Abstract
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) are evidence- and consensus-based clinical practice guidelines addressing malignancies that affect more than 97% of all patients with cancer in the United States. The NCCN Guidelines are used extensively in the United States and globally. Use of the guidelines outside the United States has driven the need to adapt the guidelines based on local, regional, or national resources. The NCCN Guidelines Panels created, vetted, and continually update the NCCN Guidelines based on published scientific data on cancer detection, diagnosis, and treatment efficacy. The guidelines are developed within the context of commonly available resources, methods of payment, societal and cultural expectations, and governmental regulations as they exist in the United States. Although many of the cancer management recommendations contained in the NCCN Guidelines apply broadly from a global perspective, not all do. Disparities in availability and access to health care exist among countries, within countries, and among different social groups in the same country, especially regarding resources for cancer prevention, early detection, and treatment. In addition, different drug approval and payment processes result in regional variation in availability of and access to cancer treatment, especially highly expensive agents and radiation therapy. Differences in cancer risk, predictive biomarker expression, and pharmacogenetics exist across ethnic and racial groups, and therefore across geographic locations. Cultural and societal expectations and requirements may also require modification of NCCN Guidelines for use outside the United States. This article describes the adaptation process, using the recent Latin American adaptation of the 2013 NCCN Guidelines for Colorectal Cancer as an example. (J Natl Compr Canc Netw 2014;12:643–648)

NCCN has developed a comprehensive set of clinical practice guidelines across the continuum of cancer care to assist health care professionals and patients in making clinical decisions. The current set of NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) cover the malignancies that affect more than 97% of all patients with cancer in the United States and a variety of supportive care issues. The NCCN Guidelines are widely recognized as the standard for clinical policy in oncology in the United States and are used in the academic and community settings. The NCCN Guidelines are available in multiple formats and derivatives, and are used at the point of care for decision-making, in making payment decisions by third-party payers, as standards for quality of care assessment, and as educational tools.

The NCCN Guidelines are developed by multidisciplinary panels of disease experts and patient advocates from the 25 NCCN Member Institutions. The panels use an evidence-based consensus process of guideline development, wherein recommendations are based on high-level evidence when available, and on expert consensus when high-level evidence does not exist. Currently, 47 NCCN Guidelines Panels are established, comprising more than 950 expert clinicians/investigators from NCCN Member Institutions and patient advocates who are responsible for developing the guidelines and assuring that they are current and represent state-of-the-art cancer care.
The complete library of the NCCN Guidelines is available free of charge on the NCCN Web site (NCCN.org), and many guidelines are also available through print publication in JNCCN—Journal of the National Comprehensive Cancer Network. More than 4 million copies of the NCCN Guidelines are downloaded each year by more than 500,000 registered users of the NCCN Web site. Approximately 36% of the NCCN Guidelines downloads are by users who report that they live outside the United States.

The process for updating the NCCN Guidelines begins with the identification of new scientific evidence, which is then evaluated by the appropriate NCCN Guidelines Panel. The NCCN Guidelines are reviewed annually by panel members and other experts at each of the 25 member institutions to identify potential changes for discussion at the panel meeting. Submissions from entities or individuals outside NCCN are also accepted for review by the appropriate guidelines panel. The panels consider potential modifications to the NCCN Guidelines through a discussion of the quality, consistency, and quantity of the evidence, and a formal vote is taken on all recommended changes. A category of evidence is assigned to each recommendation, which evaluates the level of evidence supporting the recommendation and the extent of agreement among panel members (available at NCCN.org and in the NCCN Guidelines for Prostate Cancer, in this issue). After the modifications are identified, the NCCN Guidelines are changed to reflect those decisions, and the algorithms and a manuscript describing the rationale for the recommendations are published on NCCN.org.

A formal conflict of interest policy and procedures are in place to minimize the potential for intentional or unintentional bias in the NCCN Guideline development and modification process. Funding for the NCCN Guidelines development process comes exclusively from NCCN Member Institution dues. The conflict of interest policy requires that all panel members disclose their financial conflicts of interest verbally at the panel meetings and in written documents that are publically available on NCCN.org. Panel members with meaningful financial conflicts of interest are excluded from participating in guideline development. Potential panel members with substantial financial conflicts of interest are excluded from participating in any NCCN Guidelines Panel.

International Adaptations of the NCCN Guidelines

The relevance of health care guidelines is defined partly by the degree to which they can realistically be applied in the care delivery setting for which they are intended. Globally, health care expenditure (public and private) varies by country from less than 2% to more than 18% of national gross domestic product (GDP). Considering population and national economic differences, resource disparities are more dramatic, wherein annual health expenditure per capita varies by less than $20 to more than $8000 per person-year, representing a more than 400-fold differential.2 Currently, most patients with cancer globally live in middle-income countries that spend 5.7% of GDP on health care (4.3% of GDP in lower-middle income countries; 6.1% of GDP in upper-middle income countries). Although upper-middle income countries have the greatest potential for improved cancer outcomes, these same countries in 2011 spent only $418 per capita on health, compared with $8600 per person in the United States.3 These dramatic differences provide clear evidence that resource allocation is an important question for improving cancer care globally, especially in relation to the use of expensive therapies that may achieve marginal improvements in outcome for a limited number of individuals within a target population.

