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Preface: Escalation, De-escalation, Adaptation, Speciation, Customization: The New Approaches to Breast Cancer **xiii**

Harold J. Burstein

Disparities in Breast Cancer Outcomes and How to Resolve Them **1**

Otis W. Brawley and Dina George Lansey

There has been a 40% decline in breast cancer age-adjusted death rate since 1990. Black American women have not experienced as great a decline; indeed, the Black-White disparity in mortality in the United States is greater today than it has ever been. Certain states (areas of residence), however, do not see such dramatic differences in outcome by race. This latter finding suggests much more can be done to reduce disparities and prevent deaths. Interventions to get high-quality care (screening, diagnostics, and treatment) involve understanding the needs and concerns of the patient and addressing those needs and concerns. Patient navigators are 1 way to improve outcomes.

Testing for Inherited Susceptibility to Breast Cancer **17**

Mark Robson

When BRCA1 and BRCA2 were first identified, the initial models for delivering testing were shaped by concepts of genetic exceptionalism and a lack of data regarding therapeutic implications and the effectiveness of risk reduction. Since then, interventions have been effective, and treatment implications have become clear. The sensitivity of guideline-based testing is incomplete, leading to calls for universal testing. Completely universal testing, however, is not necessary to identify the great majority of BRCA1 or BRCA2 variants. Broader testing (both in terms of eligibility and genes tested) will identify more variants, particularly in moderate penetrance genes, but the clinical implications remain less clear for these variants.

Breast Cancer Pathology in the Era of Genomics **33**

Hannah Y. Wen and Laura C. Collins

The era of genomic medicine provides an opportunity for pathologists to offer greater detail about the molecular underpinnings of a patient's cancer and thereby more targeted therapeutic options. In this review article, the role of genomics in breast cancer pathology is discussed, as it pertains to risk management, classification of special tumor types, predictive and prognostic testing, identification of actionable therapeutic targets, and monitoring for disease progression or development of treatment resistance.

Surgical Management of the Axilla for Breast Cancer 51

Alison Laws, Olga Kantor, and Tari A. King

This review discusses the contemporary surgical management of the axilla in patients with breast cancer. Surgical paradigms are highlighted by clinical nodal status at presentation and treatment approach, including upfront surgery and neoadjuvant systemic therapy settings. This review focuses on the increasing opportunities for de-escalating the extent of axillary surgery in the era of sentinel lymph node biopsy, while also reviewing the remaining indications for axillary clearance with axillary lymph node dissection.

Role of Ovarian Suppression in Early Premenopausal Breast Cancer 79

Prudence A. Francis

The benefit from removing ovaries to control premenopausal breast cancer growth was identified more than 100 years ago. Subsequent identification of estrogen receptor (ER) enabled targeting of this approach. Development of gonadotropin-releasing hormone agonists facilitated a reversible method of ovarian function suppression, suitable for young women with early breast cancer. Clinical trials have established the value of including ovarian suppression to reduce recurrence of ER-positive premenopausal early breast cancer. Ovarian suppression administered with chemotherapy can reduce the risk of premature menopause in ER-negative cancer, and increase the prospect of future pregnancy in premenopausal women, regardless of tumor hormone receptor status.

Adjuvant Systemic Therapy for Postmenopausal, Hormone Receptor-Positive Early Breast Cancer 89

Stephen R.D. Johnston

There is now a deeper understanding of the biology of hormone receptor-positive (HR+) early breast cancer (EBC) that can be used to inform assessment of risk and prognosis, and also guide more effective adjuvant systemic therapies. For postmenopausal HR+ EBC endocrine therapy remains the mainstay of treatment with extended duration up to 10 years for some, the addition of targeted CDK 4/6 inhibitors for those with node-positive high-risk disease, and de-escalation of chemotherapy use for those in whom it is unlikely to be of benefit. As such, systemic adjuvant therapy is now highly tailored and individualized.

Systemic Therapy for Early- and Late-Stage, Human Epidermal Growth Factor Receptor-2-Positive Breast Cancer 103

Nicholas P. McAndrew and Sara A. Hurvitz

Systemic therapy for both early-stage and metastatic human epidermal growth factor receptor-2-positive (HER2+) breast cancer has seen significant evolution over the last 20 or more years. Innovative trials leveraging the prognostic and predictive information that neoadjuvant chemotherapy provides has led to preoperative systemic therapy becoming the overwhelmingly favored sequencing in the early-stage setting. However, deintensification of therapy is important to consider for patients with good-risk disease or significant comorbidities. Finally, with the abundance of newly approved agents, drug sequencing in the second-line setting has become an important and individualized decision for patients with metastatic disease.

