Modification and Implementation of NCCN Guidelines™ on Breast Cancer in the Middle East and North Africa Region

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Key Words

NCCN Clinical Practice Guidelines in Oncology, NCCN Guidelines, Middle East and North Africa, breast cancer

Abstract

Published data from the Middle East and North Africa (MENA) region indicate suboptimal quality of cancer care, while the World Health Organization predicts an increase in cancer cases in developing countries. Major advances in breast cancer management mandate the development of guidelines to improve the quality and efficacy of oncology practice in the MENA region. A Breast Cancer Regional Guidelines Committee was organized and activated, comprising experts from various regional cancer institutions. The multidisciplinary team included 12 medical oncologists, 3 radiation oncologists, 2 radiologists, 2 surgeons, and 1 pathologist. The committee members agreed on adapting the current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Breast Cancer for use in the MENA region to achieve common practice standards for treating patients. The members suggested several modifications to the guidelines, especially those related to risk factor profiles. United States–based NCCN experts reviewed these recommendations before final approval. The MENA–NCCN Breast Cancer Guidelines modification process was the first initiative in the development of common practice guidelines in the region. This project may serve as a foundation for the development of evidence-based practice standards, and improve collaborative projects and initiatives. (*JNCCN* 2010;8[Suppl 3]:S8–S15)

Breast cancer is the most common malignant disease in women, with an increasing incidence worldwide, especially in developing countries such as the Middle East and North Africa (MENA) region.[1–3] However, the mortality rate has declined dramatically in developed

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countries, including the United States, Canada, Australia, and Europe. This reduction could be attributed to the efficacy of mammography in detecting early-stage breast cancer,[4,5] and to the introduction of adjuvant systemic therapy.[6]

All published clinical epidemiologic data on breast cancer in the MENA region are based on hospital-based registries. Nonetheless, most of the regional and national registries are published as an annual report in a booklet format.[3,7]

Breast cancer represents 14% to 42% of all cancers in Arab women. Age-adjusted standardized incidence rates (ASR) were reported to vary from 9.5 to 50 cases per 100,000 women per year. Median age at presentation is 48 to 52 years, with 50% of cases in women younger than 50 years compared with 25% in developed countries, and 50% of the cases are in women older than 63 years.[4,5] Therefore, women in Arab countries seem to present with breast cancer almost 10 years earlier than in the United States and Europe.

The ASR for breast cancer has increased in many countries in the region, such as Lebanon (20 in 1996, 46.7 in 1998, and 69 in 2003), Jordan (from 7.6/100,000 women in 1982 to 32.8/100,000 in 1997), Palestine (increased by 93%), and Egypt (up to 49.6). Reports from the Gulf Center for Cancer Registration (GCCR) presented data from 6 Gulf countries: Kingdom of Saudi Arabia (KSA), United Arab Emirates (UAE), Kingdom of Bahrain, Sultanate of Oman, State of Qatar, and State of Kuwait. The GCCR data showed that breast cancer was the most common cancer in the GCCR states from January 1998 to December 2005, with 8349 breast cancers registered from all GCCR states, accounting for 11.6% of all malignancies and 23.2% of all female cancers. The overall breast cancer ASR for all GCCR states was 18.2 per 100,000 population. Although Bahrain reported the highest incidence of breast cancer, it was the pioneer in establishing a National Screening Program for detecting breast cancer at a very early stage. The ASR per 100,000 women was 53.4 for Bahrain, followed by Qatar (48.2), Kuwait (46.6), UAE (22.8), Oman (17.5), and KSA (14.8;[8] Figure 1).

