Handbook of
Advanced Cancer Care

edited by

Michael J. Fisch

and

Eduardo Bruera

CAMBRIDGE
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE
The Pitt Building, Trumpington Street, Cambridge, United Kingdom

CAMBRIDGE UNIVERSITY PRESS
The Edinburgh Building, Cambridge CB2 2RU, UK
40 West 20th Street, New York, NY 10011-4211, USA
477 Williamstown Road, Port Melbourne, VIC 3207, Australia
Ruiz de Alarcón 13, 28014 Madrid, Spain
Dock House, The Waterfront, Cape Town 8001, South Africa

http://www.cambridge.org

First published 2003

Printed in the United Kingdom at the University Press, Cambridge

Typefaces Minion 10.5/14 pt, Formata and Formata BQ *System* LaTeX 2$_\varepsilon$ [TB]

A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication data
Handbook of advanced cancer care / [edited by] Michael J. Fisch, Eduardo D. Bruera.
p. cm.
Includes bibliographical references and index.
ISBN 0 521 01043 8 (pbk.)
1. Cancer – Palliative treatment – Handbooks, manuals, etc. 2. Terminal care – Handbooks, manuals, etc.
3. Cancer – Nursing – Handbooks, manuals, etc. I. Bruera, Eduardo. II. Fisch, Michael J., 1964–
RC271.P33 C356 2003
616.99′406 – dc21 2002073305

ISBN 0 521 01043 8 paperback

Contents

Part III Management of specific symptoms and syndromes

1

Principles of diagnosis and staging

John J. Kavanagh

U.T. M.D. Anderson Cancer Center, Houston

Introduction

The development of prognostic data and therapeutic outcomes in cancer is dependent upon meaningful communication among physicians, educators, health administrators, and all parties concerned with improving the care of malignancies. In order to ensure accurate descriptions of cancers, and allow comparisons of data and treatment methodologies, various cancer staging systems were developed. As cancer care became more complex over the years, multidisciplinary methods of treatment became essential. The importance of reproducible and functional staging systems for cancer are the cornerstone in the conduct of trials, introduction of new technologies, and comparisons of treatment. This is a summary of the evolution and current uses of these various staging methodologies.

Principles of cancer staging

The utility of a cancer staging system will depend on its accurate reflection of the natural history of the disease and the functional ability of healthcare givers to utilize these staging descriptions. Malignancies reflect a continuum of varying natural histories and are a dynamic process. Although no staging system can precisely take into account all variables, there must be enough functionality that will reflect this natural history. The staging ideally represents a point in time where the malignancy can be easily defined, utilized by all parties caring for the patient, and results in the accumulation of meaningful information. Therapeutic modalities can be used for comparing outcomes, planning policy, and advising individual patients. The staging system must also be flexible enough that it takes into account the development of new knowledge allowing appropriate modification of the various stages as necessary.

A second principle is the functional utility of the system in the hands of the caregivers. It must be efficient and practical in nature. The staging must interdigitate with the actual care patterns and allow the incorporation of these data for analysis.

The staging should also be detailed enough to allow meaningful conclusions, but not too complex that it can only be used by highly skilled personnel. One of the most important considerations in the collection of data is that it not be perceived as inefficient and/or irrelevant to patient care.

A third and increasingly important principle is the integration of the collection of data into a format that reflects modern information technology. The databases developed must be consistent and allow computer-based analysis on an international basis. As information is distributed to the caregiver the information flow becomes just as important for individual treatment planning. This relatively new concern over information technology integration is being addressed by several groups such as statisticians, computer scientists, and epidemiologists. Yet to be addressed will be issues of confidentiality, proprietary rights, and access to the information.

A fourth principle of staging is cost efficiency. With the increased use of healthcare economic analysis, staging systems must now consider their intrinsic cost. Careful consideration must be given to the necessity of various staging procedures. In addition, there will be increasing use of outcomes analysis concerning the utility of various staging evaluations themselves.

A fifth, and most important aspect of a staging system, is its validity and reproducibility. Succinctly, is the decision making based on staging reflective of reproducible clinical practice? Is there sufficient objectivity in the decisions regarding staging of a patient that it may be translated on an international basis? Are the staging procedures involved too complex or subjective in interpretation that compromise the consistency of data reporting? Can the staging decisions and data be audited for confirmation and validity? These are questions that become more important as our medical statistics and clinical research designs increase in sophistication.