Biology and Treatment of HER2-Low Breast Cancer 117

Eleonora Nicolò, Paolo Tarantino, and Giuseppe Curigliano

Current guidelines recommend a dichotomous classification of HER2 as either positive or negative, to guide clinicians in treatment decisions. Until now, only patients with HER2-positive breast cancer (BC) had been demonstrated to derive clinical benefit from anti-HER2 therapies. However, novel ADCs have recently emerged, with activity in the large population of patients with HER2-low–expressing BC. Although it remains unclear whether HER2-low BC represents a distinct entity, given the therapeutic implication its crucial to accurately distinguish HER2-low from HER2-0 BC. Efforts are needed to standardize HER2 testing in BC and to introduce more sensitive assays to better discriminate HER2 levels.

Role of Immunotherapy in Early- and Late-Stage Triple-Negative Breast Cancer 133

Stefania Morganti and Sara M. Tolaney

For women with triple-negative breast cancer, the addition of pembrolizumab to chemotherapy has become a standard of care in the early-stage and first-line metastatic setting. However, many questions persist. Different chemotherapy backbones and sequencing strategies have been evaluated, but evidence supporting the superiority of one over the other is weak. Although many have been investigated, programmed cell death ligand 1 (PDL1) is the only approved biomarker. Since immunotherapy has been associated with potentially severe and permanent toxicities, the identification of better predictive biomarkers is essential. New strategies are needed to increase the proportion of patients who might benefit from immunotherapy.

Current and Emerging Role of Antibody–Drug Conjugates in HER2-Negative Breast Cancer 151

Rachel Occhiogrosso Abelman, Jennifer C. Keenan, Phoebe K. Ryan, Laura M. Spring, and Aditya Bardia

Antibody–drug conjugates (ADCs) are rapidly evolving therapies that are uniquely able to deliver potent chemotherapy specifically to cancer cells while largely sparing normal cells. ADCs have 3 components: (1) antibody targeted to a tumor-involved antigen, (2) cytotoxic payload, and (3) linker that connects the cytotoxic agent to the antibody. Once the antibody binds the target on the cell surface, the ADC is incorporated into the cell via receptor-mediated endocytosis. Inside the cells, the linker is cleaved in the lysosome and the payload is then released intracellularly. This article will review ADCs in clinical development for HER2-negative metastatic breast cancer.

The Clinical Utility of ESR1 Mutations in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer 169

Albert Grinshpun, Zachary M. Sandusky, and Rinath Jeselsohn

The estrogen receptor is a key driver of estrogen receptor-positive breast cancers. Accumulating evidence indicates that the ESR1 ligand-binding domain mutations have an important role in acquired endocrine resistance, mainly to treatment with aromatase inhibitors. The identification,

monitoring, and targeting of ESR1 mutations is an evolving field of major interest given the potential of improved outcomes in metastatic hormone receptor-positive breast cancers. Herein, the authors review the current evidence and rationale for exploiting the ESR1 mutations as a potential biomarker and therapeutic target. The authors discuss the role of ESR1 testing and current therapeutic efforts to target these mutations.

Multidisciplinary Management of Brain Metastasis from Breast Cancer **183**

Dario Trapani, Ayal A. Aizer, and Nancy U. Lin

The management of patients with breast cancer and brain metastases (BMs) is exquisitely multidisciplinary. Patients presenting with a symptomatic BM may be offered neurosurgical resection, followed by radiation. Stereotactic radiosurgery (SRS) is preferred over whole-brain radiotherapy (WBRT) in most patients presenting with a limited number of BMs, whereas WBRT with hippocampal-sparing and concomitant memantine is preferred for patients with multiple BMs. There is a growing role for systemic therapy, in some cases in lieu of local therapy, particularly in patients with HER2+ breast cancer.

Systemic Therapy for Hereditary Breast Cancers **203**

Elizabeth J. Harvey-Jones, Christopher J. Lord, and Andrew N.J. Tutt

Approximately 5% to 10% of all breast cancers are hereditary; many of which are caused by pathogenic variants in genes required for homologous recombination, including BRCA1 and BRCA2. Here we discuss systemic treatment for such breast cancers, including approved chemotherapeutic approaches and also targeted treatment approaches using poly-(ADP ribose) polymerase inhibitors. We also discuss experimental approaches to treating hereditary breast cancer, including new small molecule DNA repair inhibitors and also immunomodulatory agents. Finally, we discuss how drug resistance emerges in patients with hereditary breast cancer, how this might be delayed or prevented, and how biomarker-adapted treatment is molding the future management of hereditary breast cancer.

Evidence-Based Guidance for Breast Cancer Survivorship **225**

Elizabeth J. Cathcart-Rake and Kathryn J. Ruddy

Breast cancer survivorship care includes management of lingering physical symptoms, supports to address the emotional toll exacted by a cancer diagnosis and cancer therapies, monitoring and optimization of cardiac and bone health, general wellness promotion, reproductive health care, surveillance for cancer recurrence, care coordination, and efforts to mitigate health disparities.