Although these rates are low compared with those in developed countries, they are rising and expected to reach levels similar to those in Western countries. Many factors can attribute to this rise, including improvement in health care with subsequent prolonged life expectancy, delayed age of marriage and first pregnancy, and decline in breast feeding. Recent socioeconomic changes have resulted in a sedentary modified lifestyle, such as increased prevalence of tobacco use, decreased physical activity, and unhealthy diet consisting of fatty fast food. Advanced disease is commonly seen at diagnosis, whereas ductal carcinoma in situ (DCIS) represents fewer than 5% of the cases.[3,7,8] (Figure 2). Factors contributing to late presentations include decreased awareness, lack of knowledge, and social factors such as shyness, fear of divorce stigma, and low index of

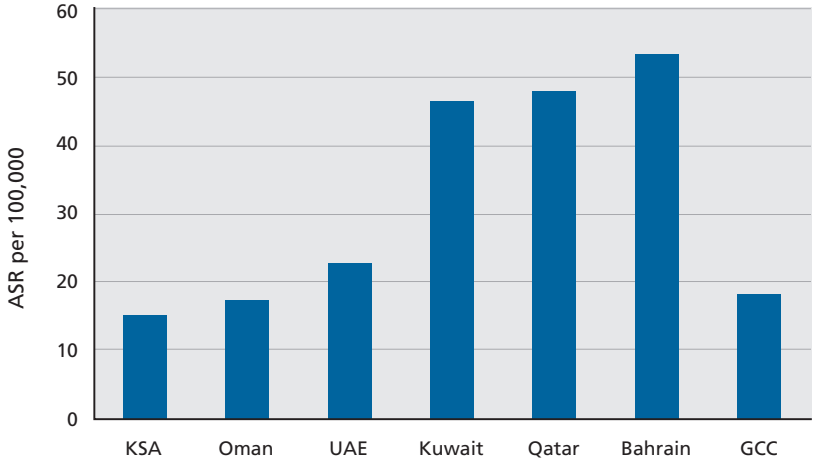


Figure 1 Age standardized incidence rate (ASR) of female breast cancer in the Gulf Cooperation Council States, 1998–2005.
Abbreviations: GCC, Gulf Cooperation Council; KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates.
From Al-Madouj AN, Al-Zahrani AS. Eight-year cancer incidence among nationals of the GCC states: 1998–2005. Gulf Center for Cancer Registration, 2005. Available at: http://www.sgh.org.sa/PDF/cancer%201998-2005.pdf. Accessed June 8, 2010.

suspicion by primary physicians.[9]

Two publications from Saudi Arabia and Lebanon reported that young age at presentation (> 35–39 years) was associated with poor prognosis[10,11] (Figure 3).

Health care standards vary among different areas within the region, and the quality of care depends on many factors, including where the patient lives and how long it takes for the patient to reach the cancer center and undergo treatment. Although a wide range of breast cancer treatment approaches are available in the MENA region, primary prevention is still rarely practiced and secondary prevention (i.e., screening and early detection) is applied sporadically in many countries that lack regular inspection strategies, quality control, and licensing for screening centers. A few national screening programs were initiated in the past 2 to 3 years in Bahrain, Egypt, KSA, and Kuwait. However, efforts should be made to study detection rates, screen-initiated testing, biopsies results, and outcomes.[10,11]

One small retrospective single-institution study in Qasseem, KSA showed that the quality of care provided to breast cancer patients did not meet international standards, possibly because of nonavailability of some resources, the absence of local guidelines, and small sample size.[12]

Radiation therapy centers in the region are scarce and mostly available in major cities, and many young women do not undergo breast-conserving surgery

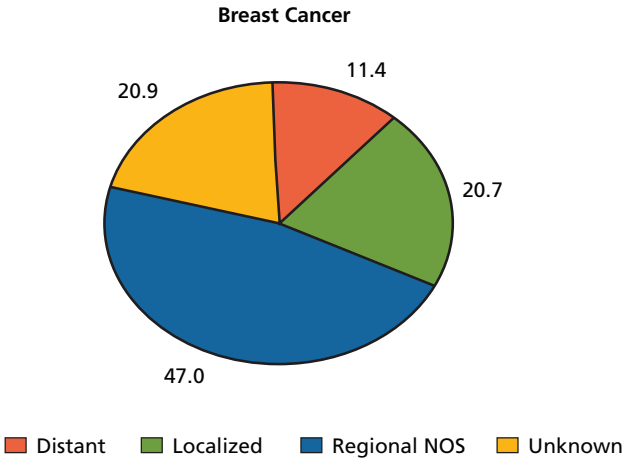


Figure 2 Stage distribution of breast cancer, 1998–2005. From Al-Madouj AN, Al-Zahrani AS. Eight-year cancer incidence among nationals of the GCC states: 1998–2005. Gulf Center for Cancer Registration, 2005. Available at: http://www.sgh.org.sa/PDF/cancer%201998-2005.pdf. Accessed June 8, 2010.

