The Abu Dhabi Declaration: Adapted Application of NCCN Clinical Practice Guidelines in Oncology in the Middle East and North Africa Region

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Abdul-Rahman Jazieh, Hamdy A. Azim, Joan McClure, and Mohammad Jahanzeb

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The Abu Dhabi Declaration: Adapted Application of NCCN Clinical Practice Guidelines in Oncology in the Middle East and North Africa Region

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In the Middle East and North Africa (MENA) region, cancer has many epidemiologic and clinical features that are different from those in the rest of the world. A critical need exists for regional guidelines for cancer care, including those for lymphoid malignancies. This article presents the consensus recommendations from lymphoma experts from the MENA region on the NCCN Guidelines on Non-Hodgkin's Lymphoma.

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Muhammad Aasim Yusuf, FRCP Edin; Vinay Kumar Kapoor, MS, FRCS; Refaat Refaat Kamel, FRCS; Ather Kazmi, MRCP, FRCR; Najam Uddin, FRCR; Nehal Masood, MD; and Abdulmajeed Al-Abdulkareem, MD, FRCS, FACS

Hepatocellular cancer incidence is higher in the Middle East and North Africa region than in the West, and hepatitis B and C infections are particularly important. Regional problems discussed in this article include delay in diagnosis, shortage of trained staff, and insufficient liver transplant facilities, and treatment cost is an ongoing concern.

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Omar Shamieh, MD, and Abdul-Rahman Jazieh, MD, MPH

Advancing palliative care in the developing countries is essential to improving patient care. Palliative care is in its early stage of evolution in the Middle East and North Africa region, and its practice encounters many challenges and barriers. Adaptation of guidelines must consider the situation and conditions in the targeted region.
The National Comprehensive Cancer Network (NCCN) and our 21 member institutions are dedicated to improving the care available to patients around the world. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) and the attendant scientific, evaluative process has become the model for the development and communication of clinical recommendations based on evidence review integrated with expert judgment.

The NCCN is pleased to extend our scientific, clinical collaboration to thought leaders in the Middle East and North Africa (MENA). The NCCN–MENA Guidelines Congress held in Abu Dhabi, running from April 23 to 26, 2009, brought together leading clinicians to review the NCCN Guidelines and supporting data and to discuss the applicability of the NCCN Guidelines to patients in this part of our world. As always, the clinical discussion highlighted areas for improvement and clarification in the NCCN Guidelines. As Drs. Azim, Jazieh, and Jahanzeb point out in the accompanying introduction, the work has begun and the initial thinking is published is this “Abu Dhabi Declaration.” Much work remains as experts identify issues for study in trials or through other research methods, issues that relate to possible differences in genetic makeup and its expression, differences in the availability of technology across the 16 countries, and other factors.

The NCCN thanks our colleagues in the Middle East and North Africa for their willingness to share their knowledge, expertise, and experience as we work to improve cancer care for patients whom we serve.
The Abu Dhabi Declaration: Why the Hustle?

Over the past decade, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) have emerged as a very useful tool for supporting and improving the quality of decision-making for oncologists worldwide. Considering that approximately 12 million cancer patients were registered by the WHO during 2008 and that the NCCN Web site (www.NCCN.org) attracts more than 150,000 visitors per month, one can conclude that the NCCN Guidelines program has potentially influenced the management of approximately 15% of all cancer patients worldwide. Although this example shows its far-reaching benefit, it also shows that there is plenty of room for expanding its application. A real need exists within the oncology community to have a reliable evidence-based tool to translate the rapidly accumulating scientific research into practical medical decisions that may offer a better and more consistent treatment outcome for patients.

The NCCN recently launched the NCCN–Middle East and North Africa (NCCN–MENA) Guidelines Congress in an attempt to provide versions of the original NCCN Guidelines tailored for cancer management in this region. However, one may ask whether it is really important to have a revised set of Guidelines specifically dedicated to a certain geographical region, when the original NCCN guidelines are satisfactory and comprehensive. We believe the answer is “YES” for 3 main reasons: differences in race, genetic, and environmental factors; differences in presenting features and stage; and differences in access to technology and drugs.

**Differences in Racial, Genetic, and Environmental Factors**

The NCCN Guidelines have been generated based on high-level evidence provided by large trials conducted mainly in the United States and Europe (hence predominantly enrolling a Western population) with a limited contribution from the rest of the world, including the Middle East.

Racial and genetic factors are known to play a vital role in the development of cancer. For example, in Europe, the United States, and Australia, people have a higher risk of developing skin cancer because they have fair skin, a characteristic that is uncommonly witnessed in other regions. Although guidelines for prevention and early detection of skin cancer are needed in these countries, they are of lesser importance in the Middle East.

Racial and genetic factors are not only relevant in cancer epidemiology but also can have significant influence on treatment strategies because of varying sensitivities to, and metabolism of, different drugs, resulting in a different prioritization of these approaches. For example, studies recently showed that Asian patients with advanced non–small cell lung cancer have a higher incidence of epidermal growth factor receptor (EGFR) mutations, and therefore experienced a greater benefit from treatment with EGFR inhibitors such as gefitinib and erlotinib. As a result of these findings, these agents were established as first-line therapies for these patients, before platinum-based chemotherapy, unlike in patients with non–small cell lung cancer in Europe and the United States. This raises an important question: can the results from large studies conducted mainly in Caucasian patient populations be accurately applied to the non-Caucasian majority in the rest of the world?

Of course, the pharmacogenomic preferential benefit of EGFR inhibitors reported in the above-mentioned studies does not necessarily exist in the same magnitude in other races or with other types of anticancer drugs. However, one may assume
that certain differences are likely to emerge from the integrated efforts of experts in the region. The same concept may also be applied to the differences in some environmental factors that may also play a role in the process of carcinogenesis and response to treatment. For example, in contrast to the West, where hepatocellular carcinoma (HCC) is less common and mainly secondary to alcoholic hepatitis and hepatitis B virus,7 in many Middle East countries, HCC is one of the most common cancers and usually secondary to hepatitis C virus (HCV).8 In a subgroup analysis of a pivotal sorafenib study, a greater benefit of this drug was seen among patients with HCV-associated HCC. Another example is bladder cancer, which is usually of transitional cell histology in Europe and the United States, but is commonly of squamous cell histology in several countries in the Middle East where schistosomiasis is rampant.9 These differences may limit the applicability of “West-centric” guidelines in the clinical practice of oncology in other regions of the world.

These issues presented significant challenges for our diverse team while setting the objectives of the NCCN–MENA project, because the geography of our loosely defined region stretches from the west of Morocco to the eastern part of India. Therefore, the so-called MENA cancer patients according to this geographic definition are in fact a large population of racially and environmentally heterogeneous people among whom one might elicit differences rather than similarities. Still, in the current project of NCCN–MENA, we made a thorough review of the available literature generated from cancer patients in our region, seeking any convincing evidence that may suggest a unique therapeutic feature attributable to racial, genetic, or environmental factors.

Differences in Presenting Features and Stage

In the Middle East and in other developing regions of the world, cancer is often diagnosed at a younger age and tends to be of more advanced-stage compared with cases reported among the Western populations.5 For example, in the Middle East, the median age of breast cancer diagnosis is younger 50 years (with 25% of patients < 40 years) compared with older than 60 years in the West. The lack of early detection programs in the Middle East has resulted in most breast cancer and other solid tumors presenting at stages III/IV compared with in Western countries. Taken together, the screening policy adopted in the West would certainly miss early detection of breast cancer in many young women, who represent a good proportion of cases in the region.

Differences in Access to Technology and Drugs

The Middle East is composed mostly of developing nations with restricted access to advanced technology and novel agents incorporated in current oncology practice. Cost–benefit analysis studies conducted in the West are difficult to apply to this region because of the differences in health systems among the developing and developed nations. Guidelines taking into account these limitations would help optimize the application of novel strategies to best use the limited resources available. Current NCCN Guidelines are cost-blind and do not address these issues, and therefore fall short in a resource-restricted setting.

Despite these limitations, we believe that this project will provide better guidance for oncologists in the MENA region. These regionally targeted projects are likely to stimulate oncologists in the region to not only practice more evidence-based medicine but also conduct local epidemiologic studies and clinical trials to better define the magnitude of the problem and customize solutions for their part of the world. We believe that the MENA region would benefit greatly if they invested in the area of predictive and prognostic biomarkers.10 Expensive and sophisticated
technologies can then be channelled to the subsets of patients who are really likely to benefit from them.

Finally, we would like to invite all oncologists in the MENA region to provide feedback on the applicability and usefulness of the first edition of NCCN–MENA Guidelines. It is vital to ensure that this project achieves its primary objective: facilitating the decision-making process in the clinic.

Our hope is that this serves as an NCCN pilot project, and that similar initiatives are launched in other regions of the world, such as Central and South Africa, Latin America, and beyond, which are underrepresented in clinical trials on which most NCCN Guidelines are based.

References

The Process of NCCN Guidelines™ Adaptation to the Middle East and North Africa Region

Abdul-Rahman Jazieh, MD, MPH; Hamdy A. Azim, MD; Joan McClure, MS; and Mohamad Jahanzeb, MD
Riyadh, Kingdom of Saudi Arabia; Cairo, Egypt; Fort Washington, Pennsylvania; and Memphis, Tennessee

Key Words
NCCN Clinical Practice Guidelines in Oncology, NCCN Guidelines, Middle East and North Africa region, MENA region

Abstract
The NCCN developed clinical practice guidelines for oncology that set the standard of cancer care in the United States. Because of wide acceptance of, need for, and interest in standardized treatment practices across the world, NCCN launched initiatives to help international groups adapt these guidelines. This article describes the initiative in the Middle East and North Africa (MENA) region. A group of oncology experts and key opinion leaders were assembled into 7 specific committees to develop treatment guidelines for breast cancer, lung cancer, colon cancer, prostate cancer, hepatobiliary cancer, lymphoma, and palliative care. The committees reviewed the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) to identify any modifications required for them to be more applicable to the MENA region based on available evidence and regional experience. These modifications were discussed with NCCN experts and summarized for each specific area. The development of these guidelines generated a strong interest in the region to develop more evidence-based practice and create further networking and collaboration. (JNCCN 2010;8[Suppl 3]:S5–S7)
close the gap in the region, or at least will help delineate these variations so that a systemic approach to remedy them can be established.

Readers should note that the guidelines referenced during this initiative and discussed throughout this document were the 2009 versions. The most recent versions of the NCCN Guidelines are available on the NCCN Web site at www.NCCN.org.

Methods

Committee Formations

Seven disease committees were formed for breast cancer, lung cancer, colon cancer, prostate cancer, hepatocellular carcinoma, lymphoma, and palliative care. These committees included multidisciplinary expertise from different countries in the MENA region.

Each committee comprised a chair and individual members with expertise in that area of oncology care, in addition to a United States–based NCCN expert from the applicable NCCN panel. The NCCN panel member helped explain the process and thoughts behind certain NCCN guideline recommendations and served as an external advisor with whom to discuss certain issues raised by committee members. The panel of committee chairs was led by a regional chair who coordinated the efforts of the whole group centrally. NCCN staff and leadership provided support and advice to the committees based on the NCCN experience.

A launch meeting was held at which the objectives and details of the initiative were presented to the committee members. Thereafter, the committees held meetings separately at convenient times and locations, and members corresponded frequently via e-mail. A large regional symposium was held at the conclusion of the first year activities to provide education for the oncologists in the region regarding NCCN guidelines, review the status of care in the MENA region, and finalize the recommendations in person among the committee members, experts in the United States, and NCCN staff.

Adaption Process

The committee members reviewed the 2009 versions of the NCCN guidelines specific to their area of expertise to determine what areas required modification for use in the MENA region. Recommendations to modify an item were requested to be evidence-based and derived from experience and publications relevant to the region, to avoid having substandard guidelines because of the stark variations in health care delivery among these countries.

All modifications and suggestions were listed according to the NCCN guidelines flow. The justification and references were put forth using a set format (Table 1). Committee members discussed these suggestions in group meetings and then with the NCCN experts. A final version of the recommendations were compiled and submitted as a manuscript for publication. During the process, committee members were asked to compile a list of potential research projects that they believed important to the region to help fill the gap in knowledge and address vital issues related to cancer care.