A final concern is the integration of laboratory based or molecular data into a staging definition. This is a new problem that confronts individuals dealing with the reporting of cancer outcomes data. There is no doubt that molecular-based prognostic data will soon enter into our clinical management. It is not clear how this will impact prospectively on staging patients. It is also unclear how such information can be used on a retrospective basis for analysis. The problem is qualitatively different than the introduction of a radiographic or surgical technique. These newer prognostic criteria will be based on either a serologic measurement or some type of pathologic evaluation of specimens. Most of these newer molecular techniques will initially be difficult, but quite quickly available to the routine laboratory.

History

There have been many systems of cancer staging over the years. Gynecologists involving numerous organizations and disciplines used a staging system for cervical

cancer that dated back to the League of Nations system for cervical cancer published in 1920.[1] The TNM (Tumor, Node, Metastasis) system was introduced by Denoix approximately 50 years ago. This was published as a formal proposal in 1944 in a bulletin of the National Institute of National Hygiene of Paris.[2] The TNM system has become a cornerstone of an international basis for describing these stages of cancer and comparing end results. The International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) were constituted to develop a joint system based on the TNM classification. This evolved gradually in the 1950s and there were various publications with differing stages. Eventually, a consensus was reached in the 1980s that resulted in the publication of the *Manual for Staging of Cancer* by the AJCC and the *TNM Classification of Tumors* by the UICC.[3] It is important to note that these institutions represent predominantly American–European consensus. The collaboration between these two organizations has been essential in creating a relatively uniform TNM system that can be internationally applied. It is also endorsed by the American College of Surgeons, American College of Physicians, American Cancer Society, and National Cancer Institute along with the multiple organizations participating in the UICC. Through the years these staging manuals have had several revisions.[4,5]

The utility of cancer staging is dependent upon the histopathologic description of the tumor. At this time the histopathologic classification is largely morphologic based. There is not agreement among pathologists as to which histopathologic classifications of cancer should be used in the TNM staging system. The World Health Organization has provided international criteria for these histologic classifications of malignancy since the 1950s. There is also a numerical coding system know as the ICD–O, i.e., International Classifications of Diseases for Oncology. The numerical coding allows for more accurate reporting of data when integrated into the staging systems. The use of this system has been recommended by multiple organizations in order to make the TNM staging more clinically meaningful.[6,7]

TNM system rules

The staging system is based on the extent of the primary tumor (T), presence of regional lymph node metastasis (N), and the extent of distant metastasis (M). Each major category is then given a numerical component. These data are then summarized and the patient is given a stage according to a diagram. Depending on each disease site there may be a clinical classification based on clinical findings and imaging modalities. This is cTNM or TNM. There may also be a pathologic classification know as pTNM. There can also be a retreatment classification which is used with recurrences requiring further treatment. This is known as rTNM. Finally, there is an autopsy staging depending on postmortem data that is known as aTNM.

Another principle of the staging is that if there is doubt concerning the accuracy of the TNM then the lower stage should be applied. In the case of multiple tumors the highest T category is selected for staging description. The TNM categories may be expanded for the purposes of research, but the original definitions may not be changed. Finally, in the case of an unknown primary, staging will be determined on the most probable primary site of origin.

Certain classifications will require histopathologic grading. The system uses a G classification. GX means grade can not be assessed. G1 is well differentiated and G4 is undifferentiated. The most undifferentiated area of the tumor is used for the purposes of grading.

An added complexity of the TNM system has been multidisciplinary or neo-adjuvant care and longer disease-free intervals. Prefixes are then used. rTNM means a recurrent tumor which has been restaged after a disease-free interval. If there are multiple primary tumors at a single site then the highest T is used and number of tumors noted, i.e., $T_3(4)$. yTNM means that the classification was performed during or following multimodality therapy.

An essential part of the TNM system is to eventually classify the patient within a stage. These stages range from I to IV. The stage will be determined by a table with the various parameters of the TNM components. Another aspect is the cancer staging data form. These are forms that correspond to particular aspects of each malignancy. The TNM and other criteria are filled out and the stage noted. This remains within the medical record and serves as the baseline stage of the patient. It may be modified in the future as previously described.

It is most important to note that the staging classifications do not address the issues of quality of life, psychosocial issues, toxicity, or morbidities of therapy. The primary purpose of the staging data is to determine the extent of the cancer and eventually analyze patterns of care and outcomes along with the conduct of clinical research.