because of lack of access to radiotherapy facilities (Table 1). Furthermore, a multidisciplinary approach is applied only in major cancer centers. In general, there is a marked deficiency in supportive care systems, trained social workers, health educators, and plastic surgeons to perform breast reconstruction.

Based on international studies, adjuvant therapy includes chemotherapy, targeted therapy with trastuzumab, and hormonal therapy.[13–15] In countries with limited resources, anthracyclines and taxanes are the

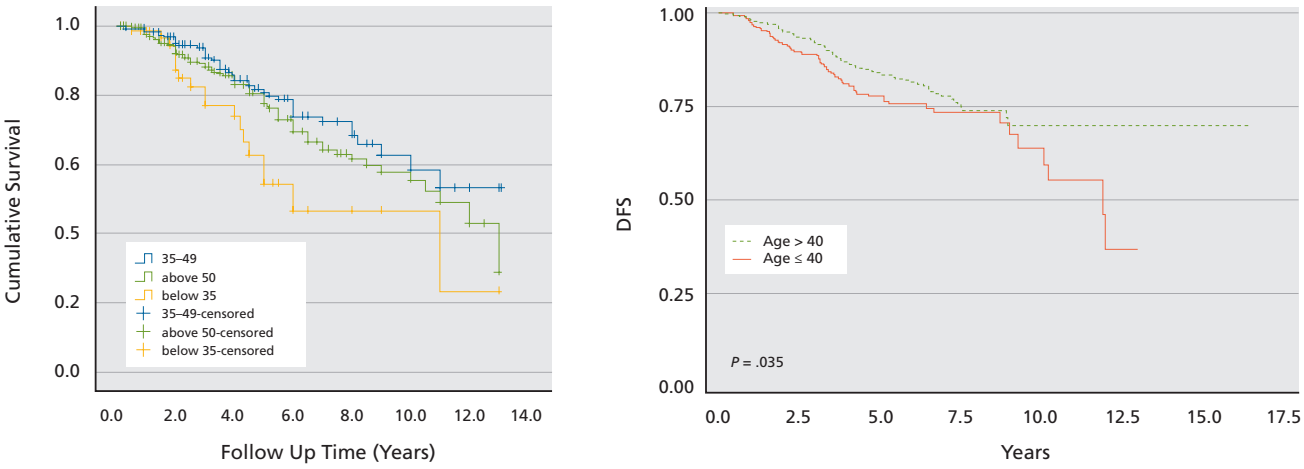


Figure 3 Relation of young age to worse prognosis in breast cancer.
Abbreviation: DFS, disease-free survival.
From El Saghir NS, Seoud M, Khalil MK, et al. Effects of young age at presentation on survival in breast cancer. BMC Cancer 2006;6:194; and Elkum N, Dermime S, Ajarim D, et al. Being 40 or younger is an independent risk factor for relapse in operable breast cancer patients: the Saudi Arabia experience. BMC Cancer 2007;7:222.

Table 1 Radiation Therapy Centers in the Arab Countries Compared With United States (Equivalent in Population Numbers)

Countries	Population	Radiation Treatment Centers	Radiation Oncologists	Radiation Technologists
Arab	301,227,000	87*	325	490
United States	298,213,000	1875	3068	5155

*Source: International Atomic Energy Agency IAEA 2007 (www.iaea.org)
Adapted and updated from El Saghir NS, Khalil MK, Eid T, et al. Trends in epidemiology and mangament of breast cancer in developing Arab countries: a literature and registry analysis. Int J Surg 2007;5:225–233.

most commonly used drugs, either in combination or sequentially, according to the recommendations of the Breast Health Global Initiative (BHGI).[16]

