

# A Flurry of Guidelines for Breast Cancer Management

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## Abstract

Eleven major guidelines in the area of breast cancer were published in 2014 alone, covering areas ranging from risk assessment and genetic counseling to the management of HER2-positive (HER+) brain metastases and chemotherapy-induced neuropathy. This mini-review and commentary summarizes new recent guidelines and the key updates contained therein.

## Introduction

In an effort to provide the best evidence-based care and to standardize treatments to represent the best benefit/harm ratios, the optimal use of resources, and to reduce variation in practice, clinical care guidelines have proliferated over the past decade. The National Guideline Clearinghouse lists 80 contemporary guidelines for breast cancer management.<sup>1</sup> Most practices have adopted guidelines or “clinical pathways” to some degree, and third-party payers are increasingly using these to determine appropriateness of care and to base payments. Attorneys also are utilizing deviations from guidelines and resultant harm as a basis for damage claims. Given the importance of guidelines, should there be a standard or, in effect, a “guideline for guidelines”? In 2011, the Institute of Medicine released “Standards for Developing Trustworthy Clinical Guidelines,” which codified 8 standards (Table 1).<sup>2</sup> However, there is no formal monitoring or quality check for published guidelines. As a result, there are considerable differences in the approaches taken and the ultimate guideline products.

Eleven major guidelines in the area of breast cancer were published in 2014 alone, a watershed year that covered areas ranging from risk assessment and genetic counseling to axillary node surgery to the management of HER2-positive (HER+) brain metastases and chemotherapy-induced neuropathy. It remains to be seen to what extent these will be followed, and more important, how these will improve population-based outcomes, which of course is the ultimate goal of guidelines. This mini-review and commentary summarizes new recent guidelines (Table 2) and the key updates contained therein.

## Updated NCCN Breast Cancer Guidelines

National Comprehensive Cancer Network (NCCN) guidelines are derived in part from systematic evidence review, but also incorporate expert opinion that may be needed for more granular situations where the literature cannot provide precise direction. Version 3.2014 updates include the use of pertuzumab in the neoadjuvant setting on the basis of improved pathologic complete response rate and the administration of weekly paclitaxel plus trastuzumab as a less-toxic regimen for low-risk HER2+ cases on the basis of low recurrence rates in an uncontrolled study.<sup>3</sup> The most surprising and eye-opening recommendation for patients with early-stage HER2+ breast cancer (level 2A), is the statement that “patients who have not received a neoadjuvant pertuzumab-containing regimen can receive adjuvant pertuzumab.” While NCCN promulgates participation in clinical trials, this recommendation ignores a lack of adjuvant data, increased toxicity (grade 3 diarrhea) and the fact that pivotal trials of adjuvant pertuzumab are ongoing. A more formal review of these recent changes is forthcoming.

In the area of local therapy, the new guidelines now recommend the imaging of clinically negative axillary nodes prior to neoadjuvant therapy, with biopsy, clipping, and surgical removal

**TABLE 1.** Institute of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines

1. Establishing transparency
2. Management of conflict of interest
3. Multi-disciplinary and expert panel composition
4. Systematic review of comparative effectiveness data
5. Establishing evidence foundations for and rating strength of recommendations
6. Clear and precise articulation of recommendations
7. External and independent review
8. Mechanism for regular updating and currency

**TABLE 2.** Major Breast Cancer Guidelines Released in 2014

Guideline	Organization
NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Version 3.2014 <sup>3</sup>	NCCN
Risk assessment, genetic counseling, and genetic testing for <i>BRCA</i> -related cancer in women <sup>4</sup>	USPSTF
Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer <sup>5-8</sup>	SSO/ASTRO (endorsed by ASCO)
Sentinel Lymph Node Biopsy for Patients with Early-Stage Breast Cancer	ASCO
Adjuvant Endocrine Therapy for Women with Hormone Receptor-Positive Breast Cancer <sup>9</sup>	ASCO
Chemotherapy and Targeted Therapy for Women with Human Epidermal Growth Factor Receptor 2-Negative (or Unknown) Advanced Breast Cancer <sup>12</sup>	ASCO
Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer <sup>13</sup>	ASCO
Recommendations on Disease Management for Patients with Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases <sup>14</sup>	ASCO
Screening, Assessment, and Care of Anxiety and Depressive Symptoms in Adults With Cancer <sup>15</sup>	ASCO
Screening, Assessment, and Management of Fatigue in Adult Survivors of Cancer <sup>16</sup>	ASCO
Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers <sup>17</sup>	ASCO

ASCO indicates American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; NCCN, National Comprehensive Cancer Network; USPSTF, US Preventive Services Task Force; SSO, Society of Surgical Oncology.

of histologically positive nodes. However, outcomes data are not presented, and as such, this is given a category of 2A, which is designated as lower-level evidence and uniform NCCN consensus that the intervention is appropriate. Interestingly, the alternative option for clinically negative axillary assessment with post-neoadjuvant therapy, followed by sentinel node biopsy is also given.