In addition to health economic differences, countries vary in relation to health care delivery models and infrastructure, methods of payment, public versus private insurance coverage, and governmental regulation.3 Different drug approval and payment processes result in regional variation in availability of and access to cancer treatment, especially highly expensive agents and radiation therapy. Disparities in availability and access to health care may also exist within a given country or among different social groups. Differences in cancer risk, predictive biomarker expression, and pharmacogenetics exist across ethnic and racial groups, and therefore across geographic locations. Cultural and societal expectations and requirements may also require modification of the NCCN Guidelines for use outside of the United States in global regions, such as Latin America.3

Interest in adapting the NCCN Guidelines for international use arose more than a decade ago, and international adaptations of the NCCN Guidelines have subsequently been developed for use in China, Japan,
Korea, Asia, Latin America, the Middle East, North Africa, Turkey, and Russia. The NCCN Guidelines are produced in the English language, which could limit use of the documents in many parts of the non–English-speaking world. Adaptations have been translated into multiple languages, including Chinese, Japanese, Spanish, Portuguese, Turkish, Russian, and Korean. Foreign editions, regional adaptations, and consensus statements of the NCCN Guidelines are derivatives that allow for consideration of metabolic differences in populations, local accessibility, cultural milieu, professional expertise, and regulatory status of health care technologies used in cancer care in the specified region. Regional experts develop and update local editions of the guidelines in collaboration with NCCN Guidelines Panel representatives. The modified guidelines are subsequently published and distributed locally to help clinicians determine appropriate and effective cancer care. Currently, 70 ex-United States editions, regional adaptations, consensus statements, and translations of the NCCN Guidelines are available on NCCN.org.

International Adaptation Process

Although many of the recommendations contained in the NCCN Guidelines apply broadly from a global perspective, not all do. For this reason, NCCN has defined a process through which regional guideline adaptations are produced, the core work being performed at an in-region scientific symposium focused on specific diseases for which an NCCN Guideline adaptation is required. Within the participating countries or regions, disease-specific experts and opinion leaders are identified to review and participate in the adaptation of the guidelines. Representatives include the major modalities of medical oncology, surgery, and radiation oncology at a minimum. Individuals are selected who are sufficiently influential that they can speak for the general oncology community in their own countries, and participate actively in implementing the NCCN Guidelines in their own regions.

The NCCN Guidelines for adaptation are circulated among the group of regional experts for review and comment in advance of the adaptation meeting. The regional experts then meet either in-person or by teleconference to discuss their preliminary review and make recommendations regarding the necessary steps for guideline adaptation. At a combined meeting of the regional experts and NCCN representatives, panel representatives present a summary of the relevant NCCN Guidelines, and regional experts present their perspectives on the NCCN Guideline in the context of their region. After an open exchange of perspectives and recommendations, the NCCN panel representatives and regional experts met to discuss potential regional adaptations of the guidelines. These proposals are reviewed by the group, and the NCCN panel representatives participate in the review and determination of whether the proposed adaptations are appropriate. The experience to date has been that the regional experts are highly knowledgeable about specific disease, scientific evidence, and content of the NCCN Guidelines. Typically, requested adaptations are reasonable and appropriate and are approved by the NCCN Panel representatives.

NCCN and regional staff then make the necessary changes to the NCCN Guidelines to generate the adaptation, and the adapted NCCN Guidelines are translated into the appropriate local languages. The translation is verified by NCCN through scientific translators and then published online exclusively at NCCN.org. Print copies of the NCCN Guidelines adaptations are distributed locally by the regional group supporting the adaptation and by other interested parties with NCCN’s permission.

Adaptation of the NCCN Guideline for Colorectal Cancer for Use in Latin America

To serve as an illustration of this concept, an adaptation of the NCCN Guidelines for Colorectal Cancer was recently developed for use in Latin America. In March 2013, a group of approximately 20 experts from Latin America met with the Chair and Vice Chair of the NCCN Colorectal Cancer Panel in Hollywood, Florida (Table 1). Before the meeting, the NCCN Guidelines for Colorectal Cancer were distributed via e-mail to all participating Latin American clinicians for review and consideration of effective application in their region. Following the process previously described for the development of an adaption of the NCCN Guidelines, questions regarding the guidelines and suggestions for modifications where sent to the NCCN Guidelines Panel representatives for deliberation. While in Florida, the NCCN Guidelines Panel representatives re-
viewed and answered the questions posed by the Latin American clinicians regarding the guidelines, their effective clinical application and experience, and the potential need for modification/adaptation of the NCCN Guidelines for use in Latin America.

