JAMA Network Clinical Guideline Synopsis

American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline for Management of Hereditary Breast Cancer

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GUIDELINE TITLE: Management of Hereditary Breast Cancer: American Society of Clinical Oncology (ASCO), American Society of Radiation Oncology (ASTRO), and Society of Surgical Oncology (SSO) Guidelines

DEVELOPER: ASCO, ASTRO, and SSO

RELEASE DATE: February 2020

PRIOR VERSIONS: None

FUNDING SOURCE: ASCO

TARGET POPULATION: Health care workers involved in management of hereditary breast cancer

MAJOR RECOMMENDATIONS (WITH EVIDENCE TYPE/EVIDENCE QUALITY/STRENGTH OF RECOMMENDATION):

- Patients with newly diagnosed hereditary breast cancer can be offered breast-conserving therapy (BCT) (consensus/intermediate/moderate).
- Patients who are *BRCA1/2* carriers are at increased risk of contralateral breast cancer (CBC); therefore, a discussion of bilateral mastectomy (with contralateral risk-reducing mastectomy [CRRM]) is warranted (consensus/intermediate/strong).
- Patients who do not have bilateral mastectomy should undergo high-risk screening of the remaining breast tissue with annual mammogram and magnetic resonance imaging (consensus/low/moderate).
- For patients who request CRRM, nipple-sparing mastectomy (NSM) is a reasonable approach (consensus/intermediate/moderate).
- There is limited evidence for CRRM in patients with moderate-penetrance genes (*PALB2*, *ATM*, and *CHEK2*). However, additional factors that predict CBC, such as age at diagnosis and family history, should be considered (consensus/low/moderate).
- Patients with *TP53* mutation carriers should be offered mastectomy because radiation therapy is contraindicated unless the risk of locoregional recurrence is high (consensus/low/moderate).
- Data regarding radiation toxicity in *ATM* carriers are low, hence the need for a discussion with *ATM* carriers interested in BCT (consensus/low/moderate).
- In advanced *BRCA*-associated breast cancer, platinum agents are recommended vs taxanes. There are no data to address platinum efficacy in other germline mutations (evidence-based/intermediate/moderate).
- Poly ADP-ribose polymerase (PARP) inhibitors are recommended for metastatic *HER2*-negative *BRCA*-associated breast cancer as an alternative to chemotherapy for first- to third-line setting (evidence-based/high/strong).
- There is no evidence to support the use of PARP inhibitor in patients with moderate penetrance genes (consensus/insufficient/moderate).
- In the adjuvant/neoadjuvant setting, there is no evidence for addition of platinum or PARP inhibitors to anthracycline-based and taxane-based chemotherapy (evidence-based/intermediate/moderate).

Summary of the Clinical Problem

Lifetime risk of breast cancer for high-penetrance genes, such as *BRCA1/2*, is approximately 70%, while the lifetime risk of the moderate-penetrance genes ranges from 35% to 60% for *PALB2* and 25% to 30% for *ATM* and truncating *CHEK2* mutations.[1] While there are many guidelines on risk management, there are few guidelines on the role of local or systemic treatment in women with hereditary breast cancer. This joint guideline offers recommendations for the management of breast cancer in patients with germline mutations in *BRCA1/2 PALB2, CHEK2, TP53*, and *ATM*.[2]

Characteristics of the Guideline Source

The guideline was developed by a 52-member multidisciplinary panel (referred to as the consensus panel) convened by Society of Clinical Oncology (ASCO), American Society of Radiation Oncology (ASTRO), and Society of Surgical Oncology (SSO). All members were required to disclose financial or other interests, including relationships with commercial entities that are likely to experience direct regulatory or commercial impact as a result of the guidelines. All funding for the administration of the project was provided by ASCO. Adherence to each of the 9 standards developed by the Institute of Medicine for the development of guidelines is good (**Table**).

