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EDITORIAL – BREAST ONCOLOGY

Management of Hereditary Breast Cancer: ASCO, ASTRO, and SSO Guideline

Kandace P. McGuire, MD[1], and Eleftherios P. Mamounas, MD[2]

[1]VCU Massey Cancer Center, Richmond, VA; [2]Orlando Health UF Health Cancer Center, Orlando, FL

Since the identification of germline mutations in *BRCA1* and *BRCA2*, there has been continuous evolution in the identification of additional susceptibility germline mutations that increase risk for breast cancer and other malignancies. With the application of next-generation sequencing, not only has the pace of discovery accelerated in the past decade but this has occurred at a considerable reduction in cost. Thus, physicians are now faced with the challenge of how to appropriately integrate this rapidly expanding information into daily practice. Although existing guidelines and recommendations have focused on the management of future cancer risk associated with germline mutations as well as surveillance and prevention strategies, guidance on the management of patients with germline mutations and newly diagnosed breast cancer has not kept up with the rapid pace of discovery.

In 2018, the Society of Surgical Oncology (SSO) entered into an agreement with the American Society of Clinical Oncology (ASCO) and the American Society of Radiation Oncology (ASTRO) to develop a guideline on the management of hereditary breast cancer. Four SSO members, specializing in breast surgical oncology, were appointed to the expert panel developing the guideline.

The recommendations within the consensus guideline were reviewed and voted on by more than 50 individuals. Additionally, the recommendations were posted for public comment. SSO Quality Committee Chair, Tari King, MD reviewed the final document and recommended that the SSO proceed with approval of the recommendations; consequently, the SSO leadership agreed that the society approve the guidelines.

In this editorial, we summarize and comment on the ASCO, ASTRO, and SSO Guideline on the Management of Hereditary Breast Cancer, published in this issue of the *Annals of Surgical Oncology*.[1] The expert panel's recommendations focused on the surgical management of patients with breast cancer and germline mutations, as well as on the use of radiation therapy and systemic therapy for such patients.

SURGICAL MANAGEMENT

Several clinical questions arise when considering surgical management for a patient with breast cancer associated with a high- or moderate-risk germline mutation. The strength of recommendations (and thus the data supporting them) are generally stronger for *BRCA1/2* carriers than for carriers of moderate-risk genes.

The panel addressed the appropriateness of breast conservation in both *BRCA1/2* carriers and moderate-risk mutation carriers. They concluded that neither *BRCA* nor moderate-penetrance gene mutations should preclude a patient with newly diagnosed breast cancer who is otherwise eligible for breast-conserving therapy (BCT) from receiving BCT. However, there is evidence to suggest increased risk of contralateral breast cancer and possible increased risk of ipsilateral new primary breast cancer in *BRCA* carriers as compared with noncarriers. Regarding the management of a patient's contralateral breast cancer (CBC) risk, the panel's recommendations vary according to the type of mutation, but no mutation is associated with an absolute recommendation for every carrier to undergo prophylactic mastectomy. Existing data suggest that several factors such as age, family history, competing

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K. P. McGuire, MD
e-mail: kandace.mcguire@vcuhealth.org

morbidity/mortality risk, and ability to undergo high-risk screening modify the genetic risk of CBC and, as a result, the role for risk-reducing mastectomy. The evidence regarding contralateral breast cancer risk is limited for mutations in moderate-penetrance breast cancer genes, aside from some data for *CHEK2 1100delC*. The panel noted that many studies demonstrating overall survival benefit with contralateral prophylactic mastectomy may be plagued by selection bias, which affects the strength of the recommendation, even in *BRCA* carriers.

In patients undergoing unilateral or bilateral mastectomy in the setting of a diagnosed breast cancer, many question the safety of nipple-sparing mastectomy. The panel's review of the literature supports the use of nipple-sparing mastectomy as reasonable in *BRCA1/2* and moderate-penetrance breast cancer gene carriers. There is at least one existing study that supports this conclusion in *BRCA* carriers, but none exist for other gene mutations, thus the panel based this recommendation on clinical opinion and extrapolation from the data in *BRCA* carriers.

For those patients not undergoing risk-reducing surgery, the surveillance recommendations are the same for all genetic mutation carriers. *BRCA1/2* and moderate-penetrance gene carriers should undergo annual mammogram and magnetic resonance imaging (MRI). While the evidence is more robust for *BRCA* carriers, the strength of recommendation was moderate, even in moderate-risk gene carriers.

