Management of Male Breast Cancer: ASCO Guideline

Hassett et al.
Introduction

- Male breast cancer is a rare disease representing < 1% of all breast carcinomas diagnosed in the United States each year.
- In 2019, an estimated 2,670 new cases of breast cancer were expected to be diagnosed among men in the United States, and about 500 men were expected to die as a result of breast cancer.
- The lifetime risk of breast cancer is about 1:1,000 for a man, whereas it is approximately 1:8 for a woman.
- There are substantial knowledge gaps concerning the optimal management of breast cancer in men.
- To date, approaches to treating men with breast cancer have been extrapolated largely from research conducted in women with breast cancer.
ASCO Guideline Development Methodology

The guideline process included:

- a systematic literature review by ASCO guidelines staff
- an expert panel provided critical review and evidence interpretation to inform guideline recommendations
- a formal consensus process
- final guideline approval by ASCO Clinical Practice Guidelines Committee (CPGC)

The full ASCO Guidelines Methodology Manual can be found at:
www.asco.org/guideline-methodology
Clinical Questions

This clinical practice guideline addresses 10 clinical questions:
1. Which adjuvant endocrine therapy should be offered to men with early-stage, hormone receptor–positive breast cancer?
2. What is the optimal duration of adjuvant endocrine treatment of men with early-stage, hormone receptor–positive breast cancer?
3. What is the role of bone-modifying agents in men with early-stage, hormone receptor–positive breast cancer?
4. Which endocrine therapies should be offered to men with advanced or metastatic, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer?
5. What is the role of cyclin-dependent kinase (CDK) inhibitors and mammalian target of rapamycin inhibitors in the treatment of men with advanced or metastatic breast cancer?
Clinical Questions

5. What is the optimal approach to managing toxicity of endocrine therapy in men with breast cancer?
6. What guidance around follow-up and management should be available to men who have been previously treated for breast cancer?
7. What testing is recommended for the detection of breast cancer after curative-intent primary therapy for patients who are not germline mutation carriers of breast cancer susceptibility genes?
8. How should post-treatment surveillance recommendations differ for men with breast cancer who carry predisposing germline mutations in breast cancer susceptibility genes?
9. Should referral for genetic counseling and genetic testing for germline mutations be recommended for newly diagnosed male patients with breast cancer?
Target Population and Audience

**Target Population**
Men diagnosed with invasive breast cancer.

**Target Audience**
Medical oncologists, radiologists, radiation oncologists, surgical oncologists, endocrinologists, oncology nurses, patients/caregivers/advocates, oncology advanced practice providers, genetic counselors.
Summary of Recommendations

CLINICAL QUESTION 1
Which adjuvant endocrine therapy should be offered to men with early-stage, hormone receptor–positive breast cancer?

Recommendation 1.1
Men with hormone receptor–positive breast cancer who are candidates for adjuvant endocrine therapy should be offered tamoxifen (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Strong)

Recommendation 1.2
Men with hormone receptor–positive breast cancer who are candidates for adjuvant endocrine therapy but have a contraindication to tamoxifen may be offered gonadotropin-releasing hormone agonist/antagonist and an aromatase inhibitor (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
Summary of Recommendations

**CLINICAL QUESTION 2**
What is the optimal duration of adjuvant endocrine treatment of men with early-stage, hormone receptor–positive breast cancer?

**Recommendation 2.1**
Men who are treated with adjuvant endocrine therapy should be treated for an initial duration of five years (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Strong)

**Recommendation 2.2**
Men who have completed five years of tamoxifen, have tolerated therapy, and still have a high risk of recurrence may be offered an additional five years of tamoxifen therapy (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Strong)
CLINICAL QUESTION 3
What is the role of bone-modifying agents in men with early-stage, hormone receptor–positive breast cancer?

Recommendation 3.1
Men with early-stage breast cancer should not be treated with bone-modifying agents to prevent recurrence but could still receive these agents to prevent or treat osteoporosis (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
Summary of Recommendations

CLINICAL QUESTION 4
Which endocrine therapies should be offered to men with advanced or metastatic, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer?

Recommendation 4.1
Men with advanced or metastatic, hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer should be offered endocrine therapy as first-line therapy except in cases of visceral crisis or rapidly progressive disease. Options include tamoxifen, an aromatase inhibitor with a gonadotropin-releasing hormone agent, and fulvestrant. Cyclin-dependent kinase 4/6 inhibitors can be used in men as they are used in women (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Strong)
Summary of Recommendations

**Recommendation 4.2**
Men who develop recurrent metastatic, hormone receptor–positive, HER2-negative breast cancer while receiving adjuvant endocrine therapy should be offered an alternative endocrine therapy except in cases of visceral crisis or rapidly progressive disease (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Strong)

**Recommendation 4.3**
Endocrine therapy for men with advanced or metastatic, hormone receptor–positive, HER2-negative breast cancer may be sequenced as in women (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
Summary of Recommendations

CLINICAL QUESTION 5
What is the role of cyclin-dependent kinase (CDK) inhibitors and mammalian target of rapamycin inhibitors in the treatment of men with advanced or metastatic breast cancer?

Recommendation 5
Targeted therapy guided by HER2, PDL-1, PIK3CA, and germline BRCA mutation status may be used in the treatment of advanced or metastatic male breast cancer using the same indications and combinations that are offered to women (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Strong)
Summary of Recommendations

CLINICAL QUESTION 6
What is the optimal approach to managing toxicity of endocrine therapy in men with breast cancer?