Results

Each committee developed lists of suggested modifications with justification and references. The status of care of the particular disease in the region was presented in a general meeting, and then the suggestions were discussed with the respective NCCN expert to address any ambiguous or controversial issues. A final version was then drafted and 7 manuscripts were written and submitted for publication. The committee members also identified various research projects required to address certain gaps in knowledge regarding the management of the diseases.

Discussion

The NCCN–MENA initiative was an enriching experience and a good learning opportunity that had a positive impact on involved parties and participants. This initiative was the first in the MENA region
Process of NCCN Guidelines Adaptation to MENA Region

with the goal of creating guidelines for standardizing cancer care across the countries. Although local guidelines for certain diseases are available, collaboration across countries had not previously occurred in the region.6

The credibility and experience of NCCN helped move the process forward, in addition to strong interest from practicing oncologists in the region for improving the standard of care and the realization of the need for a collaborative approach. Having NCCN experience and guidance coupled with the diverse backgrounds and a high level of expertise from the committee members was very complementary and productive. The interaction facilitated the exchange of thoughts and ideas on how to approach certain issues, and the experience was both educational and professionally stimulating.

Participants learned first-hand about the process of guidelines adaptation and gained better insight into the process of guideline development. During the process, participants realized that regional evidence is lacking for many of the recommendations, highlighting the need for future studies to address the issue. Therefore, identifying top priority research projects is a step in the right direction. The initiative generated obvious interest and enthusiasm, and the hope is that further actions will materialize in future meetings.

However, this initiative encountered challenges related to the diversity of the participants’ backgrounds. Countries in the region have diverse socioeconomic and health care infrastructures, and span a wide geographic area, presenting a logistic challenge in getting members connected for group discussion. This problem was minimized by using electronic communication more frequently and giving each committee chair the flexibility to select the timing and venue of their committee meeting. The entire group, including all the committees, convened in person only once. The diversity in health care practices, resources, and infrastructures (e.g., access to care and medications) also presented challenges to implementation of standardized guidelines.

To maintain NCCN standards, the best available evidence was adopted irrespective of cost-effectiveness or availability of resources. This approach was adopted so that standards were not lowered to meet the situation in deprived areas; the group avoided making “convenience guidelines.” To improve the standard of care, the group decided to include an ideal target and allow each country or even each institution to decide what practice is suitable for them. This initiative was not intended to develop guidelines for countries with limited resources, as had others.7 Notably, many countries in the region are not among those with limited resources.

Conclusions

This initiative is still in its infancy. However, as with any large-scale pioneer projects that face many challenges, the positive impact that it will have on the thousands of cancer patients will serve as motivation to the participants who already demonstrated enthusiasm and commitment.

References

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

Omalkhair Abulkhair, MD; Nagi Saghir, MD; Lobna Sedky, MD; Ahmed Saadedin, MD; Heba Elzhawary, MD; Neelam Siddiqui, MD; Mervat Al Saleh, MD; Fady Geara, MD; Nuha Birido, MD; Nadia Al-Eissa, MD; Sana Al Sukhun, MD; Huda Abdulkareem, MD; Menar Mohamed Ayoub, MD; Fawaz Deirawan, MD; Salah Fayaz, MD; Alaa Kandil, MD; Sami Khatib, MD; Mufid El-Mistiri, MD; Dorria Salem, MD; El Siah Hassan Sayd, MD; Mohammed Jaloudi, MD; Mohammad Jahanzeb, MD; and William I. Gradishar, MD

Benghazi, Libya; Al Ain, United Arab Emirates; Memphis, Tennessee; and Chicago, Illinois
Khartoum, Sudan; Damman, Kingdom of Saudi Arabia; Amman, Jordan; Damascus, Syria; Alexandria, Egypt; Riyadh, Kingdom of Saudi Arabia; Beirut, Lebanon; Giza, Egypt; Cairo, Egypt; Lahore, Pakistan; Kuwait, Kuwait; Khartoum, Sudan; Damman, Kingdom of Saudi Arabia; Amman, Jordan; Damascus, Syria; Alexandria, Egypt; Benghazi, Libya; Al Ain, United Arab Emirates; Memphis, Tennessee; and Chicago, Illinois

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. UNCCN 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 countries, mainly due to increased awareness and early detection. Despite these improvements, there are significant disparities in breast cancer outcomes among different regions. In the MENA region, disparities in access to care, quality of care, and survival rates exist, highlighting the need for evidence-based guidelines to improve the quality of care for breast cancer patients.

From the *Department of Oncology, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia; †Department of Internal Medicine, American University of Beirut, Beirut, Lebanon; ‡Clinical Oncology Department, Faculty of Medicine, Cairo University, Giza, Egypt; §Department of Oncology, Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia; ¶Department of Oncology, National Cancer Institute, Cairo, Egypt; ‖Department of Oncology, Shaoukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan; ¶¶Department of Surgery, Kuwait University, Kuwait, Kuwait; ‖‖Department of Radiation Oncology, American University of Beirut, Beirut, Lebanon; §§Department of Surgery, Khartoum Breast Care Center, Khartoum, Sudan; ¶¶¶Department of Radiology, King Fahad Specialist Hospital, Damman, Kingdom of Saudi Arabia; ¶¶¶¶Department of Oncology/Hematology, University of Jordan, Amman, Jordan; ¶¶¶¶¶Hematology/Oncology Unit, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia; ¶¶¶¶¶¶Department of Pathology, Cairo University, Cairo, Egypt; ¶¶¶¶¶¶¶Nuclear Medicine Center, National Cancer Institute, Damascus, Syria; ¶¶¶¶¶¶¶¶Breast Unit, Kuwait Cancer Center, Kuwait, Kuwait; ¶¶¶¶¶¶¶¶¶Department of Clinical Oncology & Nuclear Medicine, Alexandria School of Medicine, Alexandria, Egypt; ¶¶¶¶¶¶¶¶¶Medical Oncology, King Hussein Institute for Biotechnology and Cancer, Amman, Jordan; ¶¶¶¶¶¶¶¶¶¶Faculty of Medicine, Gazyounis University, Benghazi, Libya; ¶¶¶¶¶¶¶¶¶¶¶Department of Radiology, Cairo University, Cairo, Egypt; ¶¶¶¶¶¶¶¶¶¶¶Department of Oncology, Tawam Hospital, Al Ain, United Arab Emirates; ¶¶¶¶¶¶¶¶¶¶¶¶Department of Medical Oncology, Tawam Hospital, Al Ain, United Arab Emirates; ¶¶¶¶¶¶¶¶¶¶¶¶¶University of Tennessee, Memphis, Tennessee; ¶¶¶¶¶¶¶¶¶¶¶¶¶Northwestern University, Chicago, Illinois.

Drs. Abulkhair, Saghir, Sedky, Saadedin, Elzhawary, Siddiqui, Al Saleh, Gears, Birido, Al-Eissa, Al Sukhun, Abdulkareem, Ayoub, Deirawan, Fayaz, Kandil, Khatib, El-Mistiri, Salem, Sayd, Jaloudi, and Gradishar have disclosed that they have no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in the article or their competitors. Dr. Jahanzeb has disclosed that he is on the speakers’ bureau and an advisor for GlaxoSmithKline, Genentech, Inc., and sanofi-aventis.

Correspondence: Omalkhair Abulkhair, MD, Division of Adult Medical Oncology, Department of Oncology, King Abdulaziz Medical City, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia. E-mail: abulkhair@ngua.med.sa

© Journal of the National Comprehensive Cancer Network | Volume 8 Supplement 3 | July 2010
Breast Cancer

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

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 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.

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.

Two publications from Saudi Arabia and Lebanon reported that young age at presentation (>35–39 years) was associated with poor prognosis (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.

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.

Radiation therapy centers in the region are scarce and mostly available in major cities, and many young women do not undergo breast-conserving surgery 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. In countries with limited resources, anthracyclines and taxanes are the
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.

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

<table>
<thead>
<tr>
<th>Countries</th>
<th>Population</th>
<th>Radiation Treatment Centers</th>
<th>Radiation Oncologists</th>
<th>Radiation Technologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arab</td>
<td>301,227,000</td>
<td>87*</td>
<td>325</td>
<td>490</td>
</tr>
<tr>
<td>United States</td>
<td>298,213,000</td>
<td>1875</td>
<td>3068</td>
<td>5155</td>
</tr>
</tbody>
</table>

*Source: International Atomic Energy Agency IAEA 2007 (www.iaea.org)
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 HER2-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 leutetinizing 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 II A/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.

References


24. El Saghir NS, Hatoum H, Shamseddine W, Shamsedine AI. Prediction of prognosis and survival in early stage breast cancer using the lymph node ratio of involved lymph nodes to the total number of removed lymph nodes from the axilla [abstract]. Presented at 2007 Breast Cancer Symposium; September 7–8, 2007; San Francisco, California. Abstract 70.


Modification and Implementation of NCCN Guidelines™ on Non–Small Cell Lung Cancer in the Middle East and North Africa Region

Abdul-Rahman Jazieh, MD, MPH; Hanaa Bamefleh, MBchB, FRCPC; Ahmet Demirkazik, MD; Rabab Mohamed Gaafar, MD; Fady B. Geara, MD, PhD; Mansur Javaid, MD, FCCP, FRCP; Jamal Khader, MD; Kian Khodadad, MD; Walid Omar, MD; Ahmed Saadeddin, MD; Hassan Al Sabe, MD; Mohammad Behgam Shadmehr, MD; Amgad El Sherif, MD, FCCP; Najam Uddin, FRCP; Mohammad Jahanzeb, MD; and David Ettinger, MD

From the Department of Oncology, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia; Section of Medical Oncology, Ankara University, Cebeci Hastaneleri, Ankara, Turkey; Department of Medical Oncology, National Cancer Institute, Cairo, Egypt; Radiation Oncology, American University of Beirut Medical Center, Beirut, Lebanon; Pulmonary & Critical Care, Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan; Radiation Oncology, King Hussein Cancer Center, Amman, Jordan; Thoracic Oncology Section, National Institute of Tuberculosis and Lung Disease, Tehran, Iran; Nuclear Medicine Unit, National Cancer Institute, Faculty of Medicine, Cairo, Egypt; Department of Oncology, Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia; Al Bieruni Cancer Hospital, Damascus, Syria; Department of Surgery, National Institute of Tuberculosis and Lung Disease, Tehran, Iran; Cardiothoracic Surgery, Tawam Hospital, Al Ain, United Arab Emirates; Department of Radiology, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore, Pakistan; University of Tennessee, Memphis, Tennessee; and The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland.

Drs. Jazieh, Bamefleh, Demirkazik, Gaafar, Geara, Javaid, Khader, Khodadad, Omar, Saadeddin, Al Sabe, Shadmehr, El Sherif, and Uddin have disclosed that they have no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in the article or their competitors. Dr. Jahanzeb has disclosed that he is an advisory board member, member of the speakers’ bureau, or consultant for Genentech, Inc.; sanofi-aventis; and GlaxoSmithKline. Dr. Ettinger has disclosed that he is a consultant for Eli Lilly and Company; Genentech, Inc.; and Pfizer Inc.

Correspondence: Abdul Rahman Jazieh, MD, MPH, Department of Oncology (Mail Code 1777), P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia. E-mail: jazieha@ngha.med.sa

Lung cancer is the leading cancer worldwide; not only in incidence but also in cancer-related death, with approximately 1.2 million cases diagnosed worldwide and 18% of cancer deaths related to lung cancer.1,2 In the United States, lung cancer kills more people than the 3 most common cancers, namely breast, prostate, and co-
Current Status of Lung Cancer Care in the Middle East and North Africa Region

The Middle East and North Africa (MENA) region is diverse in many aspects, especially in economic background and health care infrastructure. Even within the same country, disparities may be present in health care resources and services. Therefore, no absolute universal statement can be made about health care in the region, although some common findings are descriptive of the status of lung cancer care in general.

The cancer care issues can be categorized into 5 areas that are related to the principles of oncology care:9 cancer diagnosis, proper staging, offering curative treatment whenever possible, offering palliative and supportive care when cure is not attainable, and participation in clinical research.