Evidence Base

The recommendations for local therapy were developed by a systematic review of a literature search of PubMed from January 1, 2010, to September 26, 2019, for surgery and from January 1, 1999, to September 26, 2019, for radiotherapy. Fifty-eight articles met eligibility crite-

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Good
Clinical practice guideline-systematic review intersection	Fair
Establishing evidence foundations and rating strength for each of the guideline recommendations	Fair
Articulation of recommendations	Good
External review	Good
Updating	Good
Implementation issues	Fair

ria for local therapy. Because of the limited high-quality evidence available for the local therapy clinical questions, recommendations were developed using the ASCO-modified Delphi formal consensus methods. Each recommendation had to be agreed by at least 75% of consensus panel respondents. Recommendations for systemic therapy were developed by a systematic review of phase 2 or phase 3 randomized clinical trials (RCTs) from January 1, 2005, to September 26, 2019. Six RCTs met eligibility criteria. Ten clinical questions were addressed, leading to 22 recommendations. Ratings for the evidence type, evidence quality, and strength of recommendation are provided with each recommendation.

Benefits or Harms

Most recommendations are based on moderate rather than strong evidence and benefit only a small proportion of women with breast cancer, although this may change with expanded genetic testing. Improved outcomes may result from standardization of care.

Because these guidelines are developed for a relatively rare condition, evidence may be limited by small studies. Patients, health care professionals, and health care systems can be compromised by costly interventions that are recommended based on limited evidence.

Discussion

Approximately 5% to 10% of breast cancers are associated with a genetic mutation, with 4% to 5% owing to *BRCA1/2* inherited in an autosomal dominant inheritance fashion. Moreover, 15% to 20% of breast cancer is familial, affecting women who have 1 or more first-degree or second-degree relatives with breast cancer. Attempts to standardize evaluation and management of these patients are imperative as more information becomes available and as new targeted therapies are developed for this group of patients.

While no difference in survival outcomes after BCT have been noted in women with *BRCA* mutations,[3] existing data suggest an increased risk of new primary breast cancers, and this may motivate patient interest in risk-reducing mastectomy surgery. Data are more limited regarding the incidence of ipsilateral breast cancer events in women with moderate penetrance gene mutations. However, it is assumed that BCT is also a safe option in such patients. The CBC risk with *BRCA1/2* mutation carriers should be discussed at the same time as treatment of the index cancer because mastectomy for the index malignancy can be combined with CRRM. Nipple-sparing mastectomy is an appropriate oncology and preventative treatment option. Patients with *BRCA1/2* mutations that undergo BCT should be monitored with magnetic resonance imaging in addition to mammography.[4] The evidence regarding CBC risk in moderate penetrance genes is limited; the role of CRRM requires a careful discussion with such patients.

Radiotherapy after BCT in mutation carriers should be offered, except in women with *TP53* mutations, where radiotherapy is relatively contraindicated. In such patients, mastectomy is the preferred option, but radiotherapy should be considered when the risk of locoregional recurrence is high.[5]

While adjuvant or neoadjuvant chemotherapy recommendations in nonmetastatic hereditary breast cancer are similar to sporadic breast cancer, platinum chemotherapy is preferred to taxanes in women with *BRCA*-associated metastatic breast cancer.[6] The EMBRACA trial showed that poly ADP-ribose polymerase inhibitors can be offered as an alternative to chemotherapy in women with metastatic *BRCA*-associated breast cancer. There are no data supporting poly ADP-ribose polymerase inhibitors or platinum in other mutation-associated breast cancers.[7]

Areas in Need of Future Study or Ongoing Research

Although these guidelines represent expert recommendation on the best practices in disease management to provide the highest level of cancer care, they are not applicable in disadvantaged populations who do not have access to genetic counseling and testing. Patients with multiple chronic conditions form a special group who may not be suitable for the recommendations.

While there is good evidence of treatment options in *BRCA1/2* mutations, there is limited evidence in the moderate penetrance genes such as *PALB2, CHEK2,* and *ATM* mutations. Further research is warranted in these areas.

ARTICLE INFORMATION

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