Several adaptations in the NCCN Guidelines were generated in the process of developing the adapted Latin American Edition of the NCCN Colorectal Cancer Guidelines. For example, guideline algorithm COL-3 of the NCCN Guidelines for Colorectal Cancer contains a footnote (footnote “k”) relating to the assessment of microsatellite instability in assessing prognosis and sensitivity to 5-fluorouracil chemotherapy in patients younger than 50 years or with stage II disease (Figure 1). However, testing for microsatellite instability is not available in all parts of Latin America, and therefore footnote k in the Latin American adaptation has additional language that reads, “Las pruebas de inestabilidad de microsatélites (IMS) para genes de reparación de emparejamiento erróneo (MMR, por sus siglas en inglés) posiblemente no estén disponibles en algunos entornos clínicos en Latinoamérica. Si están disponibles, se aconseja realizar las pruebas de IMS,” which translates to “MSI testing for mismatch repair (MMR) genes may not be available in some clinical settings in Latin America. If available, MSI testing should be done” (Figure 2). This is a typical example of an adaptation that is required because of limited resources and rather than disagreement relating to the interpretation of scientific results. As an example of the latter circumstance, further discussion was undertaken regarding footnote “p” of that same guideline algorithm (COL-3, Figures 1 and 2), which recommends the consideration of radiotherapy for T4 lesions with fixation to surrounding structures. The rationale for this recommendation was discussed, because limited scientific data are available supporting this recommendation, and the decision was ultimately made to not modify that portion of the NCCN Guideline.

Once all the modifications were agreed upon, the adapted NCCN Guidelines were translated into Spanish and Portuguese and published on NCCN.org. Support for the translation and distribution of the Latin American adaptation was provided by Bayer Healthcare Pharmaceuticals. Bayer also supported the travel and lodging of the Latin American clinicians while in Florida. Bayer Healthcare Pharmaceuticals did not participate in the adaptation process nor have any input into the adaptation process. Both the NCCN Guidelines for Colorectal Cancer and the Latin American adaptation are available free of charge on NCCN.org.
International Adaptations of NCCN Guidelines

PATHOLOGIC STAGE

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<tr>
<th>PATHOLOGIC STAGE</th>
<th>ADJUVANT THERAPY</th>
<th>SURVEILLANCE</th>
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<tbody>
<tr>
<td>Tis; T1; N0; M0</td>
<td>None</td>
<td>Colonoscopy at 1 y</td>
</tr>
<tr>
<td>T2, N0; M0</td>
<td>None</td>
<td>If advanced adenoma, repeat in 1 y</td>
</tr>
<tr>
<td>T3, N0; M0L</td>
<td>Clinical trial</td>
<td>If no advanced adenoma, repeat in 3 y, then every 5 y</td>
</tr>
<tr>
<td>(no high-risk features)</td>
<td>Observation</td>
<td>If no advanced adenoma, repeat in 3 y, then every 5 y</td>
</tr>
<tr>
<td>or Consider capcitabine or 5-FU/leucovorin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3, N0; M0 at high risk for systemic recurrence or T4, N0; M0</td>
<td>Capcitabine or 5-FU/leucovorin or FOLFOX or CapeOx or clinical trial</td>
<td>Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo</td>
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Node-positive disease, see COL-4

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<tr>
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<td>If no advanced adenoma, repeat in 3 y, then every 5 y</td>
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Colonoscopy at 1 y

- If advanced adenoma, repeat in 1 y
- If no advanced adenoma, repeat in 3 y, then every 5 y

Discussion

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Future Directions

Multiple challenges exist to the use of clinical practice guidelines internationally given the variability in levels of resources; cultural and societal expectations; training and availability of health care professionals; regulatory variations; and technology. The availability of decision-assistance tools, such as clinical practice guidelines, is crucial to the optimization of cancer treatment, and will vary depending on the setting. For instance, the availability of microcomputers with Internet access may be reduced in countries with limited resources, but cell phones are probably readily available to health care providers. Therefore, flexibility of platform for presenting the information or aid is likely to be very important across different resource settings. To begin to address this issue, NCCN made the complete library of the NCCN Guidelines, including derivatives such as international translations and adaptations, available through the Virtual Library of NCCN Guidelines formatted for iPad and Android tablet computers in 2012, and a new app for smart phones was launched at the end of 2013.

Resource-stratified clinical practice guidelines, such as those developed by the Breast Health Global Initiative, may be powerful tools for prioritizing care in low- and middle-income settings. These same resource-stratified guidelines may also serve as a roadmap to improve and expand medical care in a balanced, symmetric fashion.

The rapid expansion of genetic medicine, including pharmacogenetics, will also likely identify regional differences in patient populations that may be important in treatment selection and delivery. This will further drive the demand for and development of regional adaptations of clinical practice guidelines.

Summary

The NCCN Guidelines are widely used in the United States to define the standard of care in oncology. The successful collaborative adaptation of these guidelines for international use is a roadmap to improve and expand medical care in a balanced, symmetric fashion.
guidelines to multiple practice settings around the world allows these NCCN Guidelines to maintain relevance globally, and to help provide effective, high-quality, and efficient cancer care so that patients may live better lives. Further refinements of the NCCN Guidelines and their adaptations will continue to make them increasingly relevant to the heterogeneous practice settings around the world.

References