Confirming Diagnosis
Bronchoscopy and CT scan–guided biopsies are available only in tertiary centers in major cities, making tissue specimens difficult to obtain, although they are possible in most countries.

The laboratories in the regions are equipped for straightforward procedures, such as classic immunohistochemical staining, but generally are not ready for more sophisticated tests, such as molecular studies for customization of therapy (e.g., epidermal growth factor receptor [EGFR] mutation analysis).

Staging
Proper staging of lung cancer is essential for management and prognosis, which may require invasive procedures or imaging studies.

In the MENA region, mediastinoscopy is not used as frequently as indicated because of lack of expertise, interest, or agreement on its value. CT scanning is generally available, more so than MRI. However, PET scans are scarce because many countries do not have any machines, some have only one, and few have more than one. Therefore, PET scanning is not widely accessible.

Offering Curative Treatment
Providing curative treatment often requires a multimodality approach. However, multidisciplinary teams and tumor boards are not widely used and there is shortage of properly trained thoracic surgeons in the region.

Regarding treatment, adjuvant chemotherapy is not standard practice across the region, and many logistical challenges make concurrent chemotherapy and radiotherapy difficult to offer in some settings, including the fact that a shortage exists of adequate radiotherapy machines and expertise.

Palliative Treatment
Systemic Therapy: The MENA region has issues related to access to care, in that tertiary centers may not accept patients with metastatic cancer, instead directing resources toward curable cancers. Furthermore, access to routine chemotherapy is limited in many countries and is even more so for biologic agents. Some tertiary centers do not have new biologic and targeted therapies for economic and financial reasons.

Symptom Management: The MENA region has a clear shortage of trained palliative care physicians and support staff, in addition to lack of proper facilities. Access to pain medications such as morphine is also challenging.
Participation in Research
Like other developing countries, participation in research in the region is limited to major centers in some countries and plagued with many challenges, such as lack of research culture, infrastructure, expertise, and funding.10

The Importance of Lung Cancer Guidelines
Although the described limitations and variations may represent challenges to creating uniform guidelines, they are actually strong reasons to attempt to establish these guidelines in effort to close the oncology practice gap in the region. Identifying these limitations and variables is the first step toward addressing them.

Methodology
As a part of the initiative to adapt the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Non–Small Cell Lung Cancer11 to the MENA region, a lung cancer guidelines committee was formed.

The committee comprises various experts in thoracic oncology, including medical and clinical oncology, radiation oncology, pulmonology medicine, thoracic surgery, radiology, and pathology. The committee convened twice and corresponded frequently electronically. They reviewed the second version of the 2009 NCCN Guidelines thoroughly, identified items requiring modification for the region, and considered justification and references. Adherence to NCCN Guidelines principles and structure was required, with emphasis on the same categories of evidence and consensus as justification for adopting a modification.

A summary of the suggested modifications was then discussed thoroughly with the NCCN experts to reach an agreement on the recommendations and understand the mechanism and rationale of some of the United States guidelines recommendations. Furthermore, the committee members were asked to identify a priority list of research projects for the region. This article summarizes these recommendations.

Recommended Modifications
The committee recommended the following modifications to the second version of the 2009 NCCN Guidelines on Non–Small Cell Lung Cancer for the MENA region.

Initial Evaluation: Chemistry Profile
Recommendations: The committee suggested specifying the tests constituting the chemistry profile, including at least calcium, albumin, alkaline phosphatase, lactate dehydrogenase, renal function, and liver function tests such as total bilirubin, alanine aminotransferase, and aspartate aminotransferase.

Justifications: To prevent requesting unnecessary laboratory tests and to emphasize obtaining valuable laboratory tests that may have an impact on prognosis, may reflect the presence of distant metastases, or might impact treatment choice.

Clinical Stage IIIB, T4 (Pleural or Pericardial Effusion)
Recommendations: The term malignant should be placed before pleural or pericardial effusion for stage IIIB, T4.

Justifications: All pleural/pericardial effusions are not necessarily malignant, and only malignant fluids meet the criteria for T4, although this stage will be reclassified as stage IV in the seventh edition of the TNM staging system.12

Pretreatment Evaluation: Stage I (Peripheral T2, N0 and Central T1–2, N0) and Stage II (T1–2, N1)
Recommendations: Add endoscopic and endobronchial ultrasound procedures to the list of workup procedures.

Justifications: These techniques can be alternative procedures for evaluation of mediastinal lymph nodes, in addition to other mentioned procedures and/or imaging.13–18

Adjuvant Treatment, Stage IB, T2, N0, Margin Negative (R0)
Recommendations: For the treatment option of chemotherapy, adding “especially for tumor size T ≥ 4 cm” is recommended.

Justifications: Based on updated results of CALGB 9633, patients with tumors 4 cm or larger will benefit from chemotherapy,19 although many of these cases will be reclassified as stage II in the seventh version of the TNM staging system.

Adjuvant Treatment, Stage IIIA, T1–2, N2, Margin Negative (R0)
Recommendations: The committee suggested changing the recommendation for “Chemotherapy + mediastinal RT” to “chemotherapy +/- mediastinal RT” as a category 2B recommendation.

Justification: The committee questioned whether ad-
juvant mediastinal radiotherapy (RT) is necessary for all patients at this stage after mediastinal lymph node dissection (not sampling), and suggested that perhaps only high-risk groups should be considered for adjuvant mediastinal RT for multilevel involvement of mediastinal lymph nodes or extracapsular spread, or for inadequate lymph node dissection.

**Adjuvant RT**

**Recommendations:** Do not include recommendation of chemoradiation for N1 disease with adverse factors (category 3)

**Justification:** Studies have shown that postoperative RT is detrimental in N1 disease.²⁰

**All Stages of Positive Margins (R1, R2)**

**Recommendations:** For all stages of positive margins, the committee suggested adding “if resection is not possible” after recommendation for chemoradiation. For stage IA, committee suggested adding “if chemoradiation is not feasible” after RT, followed by chemotherapy.

**Justification:** All residual disease that is not resectable should be practically treated like unresectable stage III, with concurrent chemoradiotherapy as the preferred modality.

**Initial Treatment: Superior Sulcus Tumor T3–4, N0–1**

**Recommendations:** The committee suggested adding surgery alone as an initial modality (category 3 recommendation).

**Justification:** This NCCN recommendation is based on a phase II study that did not compare chemoradiation followed by surgery with surgery alone and does not eliminate surgery as a valid initial treatment option for resectable disease.²¹

**Initial Treatment: Chest Wall, Proximal Airway, or Mediastinum, T3–4, N0–1**

**Recommendations:** The committee suggested adding an option for unresectable tumors, with initial treatment as concurrent chemoradiotherapy + chemotherapy.

**Justification:** In some cases in this stage, the initial workup determines that the tumor is not completely resectable. In these cases, the preferred treatment could be a multimodality option of chemoradiotherapy followed by chemotherapy and preclude an unnecessary operation. According to the current NCCN algorithm all of these patients must undergo surgery.

**Initial Treatment: T1-2, N2 Nodes Positive, Negative for M1 Disease**

**Recommendations:** The committee suggested adding “especially responders” after “surgery” for patients with no progression.

**Justification:** Patients responding to treatment are more likely to benefit from surgery more than those with stable disease.

**Performance Status 3 and 4**

**Recommendations:** The committee suggests separating recommendations for performance stage (PS) 3 and 4, with erlotinib or single-agent chemotherapy (category 2B) recommended for PS 3 and palliative care for PS 4.

**Justification:** Because erlotinib has activity in previously treated patients with PS 3, it probably will have some benefits as first-line treatment. Committee members had encouraging experience with single-agent erlotinib in these patients.²²

**Therapy for Recurrence and Metastases: Cycle 1**

**Recommendations:** The committee suggested deleting “tumor response evaluation” after cycle 1, and adding a footnote after cycle 2 stating “if symptoms suggestive of disease progression, evaluation can be done after 1 cycle”.

**Justification:** No strong evidence exists for performing response evaluation after one cycle; however, this will save patients with symptoms suggesting disease progression from undergoing further treatment that will prove futile.

**Therapy for Recurrence and Metastases: 4–6 Cycles (Total)**

**Recommendations:** The committee suggested deleting “or until disease progression (category 2B),” changing the recommendation to “4 cycles for stable disease and up to 6 cycles for responders,” and adding “(category 2B) or docetaxel for all histology” after squamous histology.

**Justification:** No evidence shows benefit of therapy beyond 4 to 6 cycles of the same chemotherapy,²³ and new evidence shows maintenance with pemetrexed (for nonsquamous carcinoma) and docetaxel.²⁴,²⁵

**Performance Status 0–2 and 3–4**

**Recommendations:** The committee recommended that erlotinib be considered in patients with PS 0 through 3 after first progression. They also suggested separating PS 3 from PS 4, with the recommendation to give erlotinib to patients with PS 3 if not given previously, and
offering palliative care to patients with PS 4.  
**Justification:** The BR21 study,22 which showed a survival benefit associated with erlotinib, included some patients with PS 3, and the committee members reported similar results based on personal experience.

**Principles of Surgical Resection**  
**Recommendations:** The committee suggested adding a bullet stating that “Chemotherapy and radiation therapy are recommended to start between 4–6 weeks postoperatively, if patient recovered from surgery.”  
**Justification:** This recommendation was made to assure full recovery from surgery and avoid unnecessary delays.

**Principles of Radiation Therapy**  
**Recommendations:** The committee recommends adding “Gross tumor volume can be reduced to post-chemotherapy volume if there was reexpansion of the lung” after the first sentence of the bullet beginning “In patients who receive induction chemotherapy, attempts should be made to obtain a baseline planning CT prior to induction chemotherapy.”  
**Justification:** This modification was recommended to decrease irradiation to expanded normal lung tissue and minimize lung toxicity.  
**Recommendations:** The committee suggested modifying the radiation doses as follows:  
- Extracapsular nodal extension or microscopic positive margins: 50 Gy  
- Gross residual tumor: 66 Gy  
- Definitive RT: 70 Gy  
- Definitive RT with concurrent chemotherapy: 60–66 Gy  
**Justification:** Data do not favor high doses for postoperative RT; they do not show a dose–response relationship for RT in lung cancer except for hyperfractionation (which is uncommonly used currently). However, RT with concurrent chemotherapy using 66 Gy has shown very good median survival.

**Systemic Therapy for Advanced or Metastatic Disease**  
**First-Line Therapy:** **Recommendations:** The committee suggested changing the statement that systemic chemotherapy is not indicated in patients with PS 3 or 4 to “patients with PS 3 may benefit from single-agent erlotinib. Single-agent chemotherapy can be used in selected cases.”  
**Second-Line Therapy:** **Recommendations:** The committee recommended adding a new bullet stating “Gefinitib was shown to be noninferior to docetaxel in second-line therapy.”26

**Future Research Ideas for MENA Region**  
During the discussion among committee members, many information gaps were identified that can be addressed through future research projects.  
The following is a short list of projects the committee members identified as important:  
- Epidemiology data collection on incidence, subtypes, and treatment patterns (registry)  
- Early detection/screening studies to address what is the best recommendation  
- PET scan studies to determine best use of this technology relevant to the region  
- Radiotherapy:  
  - Stereotactic radio-surgery in lung cancer management such as inoperable disease  
  - Role of radiotherapy in N1 disease  
  - Role of prophylactic cranial irradiation in certain setting of stage III non–small cell lung cancer  
- Molecular studies, such as ERCC1, RRM1, EGFR, and Kras, in terms of their prevalence and use in clinical research and practice (pharmacogenomic studies)  
- Validate phase III data from Western countries in MENA population, in simple multisite studies to assure the capabilities to do research as a group/network

**Conclusions**  
MENA–NCCN Lung Cancer Guidelines development was a very enriching experience to participants through providing in-depth exposure to the extensive NCCN experience. Furthermore, it helped develop the first regional guidelines and encouraged networking. It also helped highlight the major gaps in practice evidence in the region, allowing the committee to propose future research ideas. Future refinement of these guidelines to incorporate emerging evidences and regional experiences is being planned.