Examples of staging

Lung cancer

The staging of lung cancer follows the TNM system. The primary site is characterized by size and invasive nature. T1 is a tumor 3 cm or less in dimension. T2 size is more than 3 cm or it involves the main bronchus, nearness to the carina, or invasion of the visceral pleura. Regional lymph node disease is usually defined by radiographic and/or surgical staging. NX means they can not be assessed and N0, no metastases. N1–N3 represent various degrees of involved lymph nodes. Distant metastases are M0 with no distant metastases and M1, with distant metastases (Table 1.1). This may be seen in the stage grouping in Table 1.2. Histopathologic

Table 1.1. Definition of TNM

Primary tumor (T)

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

T0 No evidence of primary tumor.

Tis Carcinoma in situ.

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus[a] (i.e., not in the main bronchus).

T2 Tumor with any of the following features of size or extent:
More than 3 cm in greatest dimension
Involves main bronchus, 2 cm or more distal to the carina
Invades the visceral pleura
Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.

T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.[b]

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor

N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis present.[c]

Source: Fleming ID, Cooper JS, Henson DE et al. (ed.) *AJCC Cancer Staging Handbook*, 5th edn, pp. 117–27. Philadelphia, PA: Lippincott–Raven, 1998.

[a]The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

[b]Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is nonbloody and is not an exudate. When these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3.

[c]M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral).

Table 1.2. Stage grouping

Stage grouping of the TNM subsets has been revised as follows:			
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Source: Fleming ID, Cooper JS, Henson DE et al. (ed.) *AJCC Cancer Staging Handbook*, 5th edn, pp. 117–27. Philadelphia, PA: Lippincott–Raven, 1998.

grade is from GX where no grade can be assessed and from G1–G4 for gradually less differentiation. An example of a lung staging diagram can be seen in Fleming et al., pp. 117–27.[4]

Because of the common nature of the tumor, with a fairly predictable natural history and therapy options, the staging of lung cancer has been quite useful in the conduct of studies and prognosis. Therefore, it represents one of the best models for staging cancer.

Gynecologic cancer

The International Federation of Gynecology and Obstetrics (FIGO) has been active in staging gynecologic cancers for many years. In an attempt to blend the TNM and FIGO systems there is a synthesis of both systems. The end result is essentially the same. However, it is most common that the FIGO system is used in clinical practice and in the conduct of studies. The nature of each staging system can be seen in Table 1.3 (ibid Pecorelli et al., pp. 63–78).[1]

At this time the principles of surgical staging combined with the importance of residual disease remains essential to clinical understanding and the conduct of studies in this disease. It is probable that this system will remain relatively intact pending the discovery of any unusual predictive diagnostic serum marker or radiological technique.

Table 1.3. Carcinoma of the ovary – staging

FIGO stages		TNM categories
Primary tumor cannot be assessed		TX
No evidence of primary tumor		T0
I Tumor limited to the ovaries		T1
IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface: no malignant cells in ascites or peritoneal washings	T1a
IB	Tumor limited to both ovaries; capsule intact, no tumor on ovarian surface: no malignant cells in ascites or peritoneal washings	T1b
IC	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings	T1c
II Tumor involves one or both ovaries with pelvic extension		T2
IIA	Extension and/or implants on uterus and/or tube(s); no malignant cells in ascites or peritoneal washings	T2a
IIB	Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings	T2b
IIC	Pelvic extension (IIA or IIB) with malignant cells in ascites or peritoneal washings	T2c
III Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis		T3 and/or N1
IIIA	Microscopic peritoneal metastasis beyond pelvis	T3a
IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension	T3b
IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis	T3c and/or N1
IV Distant metastasis (excludes peritoneal metastasis)		M1

Source: Pecorelli S, Jones HW, Ngan HYS, Bender HG, Benedet JL. Cancer of the ovary. In *Staging Classifications and Clinical Practice Guidelines of Gynecologic Cancers*, FIGO Committee on Gynecologic Oncology, pp. 1, 63–78. London: Elsevier, 2000.

Leukemia

The acute leukemias represent an extremely diverse group of malignancies. The original understanding was based on morphologic analysis. Now it is based on morphologic, immunologic, and cytogenetic evaluation.[8–10] These are often done in highly specialized laboratories. Therapeutic approaches can differ according to these various characteristics. The particular staging of this malignancy is dynamic in nature because of the rapidly changing nature of the field. An example is seen in Table 1.4. This description applies for acute lymphocytic leukemia. The staging

Table 1.4. Morphologic, immunologic, and cytogenetic classification of acute lymphocytic leukemia (ALL)

