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

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Key Words

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Abstract

A lung cancer committee from the Middle East and North Africa (MENA) region was established to modify the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Non–Small Cell Lung Cancer to create a platform for standard care in the region. The committee comprised different experts in thoracic oncology from the region, including the disciplines of medical and clinical oncology, radiation oncology, thoracic surgery, pulmonary medicine, radiology, and pathology. The committee reviewed version 2 of the 2009 NCCN Guidelines on Non–Small Cell Lung Cancer and identified recommendations requiring modification for the region using published evidence and relevant experience. These sug-

gested modifications were discussed among the group and with a United States–based NCCN expert for approval. The recommended modifications, with justification and references, were categorized based on the NCCN Guidelines flow. This article describes these recommended modifications. The process of adapting the first NCCN-based guidelines in the region is a step toward helping to improve lung cancer care in the region and encouraging networking and collaboration. (*JNCCN* 2010;8[Suppl 3]:S16–S21)

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-

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lon. However, the lung cancer epidemic is not limited to developed countries. Developing countries are also seeing an increased lung cancer burden because of the increased prevalence of the main risk factor: tobacco use.^{3,4}

Lung cancer varies in incidence and mortality among countries, but in Western Asian countries it is ranked number 1, and was number 3 in North African countries.⁵ It is number 1 in cancer incidence in 7 of 13 Arab countries.⁶

Furthermore, available data indicate that lung cancer is on the rise in many countries and that its health toll will mirror, and even may exceed, that of Western countries if tobacco control is not properly addressed.

For example, in the Kingdom of Saudi Arabia, lung cancer is the third most common cancer in men and twelfth in women, with an age standardized rate of 6.1 per 100,000 and 1.9 per 100,000, respectively. Its incidence increased by 57% between 2001 and 2005,⁷ and was approximately 40% in Jordan around the same period. In Egypt, lung cancer is the fourth most common cancer in men and ninth in women. According to the Gharbia Cancer registry, it represents 7.4% of all male and 2.7% of female malignancies. The Egyptian National Cancer Institute data shows that the frequency of lung cancer was not different between 2001 and 2006.⁸

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.

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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 $T \geq 4$ 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 chemoradiotherapy. For stage IA, committee suggested adding “if chemoradiotherapy 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 chemoRT 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 premetrexed (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

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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 com-

mittee 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.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
2. Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest* 2003;123:21S–49S.
3. Proctor RN. Tobacco and the global lung cancer epidemic. *Nat Rev Cancer* 2001;1:82–86.
4. Cooley ME, Kaiser LR, Abraham JL, Giarelli E. The silent epidemic: tobacco and the evolution of lung cancer and its treatment. *Cancer Invest* 2001;19:739–751.
5. International Agency for Research on Cancer. The GLOBOCAN 2002 Database. Available at: <http://www-dep.iarc.fr/globocan/database.htm>. Accessed March 31, 2010.
6. Salim EI, Moore MA, Al-Lawati JA, et al. Cancer epidemiology and control in the Arab world—past, present and future. *Asian Pac J Cancer Prev* 2009;10:3–16.
7. National Cancer Registry, Saudi Arabia. Available at: <http://bportal.kfshrc.edu.sa>. Accessed March 31, 2010.
8. National Cancer Institute: Egypt. Cairo Registry, 2006. Available at: www.nci.edu.eg.
9. Jazieh AR. The principles of oncology care: back to basics. *Am J Clin Oncol* 2009;32:330–331.
10. Sumathipala A, Siribaddana S, Patel V. Under-representation of developing countries in the research literature: ethical issues arising from a survey of five leading medical journals. *BMC Med Ethics* 2004;5:E5.
11. Ettinger DS, Akerley W, Bepler G, et al. NCCN clinical practice guidelines in oncology: non-small cell lung cancer. Version 2, 2009. The most recent version is available at: www.NCCN.org. Accessed September 20, 2008.
12. Rami-Porta R, Crowley JJ, Goldstraw P. The revised TNM staging system for lung cancer. *Ann Thorac Cardiovasc Surg* 2009;15:4–9.
13. Herth F, Becker HD, Ernst A. Conventional vs endobronchial ultrasound-guided transbronchial needle aspiration: a randomized trial. *Chest* 2004;125:322–325.
14. Herth FJ, Eberhardt R, Vilmann P. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax* 2006;61:795–798.
15. Herth FJ, Ernst A, Eberhardt R. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. *Eur Respir J* 2006;28:910–914.
16. Herth FJ, Rabe KF, Gasparini S. Transbronchial and transoesophageal (ultrasound-guided) needle aspirations for the analysis of mediastinal lesions. *Eur Respir J* 2006;28:1264–1275.
17. El-Bayoumi E, Silvestri GA. Bronchoscopy for the diagnosis and staging of lung cancer. *Semin Respir Crit Care Med* 2008;29:261–270.
18. Alberts WM; American College of Chest Physicians. Diagnosis and management of lung cancer executive summary: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:1S–19S.
19. Strauss GM, Herndon JE II, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;26:5043–5051.
20. Dautzenberg B, Arriagada R, Chammard AB, et al. A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Group d'Etude et de Traitement des Cancers Bronchiques. *Cancer* 1999;86:195–196.
21. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: initial results of the Southwest Oncology Group trial 9416 (Intergroup trial 0160). *J Thorac Cardiovasc Surg* 2001;121:472–483.
22. Shepherd FA, Rodrigues Pereira J, et al. Erlotinib in previously treated non-small cell cancer. *N Engl J Med* 2005;353:123–132.
23. Socinski MA, Schell MJ, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell-lung cancer. *J Clin Oncol* 2002;20:1335–1343.
24. Ciuleanu T, Brodowicz T, Belani C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care: a randomised, double-blind, phase III study. *Lancet* 2009;374:1432–1440.
25. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:591–598.
26. Maruyama R, Nishiwaki Y, Tamura T, et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol* 2008;26:4244–4252.