-Resource-during-COVID-19-3.23.20.pdf. Accessed April 23, 2021.

86. Darby S, McGale P, Correa C, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011; 378:1707-1716.

87. McGale P, Taylor C, Correa C, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014; 383:2127-2135.

88. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst. 2002;94:1143-1150.

89. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513-520.

90. Bentzen SM, Agrawal RK, Aird EG, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypo-fractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008;9:331-341.

91. Haviland JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14:1086-1094.

92. Murray Brunt A, Haviland JS, Wheatley DA, et al; FAST-Forward Trial Management Group. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet. 2020; 395:1613-1626.

93. Marta GN, Ramiah D, Kaidar-Person O, et al. The financial impact on reimbursement of moderately hypofractionated postoperative radiation therapy for breast cancer: an international consortium report. Clin Oncol (R Coll Radiol). 2021;33:322-330.

94. Bhattacharya IS, Kirby AM, Bliss JM, et al. Can interrogation of tumour characteristics lead us to safely omit adjuvant radiotherapy in patients with early breast cancer? Clin Oncol (R Coll Radiol). 2018;30:158-165.

95. Poortmans PM, Collette S, Kirkove C, et al; EORTC Radiation Oncology and Breast Cancer Groups. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med. 2015;373:317-327.

96. Whelan TJ, Olivotto IA, Levine MN. Regional nodal irradiation in early-stage breast cancer. N Engl J Med. 2015;373:1878-1879.

97. Thorsen LB, Offersen BV, Danø H, et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. J Clin Oncol. 2016;34:314-320.

98. Ranger A, Dunlop A, Hutchinson K, et al. A dosimetric comparison of breast radiotherapy techniques to treat locoregional lymph nodes including the internal mammary chain. Clin Oncol (R Coll Radiol). 2018;30:346-353.

99. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368:987-998.

100. Bosma SCJ, Hoogstraat M, van der Leij F, et al. Response to preoperative radiation therapy in relation to gene expression patterns in breast cancer patients. Int J Radiat Oncol Biol Phys. 2020;106:174-181.