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

Fikri Icli, MD; Hakan Akbulut, MD; Shouki Bazarbashi, MD; Mehmet Ayhan Kuzu, MD; Mohandas K. Mallath, MD; Kakil Ibrahim Rasul, FRCP Edin; Scott Strong, MD; Aamir Ali Syed, FRCS; Faruk Zorlu, MD; and Paul F. Engstrom, MD; Ankara, Turkey; Riyadh, Kingdom of Saudi Arabia; Mumbai, India; Doha, Qatar; Abu Dhabi, United Arab Emirates; Lahore, Pakistan; and Philadelphia, Pennsylvania

Key Words
NCCN Clinical Practice Guidelines in Oncology NCCN Guidelines, Middle East and North Africa, colorectal cancer, colon cancer

Abstract
Colorectal cancer is less common in the Middle East and South Asia than in western countries, with the rectum the most common primary site, unlike in the United States. A project was planned to address various local issues regarding the management of common cancers, including colorectal cancer, and to adapt the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) to the Middle East and North Africa (MENA) region. A survey of oncologists in this geographic area showed that the management practices and issues regarding colorectal cancer are similar to those presented in the NCCN Colorectal Cancer Guidelines. However, 2 major differences exist: most oncologists in the MENA region prefer chest radiograph over CT in pretreatment workup, and almost 50% of them prefer to use cetuximab in the first-line treatment of patients with the wild-type KRAS gene. The committee, comprising 9 oncologists from different countries, proposed 4 modifications to the 2009 version of the NCCN Colorectal Cancer Guidelines for use in the MENA region, relating to 1) short-course preoperative radiotherapy, 2) dose of capecitabine, 3) stereotactic radiotherapy for liver metastasis, and 4) qualification of surgeons performing colorectal surgery. The modification of NCCN Colorectal Cancer Guidelines for use in the MENA region represents a step toward creating a uniform practice in the region based on evidence and local experience. (JNCCN 2010;8[Suppl 3]:S22-S25)

Colorectal cancer is less common in the Middle East and South Asia region than in the United States (Table 1). However, it is among the 10 most common cancer types in all the countries. The age-standardized incidence rate is below 10 per 100,000 in most countries in this region, and ranges between 10 to 40 per 100,000 in a few countries such as Turkey, Qatar, Kuwait, and Israel.

In a study from Turkey, one third of patients were younger than 50 years, and the rectum was the most common site of occurrence (42.5%), followed by the sigmoid colon (23.2%). The epidemiologic features are similar in India. However, in a study from Qatar, the descending and sigmoid colon were the most common sites.

Although the management of colorectal cancer should ideally be based on evidence-based medicine, standardized practices do not exist in other parts of the world. The social, cultural, and economic differences among the countries may be responsible for this lack of standard management. The paucity of local randomized trials from the
apy as first-line treatment in patients with wild-type KRAS tumors.

Committee members met on March 8, 2009, in Istanbul to discuss the survey results and other issues, including proposals for adapting the NCCN guidelines to the MENA region. The proposals accepted by the majority were prepared for presentation at a congress in the United Arab Emirates.

Proposed Modifications

Proposal 1
Short-course preoperative radiotherapy (SCRT) may be an alternative for long-course preoperative radiotherapy (LCRT) or chemoradiotherapy in operable rectal cancer with smaller tumors (< T4).

Rationale
Preoperative SCRT was found to reduce the local recurrence in rectal cancer when compared with surgery alone. In a large randomized trial, the Dutch Colorectal Cancer Group showed a significant reduction of local recurrence risk with SCRT followed by total mesorectal excision (TME) compared with TME alone. Significant improvement was observed for rectal lesions 5 cm or smaller and those larger than 5 cm.

Another small randomized study from Bulgaria suggests that although SCRT is less effective than conventional radiotherapy in reducing local tumor recurrences in the lower third of the rectum and for advanced rectal cancer (T4 and N2), it is equally as effective in treating other occurrences. A Polish study comparing preoperative SCRT with chemoradiation showed similar survival, local control, and late toxicity for both treatments at 4 years. Another review of the 2 randomized trials on 396 patients showed that SCRT may be as effective as conventional radiotherapy/chemoradiation. A recent retrospective analysis of clinical outcome in 520 Danish patients with rectal cancer also confirmed the efficacy of SCRT in the Swedish Rectal Cancer Trial. In conclusion, the evidence favors preoperative SCRT as an alternative to conventional preoperative radiotherapy/chemoradiation in operable rectal cancer.

Proposal 2
Dose of capecitabine may be lower than 1000 mg/m².
twice daily.

**Rationale**
Many patients in this region are unable to tolerate recommended higher dosages because of severe hand–foot syndrome or diarrhea (based on personal experience of the committee). This could be related to high folate intake in the diet or issues related to food hygiene. The committee proposed a prospective trial be conducted to find the optimal dose for the patients in the region.

**Proposal 3**
Stereotactic radiation for liver metastasis could be an alternative.

**Rationale**
Resection is the standard of care for treating liver metastasis in colorectal cancer. However, more than 80% of patients have unresectable disease. Several studies have shown the efficacy of stereotactic body radiation therapy as an alternative to radiofrequency ablation in treating this condition. A phase I/II study showed that it is also safe and effective for treating grade 1 to 3 metastasis.

**Proposal 4**
Operations should be performed by surgeons experienced in colorectal surgery and TME, and the surgeries should occur at centers conducting more than 50 surgeries per year.

**Rationale**
The surgeon is an independent factor for outcome in colorectal surgery. The outcome was also related to surgical caseload and training/teaching activities. Because of the lower incidence of colorectal cancer, a dilution of cases between centers occurs in some countries. Some patients managed by general surgeons are found to lack TME for rectal cancer or adequate lymph node dissection. Although no specific

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<table>
<thead>
<tr>
<th>Questions</th>
<th>Most Relevant Answers</th>
</tr>
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<tbody>
<tr>
<td>1. Do you recommend routine chest CT before surgery in patients with resectable colorectal cancer?</td>
<td>• No: 69%</td>
</tr>
<tr>
<td>2. What is your choice for adjuvant chemotherapy of patients with T3N0M0 colon cancer (no high-risk factors)?</td>
<td>• Observation: 53 %</td>
</tr>
<tr>
<td>3. What do you prefer for adjuvant chemotherapy in patients with T3N0M0 rectal cancer?</td>
<td>• Mayo regimen: 23.5%</td>
</tr>
<tr>
<td>4. What do you prefer for adjuvant chemotherapy of patients with T1–4/N1–2/M0 rectal cancer?</td>
<td>• Mayo regimen: 57%</td>
</tr>
<tr>
<td>5. Do you recommend routine PET scan in the surveillance of patients with stage T3/4N0M0 colon cancer?</td>
<td>• FOLFOX: 72%</td>
</tr>
<tr>
<td>6. What is your choice for neoadjuvant treatment of patients with synchronous resectable liver only or lung-only metastases?</td>
<td>• No: 100%</td>
</tr>
<tr>
<td>7. What is your choice for adjuvant treatment of patients with synchronous resectable liver only or lung-only metastases after surgery?</td>
<td>• FOLFIRI or FOLFOX or CapeOX: 41%</td>
</tr>
<tr>
<td>8. Do you add bevacizumab to the active chemotherapy (FOLFIRI/FOLFOX/CapeOX) in patients with unresectable liver only or lung-only metastases?</td>
<td>• Chemotherapy + bevacizumab: 47%</td>
</tr>
<tr>
<td>9. What is your choice of first-line treatment in patients with unresectable metastatic colorectal cancer who are not candidates for any future surgical treatment?</td>
<td>• FOLFIRI or FOLFOX or CapeOX + bevacizumab: 75%</td>
</tr>
<tr>
<td>10. What is your choice of first-line treatment in patients with unresectable metastatic colorectal cancer with wild-type KRAS gene?</td>
<td>• Chemotherapy + bevacizumab: 37%</td>
</tr>
<tr>
<td>11. What is your choice of first-line treatment in patients with metastases who cannot tolerate intensive treatment?</td>
<td>• Chemotherapy + cetuximab: 47%</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, fluorouracil; CapeOX, capecitabine and oxaliplatin; FOLFIRI, leucovorin, fluorouracil, and irinotecan; FOLFOX, leucovorin, fluorouracil, and oxaliplatin; Mayo regimen, fluorouracil and leucovorin.
Colon Cancer
caseload number has been established for surgeons, the committee recommended that colorectal surgery should be performed at centers performing at least 50 operations per year.

Conclusions
This multinational project is the first in the region with the goal of establishing standard management of colorectal cancer. The recommendations are based on evidence in the literature and personal experiences that must be tested in prospective randomized studies. Continuation of this scientific cooperation between NCCN and the MENA countries may improve quality of care for patients with colorectal cancer in the region.

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

Waleed A. Hassen, MD; Farrok A. Karsan, MD; Farhat Abbas, MD; Yasar Beduk, MD; Ahmed El-Khodary, MD; Marwan Ghosn, MD, MBA; Jamal Khader, MD; Raja Xhali, MD; Danny M. Rabah, MD; Ali Shamseddine, MD; Sandy Srinivas, MD; Bethesda, Maryland; Al Ain, United Arab Emirates; Karachi, Pakistan; Ankara, Turkey; Kuwait City, Kuwait; Beirut, Lebanon; Amman, Jordan; Riyadh, Kingdom of Saudi Arabia; and Stanford, California

Key Words
NCCN Clinical Practice Guidelines in Oncology, NCCN Guidelines, Middle East and North Africa, prostate cancer

Abstract
A prostate cancer committee was established to modify the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Prostate Cancer for adaptation and implementation in the Middle East and North Africa (MENA) region. The objective was to enhance the multidisciplinary approach to the treatment of prostate cancer. The committee, comprising regional experts in the fields of urologic, medical, and radiation oncology, reviewed the 2009 version of the NCCN Guidelines on Prostate Cancer and suggested modifications based on the unique needs of the regions determined through published evidence and local expertise. The committee identified several areas in the NCCN Guidelines that they believed required modification, which are presented in this article. The treatment of prostate cancer in the MENA region has numerous challenges. The hope is that this effort to modify the NCCN Guidelines on Prostate Cancer for practical use in the MENA region will improve regional awareness and patient care. (JNCCN 2010;8[Suppl 3]:S26–S28)

Prostate cancer is a significant source of morbidity and mortality in the West, and remains the second leading cause of death from a solid malignancy in men in the United States. However, its effect on populations in the Middle East and North Africa (MENA) region is not completely known. A prostate cancer committee was established to modify the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Prostate Cancer for adaptation and implementation in the MENA region. The objective was to enhance the multidisciplinary approach to the treatment of prostate cancer. The committee, comprising regional experts in the fields of urologic, medical, and radiation oncology, reviewed the 2009 version of the NCCN Guidelines on Prostate Cancer and suggested modifications based on the unique needs of the region determined through published evidence and local expertise. The committee identified several areas in the NCCN Guidelines that they believed required modification, which are presented in this article. The treatment of prostate cancer in the MENA region has numerous challenges. The hope is that this effort to modify the NCCN Guidelines on Prostate Cancer for practical use in the MENA region will improve regional awareness and patient care.
The Region

For the purposes of this section, the MENA region refers to Afghanistan, Algeria, Armenia, Egypt, Ethiopia, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Oman, Pakistan, Qatar, Kingdom of Saudi Arabia (KSA), Somalia, Sudan, Syria, Tunis, Turkey, United Arab Emirates (UAE), and Yemen. This collection of countries is obviously extremely heterogeneous in terms of economic resources and health care infrastructure. Although generalizations are difficult, some pertinent issues and challenges are broadly applicable to this region.

Incidence

Although the exact incidence of prostate cancer in the MENA region is unknown, the reported incidence is approximately 5.8 cases per 100,000, with a mortality rate of 4.9 cases per 100,000.2 The accuracy of these data is not clear, however, because they are derived from unweighted averages from other regions. In general, prostate-specific antigen (PSA) screening is not routine, and therefore whether the lower incidence rate is secondary to the absence of screening or from a truly lower prevalence in the population is unknown. Smaller regional cancer databases, however, suggest that the true impact of this disease may be more significant than generally perceived. Young3 reported on regional cancer databases from 8 countries in the MENA region (Jordan, Egypt, Bahrain, KSA, Kuwait, Qatar, Oman, and UAE), and found that prostate cancer ranked among the top 4 malignancies in terms of frequency in 5 countries.3 Shamseddine et al.4 reported that prostate cancer represented the most frequently reported malignancy in Lebanese men.

