NCCN Guidelines Update: Breast Cancer

Presented by William Gradishar, MD, and Kilian E. Salerno, MD

Abstract

The updates to management of early invasive breast cancer in 2016 are minor but have important treatment implications for patients. The NCCN Guidelines Panel for Breast Cancer has added endocrine therapy to its recommendations for the neoadjuvant treatment of patients with ER-rich tumors. For women who are premenopausal at diagnosis, the NCCN Guidelines suggest tamoxifen for 5 years, with or without ovarian suppression, or an aromatase inhibitor for 5 years combined with ovarian suppression or ablation. For HER2-positive patients, neoadjuvant pertuzumab is acceptable, and in advanced estrogen receptor-positive disease, palbociclib can be given with endocrine therapy. Hypofractionation is now the preferred approach for whole-breast irradiation after breast-conserving therapy. Regional nodal irradiation should be strongly considered for women with 1 to 3 positive lymph nodes and is indicated for those with 4 or more positive nodes.

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Important “Tweaks” in Early-Stage Breast Cancer Guidelines

Updates to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer were relatively minor, according to William Gradishar, MD, the Betsy Bramsen Professor of Breast Oncology at the Feinberg School of Medicine, Northwestern University, and Chair of the NCCN Breast Cancer Guidelines Panel. However, they were called “important tweaks” by Dr. Gradishar and Kilian E. Salerno, MD, Assistant Professor, Radiation Oncology, and Director of Breast Radiation and Soft Tissue/Melanoma Radiation, Roswell Park Cancer Institute, and a member of the NCCN Breast Cancer Panel.

Dr. Gradishar discussed medical management, focusing on endocrine therapy in the neoadjuvant, adjuvant, and metastatic settings; the benefit of ovarian suppression; preoperative HER2-directed therapy; and fertility preservation.

Dr. Salerno presented updates in locoregional treatment and emphasized the benefits of hypofractionated whole-breast radiation therapy (RT). She also discussed issues related to regional nodal irradiation.

Neoadjuvant Endocrine Therapy

For preoperative systemic therapy, the NCCN Guidelines were modified to include the selective use of endocrine therapy. Appropriate candidates are patients with estrogen receptor (ER)-rich tumors (Allred 7–8). Although most of these patients will be postmenopausal, this approach can be considered in premenopausal women with concerns that make them unsuitable for or undesiring of chemotherapy, according to Dr. Gradishar.

Dr. Gradishar referred to ACOSOG Z1031 to show the benefit of neoadjuvant endocrine therapy. After 16 weeks of preoperative exemestane, letrozole, or anastrozole, response or stable disease was observed in 60%, 72%, and 68% of patients, respectively.¹

“Adjuvant endocrine therapy is a rational approach,” he said. “While this is mainly used in postmenopausal women, you can treat premenopausal women with aromatase inhibitors [AIs] as long as you render them postmenopausal with ovarian suppression or ablation first.”

The achievement of pathologic complete response (pCR) is not especially critical with preoperative endocrine therapy, Dr. Gradishar noted. Although pCR is

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Gradishar and Salerno

associated with improved outcomes in patients with ER-negative disease, it does not appreciably impact outcomes in those with ER-positive disease, he said.

Adjuvant Endocrine Therapy Update

Subtle changes have been made in the recommendations for adjuvant endocrine therapy, reflecting recent trial data. For premenopausal women at diagnosis, the NCCN Guidelines for Breast Cancer suggest tamoxifen for 5 years, with or without ovarian suppression, or an AI for 5 years combined with ovarian suppression or ablation (category 1). Women who remain premenopausal can consider tamoxifen for another 5 years (10 total) or no further endocrine therapy. Those who become postmenopausal can consider 5 more years of tamoxifen or switch to an AI for 5 years.

More than half of breast cancer recurrences happen after discontinuation of treatment,² and ovarian suppression or ablation is a way of protecting against these late recurrences. “That maneuver alone has an impact,” Dr. Gradishar emphasized. Recently, the SOFT and TEXT trials have confirmed the benefit of ovarian suppression plus endocrine therapy (± chemotherapy). In the joint analysis of these trials (Figure 1), this strategy improved all end points but overall survival.³

The findings suggest that ovarian suppression with an AI (exemestane was more effective than tamoxifen) may be appropriate in higher-risk patients; however, musculoskeletal issues and complaints related to estrogen deprivation can be problematic.

“Obviously, these data are in some ways very compelling, but we must individualize our choices,” Dr. Gradishar commented.

HER2-Directed Therapy

Patients with HER2-positive tumors should receive preoperative trastuzumab for 9 weeks or more. The updated NCCN Guidelines accept pertuzumab-containing regimens as well for patients with T2 or greater lesions or positive lymph nodes.

