Alexandria Journal of Medicine (2011) 47, 11–14

Alexandria University Faculty of Medicine

Alexandria Journal of Medicine

www.sciencedirect.com

REVIEW ARTICLE

Development of cancer treatment guidelines

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Received 3 December 2010; accepted 5 January 2011
Available online 26 May 2011

KEYWORDS

Cancer;
Therapy;
Guidelines

Contents

The use of guidelines in medicine has a long history. Many medical conditions, such as diabetes and hypertension, are managed by physicians who use protocols in daily practice. These guidelines are often developed by health organizations by panels of experts who weigh the evidence of clinical studies, some of which are randomized. Insurance carriers in the United States often mandate the use of guidelines because it may mean reduced medical costs. There is an increasing trend to evaluate physician performance based on utilization of established guidelines.

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Peer review under responsibility of Alexandria University Faculty of Medicine.
doi:10.1016/j.ajme.2011.01.002

Production and hosting by Elsevier

1. Why develop guidelines?

(1) The medical literature may be confusing as to the best treatment.
(2) There is a large volume of medical literature.
(3) Results of trials often lag beyond treatment developments.
(4) Some cancers present infrequently, making evaluation and treatment difficult for the inexperienced clinician.
(5) Experience is invaluable in treating cancer.

Organization	Topics	Guideline process	Where available?
American Society of Clinical Oncology (ASCO)	More common malignancies management issues	Consensus committees of experts	Journal of Clinical Oncology www.asco.org
National Cancer Institute (USA)	Controversial or management issues in common malignancies	Consensus committees of experts with invited presentations (open to public)	www.consensus.nih.gov Consensus publications mailed to the oncology community
National Cancer Center Network (member NCI-designate cancer centers)	Most malignancies – management from diagnosis to treatment to follow-up	Expert committees weighing level of evidence and producing consensus opinion, on an annual basis	www.nccn.org Journal of the National Cancer Center Network
European Society of Medical Oncology (ESMO)	Major malignancies – management from diagnosis to treatment to follow-up	Working groups of experts evaluating level of evidence and producing consensus opinion	www.esmo.org/research/esmo-clinical-practice-guidlines.html
American Cancer Society	Major malignancies – screening	Working groups of experts	www.cancer.org
Cancer Care Ontario	Major malignancies – issues in management	Working groups of experts (with results reviewed by membership)	www.cancercare.on.ca
UpToDate©, Inc.	Major malignancies – issues in management	Invited expert authors, peer-reviewed	www.uptodate.com
Cochrane© reviews	Major malignancies – issues in management	Volunteers	www.cochrane.org

(6) Bias is inherent in medical practice.
(7) Guideline development allows a critical review of possible treatments by experts.
(8) Guideline development allows cost and resource considerations.
(9) Optimal guidelines will remain current.
(10) Optimal guidelines should be accessible to any interested party.

Cancer management guidelines should be verified by clinical trials. However, these are often unavailable. Some cancer guidelines reflect only ''pattern of practice'', often that of large institutions with a large experience in those cancers. In every system, bias is inherent by the choice of participants or trials selected for inclusion. Guidelines are essentially guides to aid the physician in choosing the most cost effective course for an individual with cancer.

2. Widely available guideline resources in cancer care

In the higher income countries, several organizations have taken charge of the guideline process. Table 1 lists several organizations active in producing guidelines by similar but slightly different processes. Goals and issues covered may differ based on the type of organization. Guidelines are often published in respected medical journals, but are available on their websites. Other organizations invite experts to publish review articles on timely topics.

All these organizations use experts from different disciplines to review medical evidence. The focus of these organizations may be toward recommendations for that modality (generally medical oncology) practiced by the majority of members of the sponsoring organization. The NCI chooses controversial topics and invites investigators to present their results and data for critical review in multi day meetings in a public forum. The American Society of Clinical Oncology (ASCO) develops guidelines created by invited experts both in the evaluation and in the systemic treatment of common malignancies. It also works to rapidly evaluate very new systemic treatments and to advise on their incorporation in standard practice. The European Society of Medical Oncology (ESMO) produces broad guidelines for management and treatment of malignancies and provides specific recommendations for many malignancies. Cancer Care Ontario produces guidelines for its own province in Canada periodically on specific topics that affect delivery of care, taking into account cost-effectiveness. The NCCN has a more expansive program, with guidelines in evaluation, treatment, follow-up in all, but the rarest, malignancies. These are produced by consensus of panels of experts in each type of malignancy and reviewed annually. NCCN task forces invite their own experts and outside experts to report on very specific controversial issues and to publish in the Journal of the National Comprehensive Cancer Network. These organizations produce guidelines that are published in peer-review journals and are accessible on the internet. Many other sources of guidance are available to many physicians. UpToDate reviews

A 40 year woman finds a 1 cm hard lump in her right breast. She has a negative family history. Her physical examination is otherwise negative.

Issue	Organization	Issue addressed in guideline	Issues for resource-limited countries
• Evaluation	Ontario	None	• Availability of mammography
• Mammography	ASCO	None	• Availability of ultrasound
• Ultrasound	ESMO	Imaging	• Availability of BRCA testing
• MRI		BRCA testing	• Availability of MRI
• Type of biopsy		Biopsy technique	• Skill in core needle biopsies or fine needle aspiration biopsies by surgeon and pathologist
• BRCA testing	NCCN	Imaging	
		BRCA testing	
		Biopsy technique	
	NCI	None	

Mammography and ultrasound confirm only a 1 cm speculated mass in the upper outer quadrant of the right breast. Fine needle aspiration reveals infiltrating ductal carcinoma. The patient elects breast conserving surgery.