In general it is the committee’s perception that most patients present with late-stage disease because of the lack of PSA screening. It is also important to consider that the MENA region population is approximately 750 million.5

Because 65% of the population is currently younger than 30 years, even if the incidence of prostate cancer is lower than that of the West, the scope of the problem will only become more significant over the next 20 years as the population ages and presumably has access to improved medical care.

Diagnosis and Staging

Because PSA screening is not routine in the MENA region, patients tend to present with more advanced disease. A general lack of primary care exists in the health systems of the region, which represents a challenge to timely diagnosis. Transrectal sonography is not routinely available except in regional centers, and experience with transrectal sonographic biopsy of the prostate also seems to be limited to regional centers. Similarly, experience with the pathologic diagnosis of prostate cancer (including the nuances of grading) is also limited to referral centers. Although CT and nuclear bone scans are generally available, MRI has more limited availability.

Treatment

The definitive and palliative treatment of prostate cancer has multiple regional challenges. Definitive treatment typically involves either surgery or radiotherapy, and experience in the management of this disease is generally lacking. A brief poll of urologists, for example, found that awareness of the existence of NCCN Guidelines on Prostate Cancer varied between 5% and 86%.

Adequate experience in the surgical management of prostate cancer has been shown to improve outcomes.6 A lack of surgical experience in the localized management of prostate cancer generally exists, even in referral centers, and radiation therapy has similar issues. According to the International Atomic Energy Agency (IAEA), only 93 machines are capable of delivering greater than 10 mV of energy in a region of 730 million people.7 More importantly, 70 machines are clustered in 3 countries (Turkey, Egypt, and KSA), leaving 23 machines to service the needs of 19 countries. Only 30 of 93 machines are capable of delivering CT dosimetry and planning. Furthermore, the costs of neoadjuvant hormonal therapy in combination with radiation therapy are also challenging, and experience with brachytherapy is limited.

Similar issues arise when addressing the management of advanced disease. Although the cost of hormonal ablation is prohibitive, bilateral orchietomy is a viable option and available. Access to systemic chemotherapy is limited, palliative care specialists are few, and the availability of narcotics tends to be limited.
Recommendations

Based on these challenges, the committee recommended the following modifications to the NCCN Guidelines on Prostate Cancer.

Staging Workup
Staging with CT/MRI seems restrictive for stage 1 to 2, which limits these imaging modalities to those patients with a 20% or more probability of lymph node involvement. Given that expertise in treatment is limited, a diagnosis of metastatic disease would potentially avoid needless definitive intervention. Therefore, the committee believed that a cutoff of 10% would be more appropriate.

Expected Patient Survival
Life expectancy estimates from data obtained in the developed world may not be representative of the MENA region. Morbidity and mortality from the same illness may be more severe because of genetic factors, access to health care facilities, and availability of technology, socioeconomics, and education. Barring the availability of country-specific life expectancy tables, the committee recommends a combination of factors, including performance status, comorbid conditions, disease stage, and physician judgment based on local experience.

Initial Therapy
Although data show that a certain percentage of patients with locally advanced disease (T3b–T4) may be treated with surgery, the availability of surgical expertise for treating this patient population is extremely limited. Surgery is not recommended as an option, except in the rare institutions with a high level of surgical expertise.

Primary Salvage Therapy
Because experience with cryotherapy or brachytherapy is extremely limited, the management of postradiation recurrence with either of these modalities should be restricted to a research setting.

Systemic Salvage Therapy
As stated in the NCCN guidelines, the clinical benefit of antiandrogens in hormone-refractory disease is limited. Given that the cost of these medications is prohibitive for a significant segment of the population, the committee suggests the daily use of diethylstilbestrol in low doses (1–3 mg) in combination with warfarin as an affordable second-line alternative. Diethylstilbestrol has been shown to result in PSA declines in up to 42% of patients with rising PSA.8

Principles of Radiation Therapy
Although the NCCN guidelines do not mention high-dose-rate brachytherapy in the principles of radiation therapy, the committee believes that guidelines for the use of this technology should be incorporated.

Summary
The treatment of prostate cancer in the MENA region is a challenge and numerous obstacles hinder the delivery of what would be deemed appropriate care in the West. Although the incidence of prostate cancer seems to be less than in the West, the true incidence probably is at least partially understated. Physician awareness of appropriate treatment guidelines may not be sufficient; the hope is that this initial effort in tailoring guidelines to the region will lead to improved patient care.

References
3. Young JL. Cancer incidence in the Middle East and Gulf Cooperation Council countries. Presented at the Middle East Cancer Consortium Steering Committee Meeting; January 20, 2003; Lyon, France.
Modification and Implementation of NCCN Guidelines™ on Lymphomas in the Middle East and North Africa Region

Ali Bazarbachi, MD, PhD; Hamdy A. Azim, MD, PhD; Hussain Alizadeh, MD, PhD; Mahmoud Aljurf, MD; Ibrahim Barista, MD; Naeem A. Chaudhri, MD; Zahira Fahed, MD; Omar A. Fahmy, MD; Ardeshir Ghavamzadeh, MD; Mohamed H. Khalaf, MD; Sami Khatib, MD; Aghiad Kutoubi, MD; Semra Paydas, MD; Hanadi Rafii Elayoubi, MD; Ghazi Zaaytari, MD; Hamdy M. Zawam, MD; and Andrew D. Zelenetz, MD, PhD; Beirut, Lebanon; Cairo, Egypt; Al Ain, United Arab Emirates; Riyadh, Kingdom of Saudi Arabia; Ankara, Turkey; Damascus, Syria; Tehran, Iran; Amman, Jordan; Adana, Turkey; Doha, Qatar; and New York, New York

Key Words
NCCN Clinical Practice Guidelines in Oncology, NCCN Guidelines, Middle East and North Africa, lymphoma, non-Hodgkin’s lymphoma, Hodgkin lymphoma

Abstract
In the Middle East and North Africa (MENA) region, cancer has many epidemiologic and clinical features that are different from those in the rest of the world. Additionally, the region has a relatively young population and large disparities in the availability of resources at diagnostic and treatment levels. A critical need exists for regional guidelines on cancer care, including those for lymphoid malignancies. A panel of lymphoma experts from MENA reviewed the 2009 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Non-Hodgkin’s Lymphoma and Hodgkin Lymphoma and suggested modifications for the region that were discussed with the United States NCCN Lymphoma Panels. This article presents the consensus recommendations. (JNCCN 2010;8[Suppl 3]:S29–S35)

Overview
In the Middle East and North Africa (MENA) region, cancer has many epidemiologic and clinical features that are different from those in the rest of the world. Additionally, the region has a relatively young population and large disparities in the availability of resources at diagnostic and treatment levels. A critical need exists for regional guidelines on cancer care, including those for lymphoid malignancies. A panel of lymphoma experts from MENA reviewed the 2009 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Non-Hodgkin’s Lymphoma and the 2008 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Hodgkin Lymphoma (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org) and suggested...
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malignant lymphomas represent a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment. Most non-Hodgkin lymphoma (NHL) cases are of B-cell origin; however, histologic subtypes may vary in different parts of the world.

Prognosis depends on histologic type, stage, age, and treatment. In addition, tumor environment (e.g., immune and stromal infiltration), presence of infectious agents associated with lymphomagenesis, and molecular events involved in cell proliferation, differentiation, and apoptosis are emerging as new prognostic factors that eventually may be used for targeted therapies. Hodgkin lymphoma is characterized by a very good prognosis and a significant cure rate with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)-type chemotherapy. However, targeted therapy either alone or in combination with chemotherapy has significantly improved the prognosis of NHL of B-cell origin, particularly with the use of rituximab, an anti-CD20 monoclonal antibody. Diffuse large B-cell lymphoma (DLBCL) is a distinct histologic type within B-cell NHL characterized by large tumor cells and aggressive clinical behavior. This subtype accounts for approximately 30% to 40% of adult NHL.

Regional specificities in the incidence of lymphomas have been reported with a significantly lower incidence of follicular lymphoma and chronic lymphocytic leukemia, and a significantly higher incidence of T-cell lymphomas in Asian countries compared with Europe and North America. A high incidence of Epstein-Barr virus–associated lymphomas has been reported in some Middle East countries. In addition, HTLV-1–associated ATL is endemic in some Middle East regions. Finally, management of malignant lymphomas in developing countries is variable and largely depends on the availability of diagnostic and therapeutic resources, such as immunohistochemistry and molecular techniques, PET-CT scan, and expensive targeted therapies.

Methods

The NCCN–MENA project was launched during a preparatory meeting held in Abu Dhabi, United Arab Emirates on November 9, 2008, involving NCCN members and chairpersons of the different
The current NCCN treatment algorithm for Hodgkin lymphoma is based on PET-CT findings. However, this modality is not available or accessible everywhere. A small survey of the groups’ practices showed that Gallium scan is more widely available and accessible in the MENA region. Imaging with Gallium requires several days, but there is no need to wait after the end of treatment. A baseline scan is also required.

Some studies indicate no statistical difference between the imaging methods. However, most studies indicate that PET is superior to Gallium scan in terms of sensitivity for activity and site detection, and also has a slightly higher specificity.

**Suggested Modification**
- If PET-CT is not available, Gallium scan is recommended.
- If Gallium scan is not available, a biopsy of the residual disease is recommended.
- If Gallium scan is positive, a biopsy is recommended.
- If Gallium scan is negative, the group recommends following the NCCN guidelines for negative PET-CT scan.

**Mantle Cell Lymphoma**

**Background**
Several reports show that high-dose cytarabine is an effective chemotherapeutic agent in mantle cell lymphoma. For example, the protocol involving R-DHAP (dexamethasone, cisplatin, high-dose cytarabine, rituximab) followed by autologous stem cell transplant (ASCT) for previously untreated younger patients (< 65 years) is a very affordable and rather effective regimen, with 3-year overall and event-free survival rates of 75% and 76%, respectively, based on an intent-to-treat analysis.

**Suggested Modification**
The group recommended that suggested first-line treatment regimens include a rituximab and high-dose cytarabine–containing regimen, such as DHAP, with a corresponding footnote indicating that high-dose chemotherapy and ASCT should be given after high-dose cytarabine.

**DLBCL**

**Background**
Multiple studies have shown that advances in treatment can improve the outcome of patients with DLBCL, and that the standard CHOP regimen is not sufficient as first-line chemotherapy to cure many patients. The first improvement was reported in 2 randomized studies, which showed the superiority of a dose-dense and -intense regimen, ACVBP
Supplement

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**(doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone), over CHOP.** This regimen is now widely used in several countries in Europe and the MENA region. The second improvement was the increased survival achieved with the addition of rituximab to combination chemotherapy. The results of a recent worldwide meta-analysis on the use of AZT/IFN for treating ATL indicate a significant survival advantage in acute, chronic, and smoldering-type ATL, but not in lymphoma ATL. The recently published proposal from the International Consensus Meeting recommended a strategy for treating ATL. Suggested Modification: The group recommended adding R-ACVBP as an acceptable alternative to R-CHOP.

**Burkitt’s Lymphoma**

**Background**
Excellent results are reported in young adults treated with the pediatric LMB protocol. The second improvement was the increased survival achieved with the addition of rituximab to combination chemotherapy. Furthermore, rituximab significantly improves outcome in patients with CD20-positive Burkitt’s lymphoma.

Suggested Modification
The group suggested that the LMB protocol be added as an acceptable alternative to the current NCCN Guidelines for Burkitt’s Lymphoma (CODOX-M or HyperCVAD), and that rituximab use be considered for all tumors that are CD20-positive.

**T-Cell Lymphomas**

**ATL**

**Background**: ATL is an aggressive malignancy of mature activated CD4-positive CD25-positive T cells associated with a retrovirus-designated HTLV-I. Endemic areas include Japan, the Caribbean, intertropical Africa, Brazil, Eastern Europe (Romania), and the Middle East (particularly Iran). The diversity in clinical features and prognosis of patients with this disease has led to its subclassification into 4 categories: acute, lymphoma, chronic, and smoldering types (Table 1). The chronic and smoldering subtypes are considered indolent, but eventually have poor long-term survival.