However, locally advanced breast cancer is treated with neoadjuvant chemotherapy, mainly an anthracycline/taxane-based regimen, to improve breast conservation rates and increase complete pathologic remission.[17,18] In HER2-positive tumors, chemotherapy with targeted trastuzumab yields higher rates of clinical and pathologic remissions.[19] Evidence shows that patients with less residual disease or who experience complete pathologic response tend to have better survival.[20] However, preoperative therapy in early-stage breast cancer requires availability of adequate radiologic and pathologic evaluation is limited in some MENA region countries.[21]

With many major advances in breast cancer therapy and the WHO expectation of an increase in cancer cases in developing countries, a pressing need exists for the MENA region to develop guidelines for breast cancer management. This explains the interest in participating in NCCN Guidelines development to improve the quality of oncology practice in the region.

Material and Methods

The global need for comprehensive and evidence-based guidelines has encouraged the NCCN administration to expand their experience to include other regions such as China, Japan, and, recently, the MENA region.

In November 2008, the MENA Breast Cancer Regional Guidelines Committee (BCRGC) was organized and activated. The members are prominent experts representing various regional cancer institutions, and included 12 medical oncologists, 3 radiation oncologists, 2 radiologists, 2 surgeons, and 1 pathologist.

The committee members reviewed the 2009 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Breast Cancer and suggested modifications suitable to the region. These modifications were discussed among the group members and with a United States–based NCCN expert to establish the final version.

Results

After a series of meetings, members of the BCRGC reached agreement on a few modifications to the guidelines based on the state of breast cancer care in the region. These suggestions, which were presented during the second NCCN–MENA conference held in Abu Dhabi from April 23 to 26, 2009, emphasized 5 major modifications:

- Diagnosis at age younger than 40 years should be considered an independent risk factor of poor prognosis.
- Staging workup for stage IIB breast cancer should include bone scan and CT of the chest and abdomen as the standard of care, not optional.
- For DCIS, lumpectomy without radiation is not considered acceptable because of risk for recurrence.
- Adjuvant radiotherapy for locoregional stages I and IIA should be given after systemic chemotherapy.
- Several clinical research plans were suggested to prioritize a database bank for breast malignancies in the MENA region.

Specific Recommended Modifications

The committee recommended several modifications to the 2009 NCCN Guidelines on Breast Cancer for use in the MENA region.

DCIS

Radiation Therapy

Recommendations: Delete lumpectomy without radiation.

Justification: Patients who undergo lumpectomy without radiation have been shown to have a high risk for relapse.[22–24]

Margin Status

Recommendations: Hospitals should have guidelines for the assessment of margins. Surgeons should ink specimen margins to enable pathologists to provide better assessment.

Justification: Most hospitals in the MENA region do not have written policies for handling of specimen and inking of margins. Inking allows evaluation of negativity and distance between tumor and margins.

Primary Status

Recommendations: Sentinel lymph node biopsy is recommended for large DCIS (> 3 cm) and high-grade and extensive in situ disease.

Justification: Large and high-grade DCIS may harbor invasive disease.

The recommendation for performing sentinel lymph node biopsy is based on the tumor size and pathologic characteristics rather than type of surgery. The type of surgery chosen (mastectomy vs. lumpectomy) may be based on tumor size but not always (e.g., may be patient choice based on risk factors).

Genetic Counseling for High-Risk Women

Recommendations: Setup for infrastructure, genetic counselors, and nurses is encouraged and should be prepared along with laws to protect women and families with positive hereditary factors from discrimination at jobs and regarding insurance, particularly health insurance policies.

Justification: These important elements for genetic counseling are not currently available in the region, but are very crucial components of a proper genetic counseling process.

Adjuvant Tamoxifen (Surveillance/Follow-up)

Recommendations: Treatment with adjuvant tamoxifen during surveillance and follow-up should be considered a category 1 recommendation.

Justification: In contrast to the findings reported by NSABP B-24, other studies have shown no benefit associated with adjuvant tamoxifen in patients with DCIS.[25,26]

Invasive Breast Cancer

Workup

Recommendations: Staging workup should be standard for stage IIA or IIB disease and not optional.