Issue	Organization	Issue addressed	Issues for resource-limited countries
• Breast conserving surgery	Ontario	Surgical management of the breast	• Skill in breast conserving surgery
• Axillary evaluation		Management of the axilla[3]	• Experience in sentinel node biopsy by surgeon and pathologist
	ASCO	Sentinel node biopsy[4]	
	ESMO	Breast conserving surgery	
		Sentinel node biopsy[1]	
	NCCN	Surgical management of the breast	
		Management of the axilla[2]	
	NCI	Breast conserving surgery[5]	

The patient has 1 cm grade 3 infiltrating ductal carcinoma. There is a 1 mm metastasis in one of two sentinel nodes. Hormone receptors are negative and her2-neu is positive. Margins of resection are negative. There is no lymphovascular invasion. No ductal carcinoma-in-situ is identified.

Issue	Organization	Issue	Issues for resource-limited countries
• Tumor markers	Ontario	Management of the axilla[3]	• Availability of tumor markers and quality control
• Indications for axillary dissection		Guideline for taxanes[6]	
• Adjuvant radiotherapy		Adjuvant radiotherapy[7]	• Type of chemotherapy available
• Adjuvant chemotherapy	ASCO	Management of the axilla[4]	• Availability of trastuzimab
• Adjuvant trastuzimab		Hormone receptor testing[8]	
		Her2-neu testing[9]	
	ESMO	Tumor markers	
		Management of the axilla	
		Adjuvant radiation therapy	
		Adjuvant chemotherapy	
		Adjuvant trastuzimab[1]	
	NCCN	Management of the axilla	
		Adjuvant radiation therapy	
		Adjuvant systemic therapy[10]	
	NCI	Adjuvant chemotherapy[11]	

many health issues and is available by individual or institutional subscription, in most US medical school libraries. It summarizes the literature with recent evidence, and makes specific recommendations. The Cochrane Collaboration reviews health care interventions in cancer and other health issues which have been tested in randomized controlled trials and publishes summaries. They will include nonrandomized data when appropriate. Full texts are available by individual or institutional subscription, and are accessible on PubMed. There are many review journals that invite experts to publish a peer reviewed articles on timely topics. These include Oncology© (Williston Park, NY), Seminars in Oncology© (Elsevier, Inc.), Oncology Reviews© (SpringerLink, Inc.), Critical Review in Oncology/Hematology© (Elsevier, Inc.), Seminars in Radiation Oncology© (Elsevier, Inc.), and American Journal of Clinical Oncology© (Wolters Kluwer/Lippincott Williams & Wilkins, Inc). MedScape Oncology© (from WebMD) (www.medscape.com/oncology) provides reviews of major oncology meetings. In summary, there are many resources available to the practicing clinician. Many are topic related, but ESMO and NCCN provide broad, referenced guidelines in different formats.

3. Application of guidelines

An example of how guidelines can be used in a patient example is shown below. Issues regarding applicability to countries with limited resources are also listed.

4. Issues in resource-limited countries

Cost-efficient care of cancer is necessary in the global perspective. Guidelines provide an opportunity for fair and cost-efficient care. There are many steps in cancer care that are necessary for best outcomes. Guideline processes must recognize that "shortcuts" that may result in short-term cost savings may also be detrimental in ultimate cost and patient outcome. For example, limited pathology assessment of hormone receptors may save physician time and laboratory costs, but treatment with tamoxifen in hormone receptor negative patients increases ultimate costs and detracts from cure. Guidelines must be practical. For instance, in the patient example above, a mammogram and ultrasound are useful when breast conserving surgery is considered. If there are limited radiation therapy facilities which would not allow for postlumpectomy radiation, then the information garnered from an ultrasound is of no use. New expensive drugs and technologies prevent widespread application of available resources and new drugs. In the example above, trastuzimab is a very expensive biological agent with high effectiveness in her2-neu positive breast cancers. If it is not available, then testing for her2-neu may not be relevant. For the small breast cancers, controversy in high income countries exists regarding when adjuvant trastuzimab is appropriate. When the supply of trastuzumab is limited, the local guiding authorities must decide for whom trastuzimab is most appropriate.

The first step in developing guidelines should be a statement of expectations. Guidelines should be applicable to the circumstances of cancer care. Guidelines should be regularly evaluated for relevance and applicability. For instance, if very early breast cancers are not identified in the population, development and review of guidelines for these patients waste expert time and energy and resources needed to publish those guidelines. Guidelines should vary based on the population served and the resources available. If radiotherapy facilities are not widely available, recommendations for breast conserving therapy is not useful. Mastectomy may be preferred. However, if patients present with advanced cancers from fear of mastectomy, guidelines could be produced encouraging development of new radiation therapy resources or transfer of patients to those facilities where radiotherapy is available.

There are regular changes in the paradigm of cancer care, and guidelines must remain current. For example, in all patients treated with breast conserving surgery breast irradiation was recommended, based on an NCI consensus statement. Recent data suggest that elderly patients with positive hormone receptors could be treated with tamoxifen and no radiotherapy.[12] Recent data also show that the overall time of breast radiotherapy can be compressed from 6 to 3 weeks, certainly resource-sparing.[13,14] Unless there is a regular review of guidelines, application of new approaches and treatments may not occur.

5. Summary

Guidelines are useful in managing cancer. Guidelines are only as good as the individuals involved in the process of development and by the method of development. There are many organizations who have invested heavily in their development. These have been generally in high income countries where there are many resources, thus making these not always useful to cancer practitioners in the lower income countries. Available guidelines vary widely as to the scope and details of management. The NCCN and ESMO guidelines are particularly useful as they cover the scope of management, are evidence based, and have been developed by experts.

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