Patients with aggressive ATL (acute and lymphoma types) generally have a very poor prognosis because of multidrug resistance of malignant cells, a large tumor burden with multiorgan failure, hypercalcemia, or frequent infectious complications from a profound T-cell immunodeficiency. Numerous small phase II studies using zidovudine (AZT) and IFN-α have shown responses in patients with ATL. High doses of both agents were used: 6 to 9 million units of IFN-α in combination with daily divided AZT doses of 800 to 1000 mg/d. However, only patients with wild-type p53 and low IFN regulatory factor 4 expression seem to exhibit long-term responses to AZT/IFN therapy. The results of a recent worldwide meta-analysis on the use of AZT/IFN for treating ATL indicate a significant survival advantage in acute, chronic, and smoldering-type ATL, but not in lymphoma ATL. The recently published proposal from the International Consensus Meeting recommended a strategy for treating ATL. Suggested Modification: Diagnosis: In all patients with leukemic manifestations, ATL is usually diagnosed based on the presence of 5% or more abnormal T lymphocytes in peripheral blood according to morphology and flow cytometry. In those without leukemic manifestations, it is diagnosed based on a finding of T-cell lymphoma on biopsy of involved organs. Additionally, HTLV-1 seropositivity is mandatory for ATL diagnosis. Clonal integration of HTLV-1 provirus should be performed in most cases and is mandatory in atypical cases.

Workup: The group recommended that workup for ATL include the following:

- CBC and blood smear: lymphocytosis (absolute lymphocyte count > 4000) in acute and chronic subtypes. Typical ATL cells (“flower cells”) have markedly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm, but multiple morphologic variations can be encountered.
- Flow cytometry on peripheral blood: mature T-cell phenotype. Minimum panel: CD3, CD4, CD7, CD8, and CD25. Usually CD4-positive cells with expression of CD2, CD5, CD25, CD45RO, CD29, T-cell receptor–αβ, and HLA-DR. Most cases are CD7-negative and CD26-negative with low CD3 expression. Rare cases are CD8-positive or CD4/CD8-double positive or CD4/CD8-double negative.
- HTLV-1 serology: positive (enzyme-linked immunosorbent assay and Western blot).
- Molecular analysis: monoclonal integration of
HTLV-I provirus (Southern blot or inverted polymerase chain reaction).

- Bone marrow aspirate and biopsy: generally not required to make the diagnosis. However, bone marrow involvement is an independent poor prognostic factor.
- Radiologic imaging: CT scans of neck, thorax, abdomen, and pelvis. Skeletal survey in symptomatic patients.
- Gastrointestinal evaluation: upper gastrointestinal endoscopy (frequent gastrointestinal involvement).
- Central nervous system evaluation: CT scan, MRI, and/or lumbar puncture in all patients with acute or lymphoma subtypes or in those with neurologic manifestations.
- Biopsy of lymph nodes (excisional), skin biopsy, gastrointestinal tract biopsy, or bone marrow biopsy is required if the diagnosis is not established based on molecular assay of peripheral blood (for histology and molecular analyses of HTLV-I provirus integration), or to rule out an underlying infection (e.g., tuberculosis, histoplasmosis, toxoplasmosis).
- Chemistry: electrolyte, blood urea nitrogen, creatinine, serum calcium, and serum lactate dehydrogenase (LDH) levels.
- Stool examination for parasites.

**Treatment of Chronic/Smoldering ATL:** The group recommends treatment for all patients with chronic/smoldering ATL. Recent results from a Japanese study show poor outcome for patients treated with a “watch and wait” strategy or chemotherapy. The group recommended that treatment include the following:

- Initial therapy outside clinical trials: AZT (1 g/d orally) and IFN-α (6–10 million units per day). A recent worldwide meta-analysis showed this regimen resulted in 100% long-term survival.\(^1\)\(^4\)
- Response evaluation: complete remission is defined by normalization of lymphocytosis (if present) and LDH level (if elevated), with disappearance of all clinical manifestations (particularly skin involvement and lymphadenopathy). However, persistence of fewer than 5% flower cells on peripheral smear is allowed.
- Almost all patients with chronic or smoldering ATL should experience response to AZT/IFN. Outside clinical trials, treatment should never be interrupted in these patients. Response is usually obtained within 1 to 2 months. If no response is seen at 2 months, treatment should be discontinued. In patients who experience progression with life-threatening manifestations, treatment can be discontinued before 2 months.
- Very few patients with chronic/smoldering ATL will not experience response or will experience progression after AZT/IFN. For these patients, chemotherapy is recommended (CHOP is the most used regimen, although one randomized study showed that Japanese LSG15 [vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP)] is superior to CHOP).\(^1\)\(^7\)

---

### Table 1 Adult T-Cell Leukemia/Lymphoma Subtype According to Shimoyama Classification

<table>
<thead>
<tr>
<th></th>
<th>Healthy Carrier</th>
<th>Smoldering ATL</th>
<th>Chronic ATL</th>
<th>Acute ATL</th>
<th>ATL Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTLV-I serology</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clonal integration of provirus (blood)</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>Abnormal cells</td>
<td>&lt; 5%</td>
<td>&gt; 5%</td>
<td>&gt; 5%</td>
<td>&gt; 5%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LDH level</td>
<td>Normal</td>
<td>&lt; 1.5 N</td>
<td>&lt; 2 N</td>
<td>&gt; 2 N</td>
<td>&gt; 2 N</td>
</tr>
<tr>
<td>Skin or lung involvement</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bone marrow or spleen involvement</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bone, gastrointestinal, or central nervous system involvement</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: ATL, adult T-cell leukemia/lymphoma; HTLV-1, human T-cell lymphotropic virus type 1; LDH, lactate dehydrogenase.
**Treatment of Acute ATL:**
- Recommended initial therapy outside clinical trials: AZT (1g/d orally) and IFN-α (6–10 million units per day). This strategy is associated with an improved survival rate compared with first-line chemotherapy in worldwide meta-analysis. High doses of both agents are needed for at least 1 month. Dose reduction for hematotoxicity is allowed starting from month 2.
- Response evaluation: complete remission is defined by normalization of lymphocytosis (if present) and the LDH level (if elevated), with disappearance of all clinical manifestations and tumor sites. However, persistence of less than 5% flower cells on peripheral smear is allowed.
- Outside clinical trials, treatment should never be interrupted in patients experiencing response. Response is obtained within 1 to 2 months. If no response is achieved at 2 months, AZT/IFN should be discontinued. In patients experiencing progression with life-threatening manifestations, treatment can be discontinued before 2 months.
- Alternative first-line option and for patients who do not experience remission: inclusion in clinical trials or chemotherapy (CHOP is the most used regimen, although one randomized study showed that Japanese LSG15 [VCAP, AMP, and VECP] is superior to CHOP). Data are weak for monoclonal antibodies (anti-CD52 or -CD25).
- Young patients with an HLA–identical donor should be referred for allogeneic HSCT (myeloablative or reduced-intensity conditioning).
- Antimicrobial prophylaxis: trimethoprim-sulfamethoxazole (Bactrim) and strongyloidosis prophylaxis is recommended.
- Central nervous system prophylaxis: intrathecal chemotherapy is recommended (methotrexate, cytarabine, and corticosteroids).

**Cutaneous T-Cell Lymphomas**

**Background**
Many patients with smoldering ATL can be misdiagnosed with mycosis fungoides or Sézary syndrome if HTLV-I serology is not requested.

**Suggested modification**
- The group recommends including HTLV-I serology as part of the workup, particularly if the patient is from an endemic area.

**Conclusions**
In the MENA region, these suggested modifications should encourage the use of the NCCN guidelines for treating patients with lymphoma. At the global level, they represent an important addition to the NCCN guidelines by providing recommendations for managing patients with ATL.

**References**


Modification and Implementation of NCCN Guidelines™ on Hepatobiliary Cancers in the Middle East and North Africa Region

Muhammed Aasim Yusuf, FRCP Edin; Vinay Kumar Kapoor, MS, FRCS; Refaat Refaat Kamel, FRCS; Ather Kazmi, MRCP, FRCR; Najam Uddin, FRCR; Nehal Masood, MD; and Abdulmajeed Al-Abdulkareem, MD, FRCSC, FACS; Lahore, Pakistan; Lucknow, India; Cairo, Egypt; Karachi, Pakistan; and Riyadh, Kingdom of Saudi Arabia

Key Words
NCCN Clinical Practice Guidelines in Oncology, NCCN Guidelines, Middle East and North Africa region, MENA region, hepatobiliary cancer, cancer

Abstract
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Hepatobiliary Cancers address hepatocellular cancer, cancer of the gallbladder, extrahepatic cholangiocarcinoma, and intrahepatic cholangiocarcinoma. Hepatocellular cancer incidence is higher in the Middle East and North Africa (MENA) region than in the West, and hepatitis B and C infections are particularly important; the incidence of gallbladder cancer is among the highest in the world. Regional problems include delay in diagnosis, shortage of trained staff, and insufficient liver transplant facilities. Furthermore, costs associated with molecular and targeted therapies are an increasing concern. A committee was formed, consisting of leading specialists and decision-makers from the region, with each member being tasked to suggest modifications to the existing guidelines based on review of the literature and consultations with local colleagues. This committee met as a group, and then continued to discuss and debate the suggested modifications electronically. Several recommendations were finalized after vigorous debate. The final approved recommendations were then presented in April 2009 to the chair of the NCCN Hepatobiliary Cancers Panel for onward transmission and approval. This project represents an effort to modify and implement the NCCN Guidelines on Hepatobiliary Cancers in the MENA region, while taking into consideration local differences in patient and disease characteristics. The hope is that this will form the basis of future local, regional, and international cooperation in guideline development and research. (JNCCN 2010;8[Suppl 3]:S36–S40)

The 2009 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Hepatobiliary Cancers (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org) addresses 4 main tumor groups: hepatocellular cancer, cancer of the gallbladder, extrahepatic cholangiocarcinoma, and intrahepatic cholangiocarcinoma.

The incidence of hepatocellular cancer seems to be significantly higher in the Middle East and North Africa (MENA) region than in the West. The age-standardized incidence rate is 12.8 per 100,000 population in Egypt,8 per 100,000 in Pakistan, and 4.2 per 100,000 in Saudi Arabia,8 compared with 2.5 per 100,000 in the United States.4

The region also shares some unique regional risk factors. Hepatitis B and C infections seem to be particularly important. A predominance of hepatitis B virus surface antigen is seen in patients with hepatocellular
cancer from most Asian, African, and Latin American countries; hepatitis C predominates in Japan, Pakistan, Mongolia, and Egypt.5

Although the MENA region is not homogeneous, most countries represented in the committee have some common issues, albeit to a variable extent. These include delay in diagnosis, often from an absence of screening programs in those infected with hepatitis B or C, and a shortage of trained staff required for diagnosis and treatment, including gastroenterologists/hepatologists, radiologists, hepatobiliary surgeons, and oncologists. Furthermore, insufficient or, in some cases, nonexistent liver transplant facilities are a serious limitation to treatment for some patients. Pakistan, with a population of more than 170 million, has no liver transplant program. India has 3 centers, performing a total of 550 transplants annually. Egypt has 10 centers, with 150 to 200 transplants performed per year, whereas Saudi Arabia has 3 centers, performing 120 transplants annually.

The costs associated with diagnosis and treatment are an increasing concern in an age of molecular and targeted therapies. Sorafenib for treating hepatocellular carcinoma, for example, is too expensive to be used by most eligible patients in many countries. It is currently recommended primarily in patients with Child’s A disease, precluding its use in most patients in the MENA region. Additionally, the modest benefit in survival improvement means that both patients and physicians question the cost/benefit analysis.

Shortage of trained staff is a major problem in many countries in the region. Interventional radiologists are a rare species in many countries. Currently, only 4 centers in Pakistan offer transarterial chemoembolization, with each performing fewer than 500 procedures per year, for an estimated 15,000 new cases per year. A dearth of surgical expertise for liver resection and transplantation exists across the region.