Justification: In clinical practice, physicians in the MENA region encounter many patients with metastasis and node-negative stage IIA/IIB disease.

Adjuvant Therapy: Locoregional Treatment of Clinical Stage I, IIA, or IIB Disease or T3, N1, M0

Recommendations: Recommendation should read "postchemotherapy radiation" rather than "consider postchemotherapy radiation."

Justification: Postchemotherapy radiation is indicated because of risk for recurrence.[27]

Systemic Adjuvant Treatment: Hormone Receptor–Positive/HER2-Positive Disease

Recommendations: Patient age younger than 40 years should be considered a risk factor.

Justification: Young age (< 40 years) has been shown to be an independent factor for poor prognosis.[10,11,28]

Systemic Adjuvant Treatment: Hormone Receptor–Positive/HER2-Negative Disease

Recommendations: Adjuvant chemotherapy should be recommended for patients younger than 40 years.

Furthermore, adjuvant chemotherapy is recommended for moderately/poorly differentiated tumors, and particularly in young patients with poorly differentiated tumors. Trastuzumab is given for HER-positive tumors.

Justification: Young age carries worse prognosis by itself, especially if 21-gene reverse transcription-polymerase chain reaction (RT-PCR) assay is not performed.[10,11,28]

For patients with poorly differentiated tumors, young age was added as a criterion to emphasize the need for aggressive therapy. According to 2 studies in MENA region, young age was a contributing factor for poor prognosis in patients with breast cancer.[10,11]

Referral to Adjuvant Hormonal Therapy and Chemotherapy

Recommendations: Guidelines should specify that patients should undergo adjuvant chemotherapy followed by adjuvant hormonal therapy.[29]

Justification: The recommendation becomes clearer when it states that chemotherapy should be followed by hormonal therapy. These therapies are not given concurrently because hormonal therapy decreases the effects of chemotherapy.[29]

21-Gene RT-PCR

Recommendations: When recommending 21-gene RT-PCR assay, specify "when available."

Justification: Specifying "when available" is important because this procedure is listed as a category 2B recommendation. The specimen must be shipped overseas and the process is very costly. It may be more important to have pathologists become more familiar and reliable in reporting readily available proliferation indices, such as mitotic counts and Ki67.[30]

Tumor Size Less Than 1 cm

Recommendations: Guidelines should be modified to recommend that young women with ER-positive breast cancer should always be given adjuvant tamoxifen hormonal therapy.

Justification: The committee suggested adding adjuvant hormonal therapy, specifying that young patients should always be given tamoxifen. Young age is a poor prognostic factor and a large percentage of patients in the MENA region are young (< 50 years) and very young (< 35 years).

T1a

Recommendations: The committee suggested not recommending adjuvant therapy except in the footnote.

Justification: The committee suggested adding adjuvant hormonal therapy, specifying that young patients should always be given tamoxifen. Young age is a poor prognostic factor and large percentage of patients in MENA region are young (< 50 years) and very young (< 35 years).[7]

Estrogren Receptor–Positive/HER2-Negative Disease

Recommendations: Adjuvant hormonal therapy should be given alone with tamoxifen plus leuteinizing hormone–releasing hormone (LHRA) with zoledronic acid, at least in patients with node-negative disease.

Justification: Results of the ABCSG-12 study showed 94% survival in patients treated with hormonal therapy alone.[31]

Systemic Adjuvant Treatment: Hormone Receptor–Negative/HER2-Negative Disease

Recommendations: Adjuvant chemotherapy should be recommended for patients younger than 40 years, including those with stage IIB disease. Furthermore, chemotherapy should be recommended for patients with T1b, especially young women.

Justification: Young age alone is an independent factor associated with a worse prognosis.[10,11,28] Up to 50% of patients with breast cancer in the MENA countries are younger than 50 years.

Systemic Adjuvant Treatment: Favorable Histopathologies

Recommendations: Adjuvant endocrine therapy should be given for tumors less than 1 to 2.9 cm. Tumors 1 cm or smaller should be given no adjuvant therapy, and tumors 1 cm or greater should be treated with endocrine therapy.