Recommendation 6.1
Management of endocrine therapy toxicity is similar to the approach used for women (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)

Recommendation 6.2
Testosterone/androgen supplementation should not be used by men with breast cancer (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
Summary of Recommendations

CLINICAL QUESTION 7
What guidance around follow-up and management should be available to men who have been previously treated for breast cancer?

Recommendation 7
Physicians should counsel patients about the symptoms of recurrence including new lumps, bone pain, chest pain, dyspnea, abdominal pain, or persistent headaches. The risk of breast cancer recurrence continues through 15 years after primary treatment and beyond. Continuity of care for patients with breast cancer is recommended and should be performed by a physician experienced in the surveillance of patients with cancer and in breast examination, including the examination of irradiated breasts (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
Summary of Recommendations

CLINICAL QUESTION 8
What testing is recommended for the detection of breast cancer after curative-intent primary therapy for patients who are not germline mutation carriers of breast cancer susceptibility genes?

Recommendation 8
Ipsilateral annual mammogram should be offered to men with a history of breast cancer treated with lumpectomy, if technically feasible, regardless of genetic predisposition (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Strong)
Summary of Recommendations

CLINICAL QUESTION 9
How should post-treatment surveillance recommendations differ for men with breast cancer who carry predisposing germline mutations in breast cancer susceptibility genes?

Recommendation 9.1
Contralateral annual mammogram may be offered to men with a history of breast cancer and a genetic predisposing mutation (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)

Recommendation 9.2
Breast magnetic resonance imaging is not recommended routinely in men with a history of breast cancer (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate)
Summary of Recommendations

CLINICAL QUESTION 10
Should referral for genetic counseling and genetic testing for germline mutations be recommended for newly diagnosed male patients with breast cancer?

Recommendation 10
Male patients with breast cancer should be offered genetic counseling and genetic testing for germline mutations (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Strong)
Health Disparities

- The literature search identified eight articles on the topic of health disparities.

- Studies of disparities among male patients with breast cancer have yielded inconsistent results. The small sample sizes and inherent selection bias associated with these observational studies of patients with male breast cancer are substantial limitations.

- The Expert Panel believes that disparities are as likely to occur in men as in women and recommends:

  1. Awareness of the disparities and barriers to accessing care when considering this clinical practice guideline

  2. Health care providers should strive to deliver the highest level of cancer care to all populations, including those that are more vulnerable
The Expert Panel also notes that transgender individuals have not been evaluated in most prior studies of breast cancer disparities and believes that these individuals may also be at risk of experiencing disparities. Recent studies have begun to explore the risk of developing breast cancer among trans women and trans men.

The Expert Panel believes that the treatment of breast cancer should be the same for transgender women, with the notable exception that exogenous estrogen is not recommended for patients with a history of breast cancer.
Multiple Chronic Conditions

- The Expert Panel believes that any treatment plan should consider the complexity and uncertainty created by the presence of multiple chronic conditions and highlights the importance of shared decision making that incorporates the goals of the patient as well as the input of the specialists treating the patient’s other chronic conditions.

- The need for clinicians to consider all relevant chronic conditions when formulating a treatment and follow-up plan for a new breast cancer diagnosis is the same whether the patient is male or female.

- The Expert Panel believes it is important to note that the average age of a new breast cancer diagnosis is five years older for men (67 years) than for women (62 years). Consequently, clinicians should expect a higher comorbidity burden due to age among men with breast cancer.
Cost Considerations

- Higher patient out-of-pocket costs are a barrier to initiating and adhering to recommended cancer treatments.
- Discussion of cost can be an important part of shared decision making.
- Patient out-of-pocket costs may vary depending on insurance coverage.
- Providers treating male patients with breast cancer should be aware that men could be at greater risk of being denied coverage for some expensive breast cancer treatments, because coverage determinations focused only on women, and appeals of coverage denials may be more common.
Several qualitative studies have suggested that feelings of emasculation associated with having a “woman’s disease,” sexual stigmatization, and ignorance of the disease are common among men with breast cancer.

The lack of male-specific educational information and limited opportunities for men with breast cancer to talk with other men with breast cancer likely contribute to their sense of isolation and cancer-related distress.

Some of these problems can be ameliorated in relatively straightforward ways. Brain et al and Williams et al have suggested several practical solutions:

1. Inclusion of booklets or leaflets on male breast cancer to improve information and awareness,
2. Providing male patients a photograph of a male mastectomy to show men what they will look like after the surgery,
3. Telephone help-lines and referrals to other sources of support, and
4. Efforts to increase public awareness of male breast cancer.
Directions for Future Research

- To date, recommendations for the treatment of male breast cancer have been extrapolated from the results of clinical trials that enrolled only women, from small case series, or from personal clinical experience in treating men with breast cancer.

- Additional research is needed on a broad array of topics concerning the management of male breast cancer, even those for which agreement on the treatment approach was high.

- Several current treatment trials are enrolling both women and men, after many years of encouragement from both patient organizations (see [https://malebreastcancercoalition.org](https://malebreastcancercoalition.org)) and the International Male Breast Cancer Program.

- The FDA recently issued draft guidance for industry encouraging the inclusion of men in clinical trials studying treatments for breast cancer.

- Concern for differential efficacy in males versus females is greatest with endocrine therapies, making the inclusion of men in clinical trials of endocrine treatments particularly important.
Additional Resources

More information, including a Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/breast-cancer-guidelines

Patient information is available at www.cancer.net
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**Abbreviation:** PGIN, Practice Guidelines Implementation Network

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