Therefore, numerous challenges exist in the region. A large number of patients have hepatitis B and C infections, suggesting a huge tumor load in the future. Patients present at an advanced stage, with poor background liver function in up to half, thus precluding many treatment options. A culture of cooperation between different specialties is often lacking, with multidisciplinary care the exception rather than the norm. This results in squandering of research opportunities and lack of progress at the local, national, and regional levels.

**Typical Journey of a Patient With Hepatocellular Carcinoma in Pakistan**

Abdominal pain leads to investigation, and usually the discovery of hepatitis C infection. Abdominal imaging, usually with ultrasonography, leads to the finding of a mass or masses in the liver. Most patients will have access to biphasic CT scanning, usually at a referral center or in the private sector. However, up to 85% may be unsuitable for treatment based on extent of disease or poor liver function. The remainder are offered various treatments, but cost issues often limit patient acceptance, especially for sorafenib, which only 1 in 8 patients will accept at Shaukat Khanum Memorial Cancer Hospital in Lahore.

In a single-center experience in Pakistan, 2,586 patients were diagnosed with hepatocellular cancer over a 10-year period. Most presented with large, multifocal tumors (mean cross-sectional diameter, 8 cm). Background liver function, assessed according to Child-Pugh status, was poor (B to C) in 46%. Median survival after diagnosis was 10.5 months, with 1-, 3-, and 5-year survival rates of 45%, 20%, and 10%, respectively (Figure 1).

Regarding gall bladder cancer, the highest incidence rates worldwide were reported for women in Delhi, India (21.5/100,000); South Karachi, Pakistan (13.8/100,000); and Quito, Ecuador (12.9/100,000).6 Risk factors for gallbladder cancer include gallstones, particularly those associated with chronic cholecystitis; calcified (porcelain) gallbladder; gallbladder polyps; typhoid carrier; obesity; multiparity; and chronic infection with *Helicobacter bilis* and *H pylori*.6,7 Gallstone disease has been shown to start at a younger age in Northern India and Kashmir.8 Decreasing biliary tract cancer mortality worldwide reflects more widespread and earlier adoption of cholecystectomy. However, in many high-risk areas, including Pakistan and India, access to gallbladder surgery remains patchy and inadequate.9

**Methods**

After the successful development of regional NCCN guidelines for Korea and China, a committee was formulated in November 2008 to begin developing regional guidelines for the MENA region. The committee also had major representation from South Asia. The initial group consisted of the various committee chairs. Each committee chair then began identifying
and inviting leading specialists and decision-makers from the region to participate. Each member was asked to suggest modifications to the existing guidelines, based on review of the literature and after consultations with local colleagues. The committee met in Dubai in January 2009 to discuss and debate the various suggested modifications. Further modifications followed, with most discussion and changes occurring by email. All members were required to provide references from the literature for any modifications to be approved. The committee then met again, on the sidelines of the NCCN–MENA meeting in Abu Dhabi in April 2009, to finalize the presentation and recommendations. These were then presented to the chair of the NCCN Hepatobiliary Cancers Panel for onward transmission and approval.

**Recommended Modifications**

**Table of Contents**

The committee suggested adding “The NCCN believes that all cancer patients should be managed by a multidisciplinary team, and preferably in a specialist center.”

**Hepatocellular Carcinoma**

**Screening:** The committee suggested modifying footnote “b” to read “Imaging of those with elevated AFP [alpha-fetoprotein] should be with CT/MR, and not with ultrasound scan [USS]. If CT/MR is normal, then follow-up imaging will be with USS.” This recommendation was made because contrast-enhanced ultrasound scan is not widely available in the MENA region.

**Diagnosis:** The committee suggested amending “biopsy” to read “FNAC/biopsy” and adding a footnote stating that “FNAC appropriate if cytopathology expertise available.” The rationale for this recommendation is that fine-needle aspiration (FNA) may be easier and safer and requires less monitoring. Furthermore, it may be associated with fewer complications and is often less expensive than liver biopsy.

**Workup:** The committee recommended amending footnote “g” to read “assess liver reserve using combination of Child-Pugh score, estimation of residual liver volume, and assessment of portal hypertension (e.g., varices, splenomegaly, thrombocytopenia, and measurement of portal vein pressure, where available).” The committee believed that these additional modalities helped to more appropriately select patients who would be suitable for surgery, particularly resection.

The committee also suggested adding a footnote after “AFP” stating “AFP > 1000 is suggestive of microvascular invasion in tumors > 5 cm. These patients are not suitable for transplantation.”

**Surgical Assessment:** The committee suggested replacing “Child’s A, B” with “Child’s A” because they believed that this was more in agreement with the American Association for the Study of Liver Disease (AASLD) guidelines, which state that “Patients who have a single lesion can be offered surgical resection if they are noncirrhotic or have cirrhosis but still have well-preserved liver function, normal bilirubin, and hepatic vein pressure gradient < 10 mm Hg.” The committee believed that those with poorer liver function (i.e., patients with Child’s B) probably should be considered for transplantation rather than resection.

For transplant candidates, the committee suggested adding a footnote stating “Ablation techniques can be considered in selected patients waiting for a transplant, especially when the waiting time is more than 6 months.” The committee also suggested adding a footnote stating “Patients originally deemed unsuitable for transplant may be reconsidered for transplant after ablative therapies.”

**Unresectable Clinical Presentation:** The commit-
Supplement

Hepatobiliary Cancer

The committee recommended changing footnote “r,” dealing with the use of sorafenib, from “There are limited safety data available for patients with Child-Pugh class B. Use with extreme caution in patients with elevated bilirubin levels” to read “There are limited safety data available for patients with Child-Pugh class B and dosing is uncertain. Extreme caution is required and participation in clinical trials is recommended.” The committee members believed that data were insufficient to recommend anything more than this.

Gallbladder

For workup of jaundiced patients, the committee suggested changing “cholangiography” to “ERCP/PTC + biliary drainage (+ biopsy if possible) if obstruction confirmed.” The committee members believed that magnetic resonance cholangiopancreatography was less likely to be useful in jaundiced patients, because many or most would also require a biliary drainage procedure.

The committee also believed that “biliary drainage” should be removed from the primary treatment column, because this should be performed normally during the diagnostic workup.

Intrahepatic Cholangiocarcinoma

Although not disagreeing with resection as a possible treatment for intrahepatic cholangiocarcinoma, the committee believed it important to add a footnote stating that “There is no level 1 data with regard to the value of hepatic resection in this situation.”

Extrahepatic Cholangiocarcinoma

In workup, the committee suggested changing “cholangiography” to “ERCP/PTC + biliary drainage (+ biopsy if possible) if obstruction confirmed.” The committee also believed that “biliary drainage” should be removed from the primary treatment column, because this should be performed normally during the diagnostic workup.

For “Resected, negative margin (R0), negative regional nodes,” the committee recommended removing the chemotherapy option because they believed the benefit of adjuvant chemotherapy remains unproven, and the only randomized trial examining this did not show any benefit in treating cholangiocarcinoma. The committee also recommended that the chemotherapy + radiation therapy (XRT) option be removed because of conflicting data regarding adjuvant chemoradiation. No randomized trials specifically address this treatment, and most retrospective series consisted of a mix of R0 and R1 tumors. No clear evidence shows that adjuvant chemoradiation “improves” outcomes in patients with R0 cancers. The committee believed it reasonable to leave “Observe or clinical trial” as the only 2 available options.

Conclusions

This initiative represents the first effort in the MENA region to implement transnational guidelines, with content based on the NCCN guidelines but modified to take into consideration local differences in patient and disease characteristics. Every effort was made to recommend modifications based on the literature or, at the minimum, best practice in the region, and backed by expert opinion. This project could form the basis of future cooperation, not only in guideline development and modification, but also in research. It became painfully obvious to all involved in this effort that little local research data was available on which to base suggested modifications. This finding highlighted the need for regional cooperation and the development of research protocols to study these common diseases in the MENA region. Great disparity exists within the MENA region in terms of patients and resources, but many similarities are also present. The committee members hope to revisit this subject at regular intervals, and look forward to when all cancer care in this region follows treatment guidelines derived from robust local data.

Acknowledgments

The following also contributed to the process of guideline formulation and revision, as members of the NCCN–MENA Hepatobiliary Guidelines Review Committee: Khalid Omer Abdullah, King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia; Hassan Jaafar, Tawam Hospital, Al Ain, United Arab Emirates; Kakil Ibrahim Rasul, Hamad Medical Corporation, Doha, Qatar; Suayib Yalcin, Hacettepe University Institute of Oncology, Ankara, Turkey; and Abdel-Rahman El-Zayadi, Ain Shams University, Cairo, Egypt.
References


Modification and Implementation of NCCN Guidelines™ on Palliative Care in the Middle East and North Africa Region

Omar Shamieh, MD, and Abdul-Rahman Jazieh, MD, MPH, Riyadh, Kingdom of Saudi Arabia

Key Words
NCCN Clinical Practice Guidelines in Oncology, NCCN Guidelines, Middle East and North Africa, palliative care, cancer

Abstract
Palliative care is an important component of cancer treatment. Advancing palliative care in the developing countries is essential to improving patient care. The issues limiting its practice must be addressed, especially in light of the initiative to adapt the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) to the Middle East and North Africa (MENA) region. Palliative care is in its early stage of evolution in the MENA region, and its practice encounters many challenges and barriers. Adaptation of guidelines should take into consideration the situation and conditions in the targeted region to improve the standard of care to an internationally acceptable level. A group of experts in the MENA region reviewed the literature and collaborated to assess the current status of palliative care and recommend modifications to the NCCN Guidelines based on the unique needs of the region. (JNCCN 2010;8[Suppl 3]:S41–S47)

S
An initiative was launched to adapt several of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) to the Middle East and North Africa (MENA) region. Palliative care was one area of cancer treatment selected because of its high level of importance. To better understand how to adapt the NCCN Guidelines on Palliative Care in this region, the current status of palliative care had to be assessed. This article addresses the practice of palliative care in the MENA region.

Population and Religion
In our review, we evaluated 19 Arab countries of the MENA region, with 12 of these in Asia (Saudi Arabia, Kuwait, Qatar, United Arab Emirates, Bahrain, Oman, Yemen, Iraq, Palestinian Authorities, Jordan, Syria, and Lebanon) and the remainder in Northern Africa (Egypt, Sudan, Libya, Morocco, Tunisia, Algeria, and Djibouti). The total population of the MENA region exceeds 326 million (Table 1), with Arabic the official and most common language. The predominant religion is Islam, although other religions exist for the native population or expatriates. These countries have a wide heterogeneity of culture, religious practices and adherence, and social issues.

Palliative care principles are aligned and applicable to all religions and faiths. Although palliative care concepts and practice are more accepted by health care professionals, patients, and families, than in the past, families may tend to withhold, and persuade health care providers to withhold, information from patients, even at end of life. Furthermore, resistance to opioid use by individuals and providers in this region is usually a result of misconceptions and attitude, in addition to religious misinterpretation.

Economy and Health Care Finance
The economic classifications of these countries vary widely, ranging from those that are wealthy to those...
Family Model

An obvious shift is occurring from the traditional extended family model to a more nuclear, mobile, and isolated family structure. Families and individuals tend to rely more and more on the health care system and hospitals for the care of sick loved ones. This shift has resulted in overuse of health care resources, emergency visits, and in-patient beds for chronic and palliative care needs.

Cancer Epidemiology

Despite the advancement in medical technology and innovative therapeutics and pharmaceutical products, a huge increase in cancer incidence has occurred not only in the MENA region but also worldwide. Cancer ranges from the third to the fifth leading cause of death. In 2005, approximately 200,000 cancer deaths occurred in MENA countries, with approximately 60% of deaths in individuals younger with very limited resources. Household incomes, health care expenditure, and human development also vary widely. People tend to migrate from rural to urban areas, increasing the isolation of the rural areas and placing more governmental focus on large cities, resulting in an underserved rural population.

Health care systems in many countries have limited resources and low expenditures. The government may provide most cancer care, either partly or fully, to a portion of the population based on available resources and services; however, many countries may not have access to all treatment modalities. In view of this fact and other constraints, many patients are unable to access the system or afford treatment.

Private cancer care is provided on an out-of-pocket basis rather than through organized insurance, and most countries do not have a national cancer control program.