RADIATION THERAPY

In response to the question of the role of radiation therapy (RT) in women with breast cancer who have a *BRCA1/2* germline mutation or selected moderate-penetrance germline mutations, the panel concluded that breast or postmastectomy RT and regional nodal RT should not be withheld when indicated due to mutation status alone, except for mutations in *TP53*. For patients with *BRCA1/2* mutations, there is no evidence of a significant increase in toxicity or contralateral breast cancer (CBC) events related to RT exposure. However, for mutations in selected moderate-penetrance genes, the available evidence is limited. In particular, the panel concluded that, for patients with breast cancer who are carriers of an *ATM* mutation, RT should be offered when clinically indicated, acknowledging though that data regarding rates of toxicity between *ATM* mutation carriers and noncarriers are limited and inconsistent. The panel further commented that, although the potential absolute risks from use of RT appear to be small, more research is needed and that a discussion with *ATM* carriers interested in BCT is encouraged. Lastly, for women with breast cancer who are carriers of a germline *TP53* mutation, the panel concluded that, based on the limited available evidence from a single study, RT of the intact breast is contraindicated and mastectomy is the recommended approach. The panel acknowledged that this recommendation represents the best clinical opinion of the members since only a single case series of six patients with germline *TP53* mutations who had received RT after breast cancer surgery bears on the clinical question, demonstrating a high incidence of contralateral breast cancers, ipsilateral breast recurrences, radio-induced cancers, and new primary cancers. Based on that study, the panel went on to state that postmastectomy RT should only be considered in patients with significant risk of local regional recurrence.

SYSTEMIC THERAPY

The panel also addressed several questions relating to use of systemic therapy in breast cancer patients who also carry a *BRCA1/2* mutation or selected moderate-penetrance germline mutations. For patients with a *BRCA1/2* germline mutation and advanced breast cancer, platinum chemotherapy is preferred to taxane therapy for patients who have not previously received platinum. This recommendation was primarily based on the results of the TNT trial that compared the efficacy of single-agent carboplatin with that of docetaxel in patients with triple-negative metastatic breast cancer. In that trial, higher objective response rates and longer progression-free survival were demonstrated with carboplatin versus docetaxel for the subset of patients with *BRCA1/2* breast cancer (ORR = 68%, PFS = 6.8 months with carboplatin; ORR = 33.3%, PFS = 4.4 months with docetaxel). In contrary, there were no differences in the objective response rate between carboplatin and docetaxel in the unselected population.

In contrast, for early-stage breast cancer patients with germline *BRCA* mutations treated with (neo)adjuvant therapy, the expert panel concluded that the existing data do not support the routine addition of platinum to anthracycline and taxane-based chemotherapy. Furthermore, the panel concluded that there are no data to address platinum efficacy in other germline mutation carriers.

Lastly, the panel addressed the question of the role of poly(ADP-ribose) polymerase (PARP) inhibitors in women who have a *BRCA1/2* mutation or selected moderate-penetrance germline mutations and advanced or nonmetastatic breast cancer. The panel concluded that, for *BRCA1/2* mutation carriers with metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer, olaparib or talazoparib should be offered as an alternative to chemotherapy in the first- to third-line settings. However, the panel also commented that, for *BRCA1/2* mutation

carriers with metastatic HER2-negative breast cancer, there are no data directly comparing the efficacy of PARP inhibitors versus platinum chemotherapy. Furthermore, the panel stated that, for breast cancer patients with mutations in moderate-penetrance genes, there are currently no robust data to support use of PARP inhibitors. Lastly, the panel commented that, for patients with nonmetastatic breast cancer and germline *BRCA* mutation, there are currently insufficient data to recommend a PARP inhibitor.

The ASCO, ASTRO, and SSO Guideline on the Management of Hereditary Breast Cancer provides important information and clearly needed guidance on the optimal surgical, radiation, and systemic therapy management of breast cancer patients with germline mutations in breast cancer susceptibility genes. This information and recommendations will be of great value for practicing physicians who care for these patients. It is hoped that the increasing use of multigene panel testing will eventually lead to a much-needed expansion of knowledge regarding the clinical course of breast cancers in patients who harbor moderate-penetrance germline mutations.

DISCLOSURES The authors report no conflicts of interest.

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