Justification: No evidence exists for not giving adjuvant endocrine therapy to patients with tumors 1 to 2.9 cm. Therefore, hormonal therapy is recommended for all women with hormone receptor–positive tumors.

Preoperative Chemotherapy Guideline: Workup

Recommendations: Complete staging should be performed (chest/abdominal CT, bone scan) for stage IIA/IIB disease even if laboratory tests are normal or patients are asymptomatic.

Justification: In the committee members' clinical experience, metastatic disease is discovered not commonly in these patients.

Locally Advanced Invasive Breast Cancer: Noninflammatory

Recommendations: Full staging should be performed (chest/abdominal CT, bone scan), even in the absence of symptoms or the presence of normal laboratory tests.

Justification: In the committee members' clinical experience, metastatic disease is discovered frequently in these patients.

Surveillance/Follow-Up

Recommendations: A history and physical examination should be performed every 3 months for the first 2 years, then every 4 to 6 months for 3 years, and then annually.

Justification: Patients have a high recurrence rate in the first 2 years.

Surveillance

Recommendations: The committee members suggest adding "consider checking 25-hydroxy vitamin D levels."

Justification: Insufficient and deficient vitamin D levels have been associated with poorer outcome among women with breast cancer in Canada.[32] Aromatase inhibitors can cause secondary osteopenia and osteopo-

rosis in postmenopausal women. Because of traditional dress codes, a large number of women in the MENA region do not get enough exposure to sunlight, and studies have shown that despite living in sunny countries, women may have vitamin D deficiency because of poor exposure to sunlight. Vitamin D levels should be checked and may need to be corrected.[32,33]

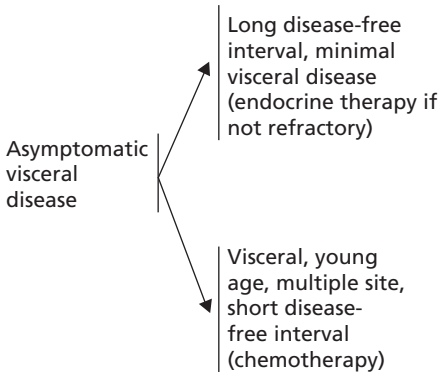
Recurrent or Initial Workup for Stage IV

Recommendations: Rebiopsy at recurrence is recommended.

Justification: This recommendation is made to confirm the diagnosis and tumor pathologic profile (estrogen receptor, progesterone receptor, and HER2 status).

Systemic Treatment of Recurrent or Stage IV Disease

Recommendations: The committee recommends administering adjuvant radiation therapy to supraclavicular lymph nodes. The committee also prefers the term *visceral disease* over *visceral crisis* and would rather classify treatment for asymptomatic visceral disease based on either presence of minimal visceral disease with a long disease-free interval or presence of visceral disease, young age, multiple disease sites, and a short disease-free interval. Therefore, the treatment nodes would appear as:



Justification: Radiation volumes for recurrence should include all regional lymphatic basins. The modified terminology was preferred because visceral disease is understood as disease involving visceral organs such as liver and lungs. The treatment classification was proposed because the presence of visceral disease with young age, multiple sites of disease, and short disease-free intervals is an indication for chemotherapy.

Phyllodes Tumor

Phyllodes Tumor Recurrence: Treatment

Recommendations: Mastectomy is recommended rather than re-excision.

Justification: Whole organ resection is the best option in case of recurrence.

Conclusions

The process of reviewing the NCCN Breast Cancer Guidelines and discussing their applicability in the MENA region was a unique and productive experience. As a result, the key opinion leaders in the breast cancer field in the MENA region were able to provide their input and clinical recommendations that might be more practical in daily use. Furthermore, the committee members highlighted the deficiencies in the standards of oncology practice and the urgent need for a common database, and provided potential research ideas. This experience is evidence of the interest in and possibility of establishing a multidisciplinary working group, comprising representatives from different countries, to improve cancer care in the MENA region.

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