Category	Karyotype	Cell markers								FAB morphology
		Tdt	Ia	CD19	CD10	Cylg	Slg	CD7	CD2	
Early T precursor ALL	t or del 9p	+	−	−	−	−	−	+	−	L_1 or L_2
T-cell ALL	t(11;14), 6q−	+	−	−	−	−	−	+	+	L_1 or L_2
Early B precursor ALL	t(4;11), t(9;22) = Ph+	+	+	+	−	−	−	−	−	L_1 or L_2
Common ALL (cALLa)	6q−, near haploid t or del (12p), t(9;22) 9p− hyperdiploid (> 50)	+	+	+	+	−	−	−	−	L_1 or L_2
Pre-B ALL	t(1;9), t(9;22) 6q− hyperdiploid (> 50) t(8;14), t(2;8), t(8;22)	+	+	+	+	+	−	−	−	L_1 or L_2
B-cell ALL	Burkitt's lymphoma translocation, t(8;14), t(8;22), t(2;8), 6q−	−	+	+	±	±	+	−	−	L_3

Source: O'Donnell JR. Acute leukemias. In *Cancer Management: A Multidisciplinary Approach*, 3rd edn, pp. 575–96. Melville, NY: PRR, 1999.

Note: cALLa, common acute lymphocytic leukemia antigen; CD, cluster of differentiation; Cylg, cytoplasmic immunoglobullin; Ia, I antigen; Ph, Philadelphia chromosome; Slg, surface immunoglobulin; Tdt, terminal deoxynucleotide.

systems for the acute leukemias are subject to extensive debate and differing philosophies on therapy. Such staging systems will remain within the realm of fairly specialized hematologists who have an interest in these diseases. Cooperative group studies engaging in the treatment of the disease tend to pick the most essential characteristics for the purposes of stratification and therapy. There is significant debate concerning the "staging" of the hematologic malignancies with the introduction of newer molecular markers.

Summary

The staging of malignancy has evolved over many years. The most commonly used solid tumor staging system is the AJCC/UICC, arrived at through a number of consensus meetings. This has worked very well in a number of solid tumors for the purpose of prognosis, treatment, and the conduct of treatment trials. In the area of gynecology the FIGO and UICC has a synthesized version, which has proved functional in nature. The hematological diseases and lymphomas remain fairly specialized and subject to significant change, based on morphologic, immunologic,

and cytogenetic techniques. These diseases require very specialized approaches and consensus before beginning a trial.

Staging systems, however, do not address the quality of life of patients, nor do they address any issues of palliative care. Staging systems are focused on the essential statistical issues of stratification, characterization of patients, and cancer survival analysis including life tables, Kaplan–Meier methods, and multivariate analyses. In the future, one would anticipate that there will be a greater integration of psychosocial instruments into staging, to allow investigators a better sense of the quality of life and palliative care issues of patients with cancer.

REFERENCES

1 Pecorelli S, Jones HW, Ngan HYS, Bender HG, Benedet JL. Cancer of the ovary. In *Staging Classifications and Clinical Practice Guidelines of Gynecologic Cancers*, FIGO Committee on Gynecologic Oncology, pp. 1, 63–78. London: Elsevier, 2000.

2 Denoix PF. TNM classification. *Bull Inst Nat Hyg Paris* 1994;1:1–69 and 1944;5:52–82.

3 Rubin P, McDonald S, Keller JW. Staging and classification of cancer: A unified approach. In *Principles and Practice of Radiation Oncology*. 2nd edn, pp. 162–72. Philadelphia, PA: Lippincott–Raven, 1992.

4 Fleming ID, Cooper JS, Henson DE et al. (ed.) *AJCC Cancer Staging Handbook*, 5th edn, pp. 117–27. Philadelphia, PA: Lippincott Raven, 1998.

5 International Union Against Cancer. *TNM Classification of Malignant Tumors*, 4th edn. Berlin: Springer–Verlag, 1987.

6 World Health Organization. *WHO International Histological Classification of Tumors*, Vol. 1–25. Geneva: WHO, 1967–1981; 2nd edn, Berlin: Springer–Verlag, 1988–1992.

7 World Health Organization. *WHO International Classification of Diseases for Oncology*, 2nd edn. Geneva: WHO, 1990.

8 World Health Organization. *International Classification of Diseases for Oncology*. Geneva: WHO, 1976.

9 O'Donnell JR. Acute leukemias. In *Cancer Management: A Multidisciplinary Approach*, 3rd edn, pp. 575–96. Melville, NY: PRR, 1999.

10 Krueger GR, Medina JR, Nein HO et al. A new working formulation of non-Hodgkin's lymphomas: A retrospective study of the new NCI classification proposal in comparison to the Rappaport and Kiel classification. *Cancer* 1983;52:833.

11 Hoelzer D, Thiel E, Loffler H et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood* 1988;71:123–31.