### Table 1  Cancer Mortality and Opioid Consumption in the Middle East and North Africa Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Population19</th>
<th>Mortality From Cancer (Estimated Cause of Death 2005)</th>
<th>Opioid Consumption 2007 (kg)20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>33.4 M</td>
<td>19,000</td>
<td>2</td>
</tr>
<tr>
<td>Bahrain</td>
<td>0.7 M</td>
<td>370</td>
<td>1</td>
</tr>
<tr>
<td>Djibouti</td>
<td>0.5 M</td>
<td>460</td>
<td>NA</td>
</tr>
<tr>
<td>Egypt</td>
<td>83 M</td>
<td>42,000</td>
<td>9</td>
</tr>
<tr>
<td>Iraq</td>
<td>27.5 M</td>
<td>15,000</td>
<td>NA</td>
</tr>
<tr>
<td>Jordan</td>
<td>6 M</td>
<td>3700</td>
<td>11</td>
</tr>
<tr>
<td>Kuwait</td>
<td>2.5 M</td>
<td>700</td>
<td>11</td>
</tr>
<tr>
<td>Lebanon</td>
<td>4 M</td>
<td>2600</td>
<td>4</td>
</tr>
<tr>
<td>Libya</td>
<td>6 M</td>
<td>2700</td>
<td>NA</td>
</tr>
<tr>
<td>Morocco</td>
<td>33 M</td>
<td>13,000</td>
<td>9</td>
</tr>
<tr>
<td>Oman</td>
<td>3.2 M</td>
<td>1200</td>
<td>2</td>
</tr>
<tr>
<td>Palestinian Authority</td>
<td>4 M</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Qatar</td>
<td>0.9 M</td>
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<td>1</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>27.6 M</td>
<td>12,000</td>
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<td>Sudan</td>
<td>39 M</td>
<td>22,000</td>
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</tr>
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<td>Syria</td>
<td>19 M</td>
<td>5000</td>
<td>NA</td>
</tr>
<tr>
<td>Tunisia</td>
<td>10.1 M</td>
<td>6000</td>
<td>20</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>4.4 M</td>
<td>1200</td>
<td>2</td>
</tr>
<tr>
<td>Yemen</td>
<td>22 M</td>
<td>10,000</td>
<td>NA</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>326.8 M</strong></td>
<td><strong>157,090</strong></td>
<td><strong>85</strong></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.

*Cancer mortality exceeds 200,000 accounting for all MENA countries.*
than 70 years (Table 1).\textsuperscript{5}

Cancer incidence is underreported in most of these countries, either because of the lack of cancer registries or the absence of effective data collection.

**Traditional Cancer Care Model**

The traditional cancer care model in MENA countries almost follows an older cancer care model, which is marked by delayed patient presentation as a result of late detection, poor access, and late referrals, followed by an active anticancer treatment approach at diagnosis, ending with death or cessation of anticancer therapy. Less attention is paid to pain and symptom management, and poor end-of-life care is available, if at all. Except for a few centers mentioned later, no hospice palliative care model exists in most of these countries. Even in countries in which palliative care service is available, patients tend to be referred to palliative care late in the trajectory of their illness.

**Need for Palliative Care**

The needs of patients with cancer in the MENA region does not differ greatly from those of patients in the rest of the world. Patients diagnosed with cancer have multiple domains of suffering, including physical, social, spiritual, practical, and psychological, as a result of multiple levels of interactions with the disease itself, or with relatives, care providers, health care systems, and the community.

Palliative care should start from cancer diagnosis for all patients, regardless of the type or stage, and continue through the cancer journey for both survivors and advanced cases to end-of-life care. Palliative care should be delivered simultaneously with disease-modifying treatment. The need for palliative care increases as the disease progresses, until it is the only focus of care.\textsuperscript{6}

More than 80% of cancer cases are advanced at presentation, making palliative care the only option for patients and highlighting the importance of making palliative care services available for those patients and their families.\textsuperscript{6}

Using the WHO formula\textsuperscript{6} and multiplying cancer mortality (Table 1)\textsuperscript{5} by the percentage of advanced cases provides an approximate number of patients in the MENA region needing palliative care before they die in the given year, which was 160,000 for 2005 ($200,000 \times 0.8 = 160,000$). Similarly, assuming one caregiver is needed per patient with advanced cancer, the number of caregivers can be estimated ($> 160,000$ in 2005).\textsuperscript{6}

**WHO Definition of Palliative Care**

The WHO defines palliative care\textsuperscript{7} by noting that palliative care improves quality of life of patients and families facing a life-threatening illness by preventing and relieving suffering through early identification, assessment, and treatment of pain and other physical, psychosocial, and spiritual problems. Palliative care:

- Provides relief from pain and other distressing symptoms;
- Affirms life and considers dying a normal process;
- Intends neither to hasten nor postpone death;
- Integrates the psychological and spiritual aspects of patient care;
- Offers a support system to help patients live as actively as possible until death;
- Offers a support system to help the patient’s family cope during the illness and through bereavement;
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- Will enhance quality of life and may also positively influence the course of illness; and
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes investigations needed to better understand and manage distressing clinical complications.

**Current Palliative Care Services**

Palliative care provision and development varies widely among countries. Based on a pilot study report from the International Observatory on End of Life Care, countries were divided into 4 categories based on the level of hospice and palliative care development. Countries in the first level, or category 1, have no available services for palliative care. Those in the second level, or category 2, are in the capacity-building stage, in which the need for palliative care is recognized and some awareness courses are
available. Countries in the third category, or level 3, have a local provision, with one or more palliative care programs established. Those in the fourth category, or level 4, have palliative care fully integrated into the health care system.8

None of the MENA countries approached integration. Although some cancer centers in a few countries have succeeded in integrating palliative care into their existing institutions, the program is not developed in the entire country.

An increasing number of countries are establishing a localized provision of palliative care, including Egypt, Iraq, Jordan, Morocco, Saudi Arabia, and United Arab Emirates.9 At the time of this report, Qatar, Tunisia, Sudan, and Kuwait started or are starting to implement palliative care services.

Countries that have begun implementing various palliative capacity-building activities but have no formal services available are Algeria, Bahrain, Lebanon, Oman, and Palestinian Authority.9 Djibouti, Libya, and Syria have no known palliative care activities. Few countries are privileged to have well-established centers of excellence for comprehensive cancer care, such as the Kingdom of Saudi Arabia.10

Most palliative care services in these countries deliver excellent care to a certain portion of population, but do not offer wider coverage. In addition, palliative care is still not included in the cancer control plan or any national health care policy.

Barriers to Palliative Care Provision

Many barriers exist to the availability, access, and provision of palliative care, such as those summarized in Table 2.

Opioid Availability

Pain is underreported and undertreated in most of the world.6 Morphine consumption has been used by the WHO to measure pain control and, ultimately, provision of palliative care.3 According to the International Narcotics Controlling Board report in 2007, the total estimated reported morphine consumption is 84 kg for all MENA countries.11,12

Opioid availability varies across the region. Highest consumption has been reported in Tunisia based on the absolute quantity, total population, and total reported cancer mortality.

Barriers to pain control are almost universal, and include fear of opioids, unavailability of medications, poor access to medication, lack of education, and fear of addiction.13

The amount of morphine needed can be predicted through calculating the estimated need of oral morphine for each patient who died of cancer. Assuming that each patient will require 100 mg/d of oral morphine in the last 3 months of life, an estimated 10 g of oral morphine will be needed per patient. Then, in multiplying this number by the esti-
mated number of patients who died of cancer (Table 1; 200,000), the predicted need of oral morphine required to control pain in those patients is determined to be approximately 2000 kg. This number is less than 5% of the reported consumption of less than 100 kg.

Notably, this estimation does not take into account the other needs for opioids to control pain in cancer survivors, such as non-cancer-related or postoperative pain, further illustrating the huge gap existing between the actual need and the current consumption.

One major factor contributing to opioid underuse in the MENA countries is that they are not available. However, simply making opioids available will not solve the problem; a simultaneous and effective educational program is needed for health care workers, patients, families, communities, religious workers, government, and leaders, along with sufficient manpower to develop palliative care initiatives.

Another important factor contributing to inadequate pain control is the existence of rigid and strict opioid or narcotic policies (Table 2), which are implemented as a result of fear regarding abuse and misuse. These policies must be revised and made flexible to allow sufficient supply and effective pain control, while at the same time maintaining accountability.

Years ago, WHO advocated establishing recommendations and guidelines to improve cancer pain control. The recommended strategy is summarized in the following steps:

- The country should make cancer pain relief a high priority in the form of health care policy.
- An educational program should target officials, policy makers, and regulators to increase awareness of the possibility and importance of managing cancer pain.
- An educational program should be established to train health care providers to treat cancer pain.
- Analgesics, including opioids, should be made available.

**Education**

Palliative care educational opportunities are scarce in MENA countries. Formal palliative care education is minimal. Most palliative care expertise is gained through education in countries with more advanced palliative care programs, such as North America and Europe. An increasing number of sensitization courses are occurring in the MENA countries, such as in Jordan, Egypt, and Saudi Arabia.

More formal palliative care training in the form of advanced fellowships and well-developed palliative care curricula in medical schools do exist in countries like Saudi Arabia; however, other countries have no educational provision at all.

Palliative care education is an integral part of establishing an effective palliative care program. The level of educational needs varies among specialty institutions and communities. Basic palliative care knowledge is essential to all health care providers, regardless of specialty, service, or settings. More advanced skills and expert training will be needed for services, with the highest demand in disciplines such as oncology, intensive care, and infectious diseases to ensure implementation of best palliative care practices.

A palliative care curriculum should be incorporated into undergraduate nursing and medical school education, residency training programs, and high-demanding fellowships such as oncology.

**Funding**

The field of palliative care seems to be a great opportunity for countries with limited resources to provide care for patients while developing the other components of a comprehensive cancer control program, ranging from prevention and early detection to optimal treatment. Palliative care should be delivered in a cost-effective manner and can be provided in less-served cities and communities in all countries, not just those with limited resources.

However, funding for palliative care is challenging for many reasons, including underrecognition of the importance of this field, resulting in inadequate resource allocation and government support. Existing and evolving programs in countries with limited resources must identify sources of financial support. Establishing a national policy for palliative care might allow governments to take some responsibility for funding.

Countries with a disadvantaged financial and economic situation may seek support and funding from community resources, nongovernmental entities, local philanthropist associations, or international organizations, such as the International Association for Hospice and Palliative Care.
Recommendations to Improve Palliative Care in MENA Countries

Every country should aim to integrate pain relief and palliative care into the mainstream of health care. Pain relief and palliative care should be available to all populations, although this article only focuses on those with cancer. However, palliative care can benefit all patients with advanced illness, including those with HIV, dementia, and organ failure.

Furthermore, palliative care should be available to patients everywhere, not only those in major cities or tertiary cancer centers. Access to these services should be available to peripheral cities and disadvantaged communities. Initiatives to improve palliative care should include policy development, program implementation, opioid availability, and education. Palliative care education should be available to all health care providers, medical and nursing schools, and training programs.

The most effective strategy for implementing a palliative care program is a public health initiative that incorporates all levels of the health care system, government leadership, and the community. This approach should benefit not only patients and families but also society as a whole.

NCCN Guidelines for Palliative Care and Cancer Pain Management

The successful implementation of NCCN palliative care and cancer pain management guidelines depends on acceptance of the following principles:

- Palliative care is an integral part of effective and comprehensive cancer care.
- Palliative care should be introduced as early as the time of diagnosis.
- All health care providers, health care leaders, pharmaceutical leaders, government leaders, and religious scholars dealing with patients with cancer must be aware of the importance of palliative care.
- Basic palliative care education is needed for all oncologists and cancer care providers at all levels of care, including inpatient, outpatient, and extended care facilities in both private and public sectors.
- Opioids and essential drugs must be available to manage pain and distressing symptoms.
- Cancer and palliative care should be delivered using an interdisciplinary approach; treatment programs should involve effective multidisciplinary teams to deliver the most comprehensive care.

Adapting the NCCN guidelines to the MENA region may trigger a systemic evaluation of the status and needs regarding palliative care so that the highest possible standards of care can be implemented.

References