#### USPSTF Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer in Women

The US Preventive Services Task Force (USPSTF) systematic review ascertains that the 5 commonly used models to estimate likelihood of a deleterious *BRCA* mutation are accurate and inform risk perception while decreasing testing in low-risk individuals, thus decreasing unnecessary anxiety and depression.<sup>4</sup> However, genetic testing and enhanced screening with MRI at this time has not been shown to improve breast cancer morbidity and mortality, although it is associated with smaller lesion size at diagnosis at the cost of more false-positives results, procedures, and anxiety. On the other hand, preventive surgery in known mutation carriers does lower breast cancer incidence by 85% to 100%, and breast cancer mortality by 81% to 100%, while prophylactic salpingo-oophorectomy reduces ovarian cancer by 69% to 100%, and all-cause mortality by 55% to 100%. USPSTF

concludes rather softly that “studies of risk assessment, genetic counseling, genetic testing, and interventions to reduce cancer and mortality indicate potential benefits and harms that vary according to risk.” The more commonly held view, albeit perhaps not as formally supported by available data, might be that genetic testing of high-risk individuals is recommended, but the consequences of enhanced screening must be discussed with patients. Prophylactic surgery, particularly salpingo-oophorectomy in mutation carriers, is recommended, but the timing of surgery remains unclear, and the use of medical preventive therapies has a less certain effect on cancer and mortality risks.

#### Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

The release of these guidelines jointly by the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO), and later endorsed by the American Society of Clinical Oncology (ASCO), have generated significant controversy because they state that the best evidence shows that very close but negative margins with only a cell layer of margin when performing breast-conserving surgery for invasive (Stage I-II) breast cancer is adequate with respect to local control.<sup>5-8</sup> In fact, a review of the literature did suggest higher rates of local recur-

rence with positive margins, but could find no threshold for a margin width that convincingly showed an incremental improvement in outcome with larger margins. The argument against this position is that closer negative margins could increase the error rate in missing a truly positive margin. Reflecting this concern, the ASCO endorsement added a caveat that institutions should carefully track outcomes in the context of margins to continually gather data that may influence subsequent updates. In addition, it emphasized the importance of postlumpectomy mammography when the tumor is associated with microcalcifications and calls for some flexibility in surgical management and the possible need for re-excision.

#### Adjuvant Endocrine Therapy for Women with Hormone Receptor-Positive Breast Cancer

A focused update on adjuvant hormonal therapy (from the previous ASCO guideline version from 2010) primarily addressed the duration of hormonal therapy with the results of the ATLAS and aTTom trials showing improvements in disease-free and overall survival with 10 years compared with 5 years of tamoxifen.<sup>9-11</sup> While the prior guidelines had recommended extended adjuvant hormonal therapy with an aromatase inhibitor after 5 years of tamoxifen for postmenopausal women, it now recommends 10 years of tamoxifen for women who are premenopausal after 5 years of tamoxifen, and advises 5 years of either tamoxifen or an aromatase inhibitor for postmenopausal women after 5 years of tamoxifen. However, these guidelines do not address smaller, low-risk tumors where the incremental benefit may be outweighed by increased toxicities, primarily uterine cancer. They also do not incorporate other side effects of hormonal therapy such as hot flashes, genitourinary effects, or bone mineral loss apart from monitoring.

#### Sentinel Lymph Node Biopsy (SLN Bx) for Patients with Early-Stage Breast Cancer

As new data are available from randomized trials in patients with positive sentinel nodes, these ASCO guidelines now call for omission of full axillary dissection (ALND) in select patients with positive sentinel nodes.<sup>12</sup> These are based primarily on the ACOSG Z0011 trial in which patients with 1 to 2 positive sentinel nodes who underwent breast-conserving surgery and radiation were found to have no worse local or distant recurrence compared with ALND.<sup>13</sup> Hence, the guidelines follow these trial criteria for ALND omission. With less level of evidence available, these guidelines affirmed that patients with multi-centric invasive cancer or with ductal carcinoma in situ who undergo mastectomy are also candidates for SLN Bx, but those with T3 or T4 disease are not. Finally, there is a clear affirmation based on high level of evidence that ALND should not be performed in patients without sentinel node involvement based on long-term follow up showing no difference in recurrence or mortality

and higher incidence of short- and long-term complications of ALND.

#### Chemotherapy and Targeted Therapy for Women with HER2-Negative (or Unknown) Advanced Breast Cancer

For human epidermal growth factor receptor 2 (HER2)-negative and hormone receptor-positive (HR+) advanced breast cancer, hormonal therapy is being recommended as initial treatment in almost all cases, and in the case of rapidly progressive disease, where initial chemotherapy tends to be used in practice, it is stated that there is very little evidence that initial chemotherapy is more beneficial than a trial of hormonal therapy and close observation.<sup>14</sup> No guidance is provided on specific agents or sequence of hormonal therapy, and the topic of combination hormonal therapy is not addressed. There is no mention of hormonal resistance, such as progression while on hormonal therapy, as an indicator for initial chemotherapy. Similarly, the use of everolimus is not addressed in later lines of therapy; it is not clear whether the timeline of literature review was prior to the approval of this agent or whether the lack of a survival benefit with everolimus played a role in this omission.