In HER2-positive subtypes, pCR is associated with improvements in event-free survival, as shown in a meta-analysis by Cortazar et al.⁴ Whether dual HER2-targeting will ultimately prove the most effective strategy remains to be confirmed,^{5,6} but updated preliminary results from NeoSphere showed the greatest improvement in 5-year progression with

Figure 1. Joint analysis of the TEXT and SOFT trials. Abbreviation: OFS, ovarian function suppression.

pertuzumab/trastuzumab/docetaxel.⁷

“Based on the data at this point, we felt it’s prudent to offer a pertuzumab-containing regimen to patients,” Dr. Gradishar said, adding that the adjuvant APHINITY results will be informative on this issue.

Including Palbociclib

The NCCN Guidelines for Breast Cancer were modified to reflect the results of the PALOMA trials of palbociclib. This agent joins everolimus as an add-on to endocrine therapy in advanced disease, based on PALOMA-1/TRIO-18. This trial showed an almost doubling in time to progression with letrozole/palbociclib versus letrozole alone in the first-line metastatic setting.⁸ In PALOMA-3, fulvestrant plus palbociclib reduced progression risk by 63% as second-line treatment.⁹

“Now we have a series of different treatments, and as we go forward we will see even more of this,” Dr. Gradishar predicted.

Fertility Preservation

In another update, the panel recommended that all patients of child-bearing age with early-stage breast cancer see an oncology fertility specialist if they are interested in preserving fertility. A growing number of fertility preservation options have become available.

Hypofractionation as Preferred RT Strategy

The NCCN panel now recommends that whole-breast RT be delivered by hypofractionation, a shorter treatment course that uses larger doses per fraction.

“There is no excuse for radiation oncologists not to adopt hypofractionation,” said Dr. Salerno.

In short, the guidelines for RT of invasive breast cancer after breast-conserving surgery include the following: RT to the whole breast, with or without a boost; accelerated partial breast irradiation (APBI) in select patients; and omission of RT in select patients, as detailed in an updated “Principles of Radiation Therapy” page (available online, in these guidelines, at NCCN.org).

Whole-breast RT may be delivered using a hypofractionated course of 40 to 42 Gy in 15 to 16 fractions. This is now the preferred regimen for whole-breast RT after breast-conserving surgery based on clinical trial data from a Canadian trial¹⁰ and the START-B trial.¹¹

Dr. Salerno said that results of hypofractionation are “at least equivalent to or better than” results seen with conventional fractionation in terms of local control, breast cosmesis, and toxicities, and she emphasized it is *not* to be routinely used in the postmastectomy setting or when treating regional nodes.

For APBI, the panel currently endorses the guidelines issued by the American Society for Radiation Oncology (ASTRO) for determining suitability.¹² ASTRO is currently drafting a new consensus statement.

Omission of RT altogether is acceptable in select women with lower risk for recurrence. These tend to be patients 70 years old or older with ER-positive, clinically node-negative, T1 tumors who received adjuvant endocrine therapy (category 1).

Regional Nodal Irradiation

The NCCN Guidelines for Breast Cancer include updated language regarding the role of regional nodal irradiation, Dr. Salerno indicated, and detailed the important changes per group:

- 4 or more positive lymph nodes after lumpectomy: RT to whole breast, with or without boost, and regional nodal irradiation (category 1);
- 4 or more positive lymph nodes after mastectomy:

RT to chest wall plus regional nodal irradiation (category 1);

- 1 to 3 positive lymph nodes after lumpectomy: RT to whole breast with or without boost (category 1); strongly consider regional nodal irradiation based on risk estimate;
- 1 to 3 positive lymph nodes after mastectomy: strongly consider radiation therapy to chest wall plus regional nodal irradiation;
- For regional nodal irradiation, the nodal volumes treated include the supraclavicular area, infraclavicular region, internal mammary nodes, and any part of the axillary bed considered at risk.

The recommendations largely rely on data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis¹³ and the 2 most recent trials, MA.20¹⁴ and EORTC 22922.¹⁵ In MA.20 and in EORTC 22922, after 10 years of median follow-up, regional nodal irradiation improved locoregional disease-free survival, distant disease-free survival, and breast cancer mortality, but not overall survival.

After neoadjuvant therapy, RT is recommended as per maximal stage according to clinical staging presystemic therapy or pathologic staging. For inoperable or locally advanced disease, RT should be delivered to the breast (with or without boost) or chest wall, with regional nodal irradiation.

Treatment of recurrence depends on extent of disease and prior therapies received. These recommendations have been simplified within the updated NCCN Guidelines for Breast Cancer.

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Gradishar and Salerno

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