Single-agent chemotherapy is recommended after exhaustion of hormonal therapy or in HR-negative cases with very little direction as to when doublet therapy may be indicated. Continuation of chemotherapy in the absence of progression is favored over the use of a chemotherapy holiday based on a small survival advantage, but attention to quality of life is called for to individualize therapy, including the duration of treatment. No preference for class or specific chemotherapy agent is made, and HR status was not felt to be a basis for choice of agent. These guidelines emphasize the need for individualized decision making based on side effects, prior therapies, and patient preferences, but point to the little evidence available to guide physicians with detailed protocols.

#### Systemic Therapy for Patients With Advanced HER2+ Breast Cancer

Few fields have changed as rapidly as the treatment of HER2+ breast cancer, with the recent approval of newer agents while median survival of advanced disease has more than doubled. The revised ASCO guidelines are rather straightforward and based on FDA-approved regimens and the available evidence, including taxane plus trastuzumab and pertuzumab in the first-line and ado-trastuzumab emtansine (T-DM1) in the second-line settings and beyond, along with various other combinations such as capecitabine/lapatinib and trastuzumab with several other chemotherapy agents or lapatinib in later lines.<sup>15</sup> Less-strong recommendation is made for the use of pertuzumab-based therapy in the second line or beyond if the drug had not been used previously. Also, for select patients with HER2-negative and HR+ disease, hormonal therapy alone or with trastuzumab or lapatinib could

be considered. It was felt that even later lines of therapy should incorporate anti-HER2 therapy unless contraindicated. Specific cardiac monitoring recommendations are not made, and the use of trastuzumab in the setting of cardiomyopathy must balance the risks and benefits of cardiac and cancer end points.

### Recommendations on Disease Management for Patients with Advanced HER2+ Breast Cancer and Brain Metastases

Patients with HER2+ brain metastases have a significantly better outcome than those with HER2-negative cancers, particularly in comparison with triple-negative cases. This is in part due to better systemic control of disease, although there may be other biological factors. Given the fact that patients can do well for quite some time, guidelines are more important since treatment can have a significant impact. The first set of ASCO guidelines issued for this situation emphasize that the basic tenet of treatment is first addressing local control with surgery and/or radiotherapy, including stereotactic radiation when feasible.<sup>16</sup> Systemic therapy decisions should be guided by the status of systemic disease. In the absence of systemic disease or systemic progression, no change in systemic therapy is recommended. The guidelines also affirm that routine screening for brain metastases in the setting of metastatic breast cancer has not been shown to be helpful in the absence of signs or symptoms, even though the prevalence of central nervous system (CNS) disease may be as high as 10% to 15% in this situation.

### ASCO Supportive Care Guidelines

A growing literature in symptom management for breast cancer now justifies guidelines for the monitoring and management of depression and anxiety, fatigue, and chemotherapy-induced neuropathy. Recommendations include the administration of validated measures for depression and anxiety at key milestones, or when clinically indicated, identification and utilization of resources and referrals for treatment, monitoring of counseling and pharmacologic therapy compliance and side effects, and the adjustment of treatment over time in an iterative process.<sup>17</sup>

Fatigue is rated by patients as one of the most serious side effects of cancer and its treatment. ASCO guidelines revolve around a proper evaluation to identify potentially treatable causes such as medication side effects as well as endocrine, hematologic, and cardiac causes. Contributing factors such as depression, sleep disturbances, alcohol use/abuse, and nutritional causes should be evaluated.<sup>18</sup> Correcting these issues and implementing scheduled activities and sleep and an exercise/activity regimen are first-line recommendations. Pharmacologic interventions with the exception of transient sleep aids are generally not helpful.

It is estimated that nearly 40% of patients treated with chemotherapy for breast cancer experience short- and long-term peripheral neuropathy. ASCO guidelines based on 42 randomized

trials that assessed pharmacologic agents to prevent neuropathy conclude that no drug treatment has proven efficacy in preventing neuropathy.<sup>19</sup> For symptomatic neuropathy, responses to medication are marginal and highly variable, with duloxetine being one of the few recommended as a trial to be continued only if there is clinical improvement. Less enthusiastically recommended based on the low quality of data, and only after a discussion with the patient about the uncertain data, are gabapentin, tricyclic antidepressants, and a topical gel treatment containing baclofen, amitriptyline, and ketamine. Acetyl-L-carnitine actually causes worsening of neuropathy and is not recommended.

### Conclusion

A high number of new guidelines issued in 2014 in breast cancer highlight numerous areas where variation in practice and suboptimal outcomes may be improved by the adoption and implementation of guidelines. However, further work including self-assessment of practices, quality assurance programs, and larger-scale research using electronic medical records, patient-related outcomes, and payer information will be needed to measure the impact of guidelines as they are continually refined and updated with larger-scale trials.

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