UNION FOR INTERNATIONAL CANCER CONTROL

TNM Classification of MALIGNANT TUMOURS

Eighth Edition

Edited by James D. Brierley,
Mary K. Gospodarowicz and Christian Wittekind

WILEY Blackwell

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Classification of Malignant Tumours

Union for International
Cancer Control (UICC)

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This edition first published 2017 © 2017 UICC
Published 2017 by John Wiley & Sons, Ltd

Registered Office
John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Offices
9600 Garsington Road, Oxford, OX4 2DQ, UK
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Library of Congress Cataloging-in-Publication Data

Names: Brierley, James, editor. | Gospodarowicz, M. K. (Mary K.), editor. | Wittekind, Ch. (Christian), editor.
Title: TNM classification of malignant tumours / editors in chief, James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind ; editors, B. O'Sullivan [and 7 others].
Description: Eighth edition. | Oxford, UK ; Hoboken, NJ : John Wiley & Sons, Inc., 2017. | Includes bibliographical references.
Identifiers: LCCN 2016039430 | ISBN 9781119263579 (paper) | ISBN 9781119263548 (Adobe PDF) | ISBN 9781119263562 (epub)
Subjects: | MESH: Neoplasms–classification
Classification: LCC RC258 | NLM QZ 15 | DDC 616.99/40012–dc23
LC record available at https://lccn.loc.gov/2016039430

Cover image: © UICC

Set in 9.25/12pt Joanna MT by SPi Global, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

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They are called wise
who put things in their right order
Thomas Aquinas

This Eighth Edition is dedicated to Dr Leslie H. Sobin MD, a pathologist and previous long term Chair of UICC TNM Prognostic Factor Committee. Les, as he is known to colleagues all over the world, has devoted most of his career to help promote globally unified classifications of disease in particular in pathology and cancer staging. This is the first edition since the fourth that has not benefitted from his direct involvement; however his imprint is found throughout this edition.

Contents

Preface

In this eighth edition of *TNM Classification of Malignant Tumours*, many of the tumour sites are unchanged from the seventh edition[1]. However, some tumour entities and anatomic sites have been newly introduced and some tumours contain modifications: this follows the basic philosophy of maintaining stability of the classification over time. The modifications and additions reflect new data on prognosis as well as new methods for assessing prognosis.[2] Some changes had already appeared in the *TNM Supplement*[3] as proposals. Subsequent support warrants their incorporation into the classification. New proposals for tumours of parathyroid carcinoma, and paraganglionoma will be published in the next edition of the *TNM Supplement*.

In the seventh edition a new approach was adopted to separate stage groupings from prognostic groupings in which other prognostic factors are added to T, N, and M categories. These new prognostic groupings were presented for oesophagus and prostate. In this eighth edition, the term 'stage' is used when only descriptions of anatomic extent of disease are used and 'prognostic group' for when additional prognostic factors are incorporated.

Changes made between the seventh and eighth editions are indicated by a bar at the left-hand side of the text. To avoid ambiguity, users are encouraged to cite the edition and year of the TNM publication they have used in their list of references.

A TNM homepage with Frequently Asked Questions (FAQs) and a form for submitting questions or comments on the TNM can be found at: http://www.uicc.org. Readers are also encouraged to go to http://www.uicc.org for updates and errata.

The UICC's TNM Prognostic Factors Project has a process for evaluating proposals to change the TNM Classification. This procedure aims at a continuous systematic approach composed of two arms: (1) review formal proposals from investigators and (2) an annual literature search for articles concerning improvements to TNM. The proposals and results of the literature search are evaluated by a UICC panel of experts as well as by the TNM Prognostic Factors committee members.[5] The national TNM Committees participated in this process. More details and a checklist that will facilitate the formulation of proposals can be obtained at www.uicc.org.

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Acknowledgments

The Editors have much pleasure in acknowledging the great help received from the members of the TNM Prognostic Factors Project Committee and the National Staging Committees Global Representatives and international organizations listed on pages XVI, all of whom volunteered their time.

We thank Professor Patti Groome and Ms Colleen Webber for supervising and performing the literature watch from its inception until 2015 and 2016, respectively. The eighth edition of the *TNM Classification* is the result of a number of consultative meetings organized and supported by the UICC and AJCC secretariats.

This publication was made possible by grants *1U58DP001818 and 1U58DP004965* from the Centers for Disease Control and Prevention (CDC) (USA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the CDC.

Organizations Associated with the TNM System

CDC	Centers for Disease Control and Prevention (USA)
FIGO	International Federation of Gynaecology and Obstetrics
IACR	International Association of Cancer Registries
IARC	International Agency for Research on Cancer
IASLC	International Association for the Study of Lung Cancer
ICCR	International Collaboration on Cancer Reporting
WHO	World Health Organization

National Committees

Australia and New Zealand	National TNM Committee
Austria, Germany, Switzerland	Deutschsprachiges TNM-Komitee
Belgium	National TNM Committee
Brazil	National TNM Committee
Canada	National Staging Steering Committee
China	National TNM Cancer Staging Committee of China
Denmark	National TNM Committee
Gulf States	TNM Committee
India	National TNM Committee
Israel	National Cancer Staging Committee
Italy	Italian Prognostic Systems Project
Japan	Japanese Joint Committee
Latin America and Caribbean	Sociedad Latinoamericana y del Caribe de Oncología Médica
Netherlands	National Staging Committee
Poland	National Staging Committee
Singapore	National Staging Committee
Spain	National Staging Committee
South Africa	National Staging Committee
Turkey	Turkish National Cancer Staging Committee
United Kingdom	National Staging Committee
United States of America	American Joint Committee on Cancer

Members of UICC Committees Associated with the TNM System

In 1950 the UICC appointed a *Committee on Tumour Nomenclature and Statistics*. In 1954 this Committee became known as the *Committee on Clinical Stage Classification and Applied Statistics* and in 1966 it was named the *Committee on TNM Classification*. Taking into consideration new prognostic factors the Committee was named in 1994 the *TNM Prognostic Factors Project Committee*, and in 2003 the main committee was named "TNM Prognostic Factors Core Group". A list of members who have served on these committees is available at: www.uicc.org

UICC TNM Prognostic Factors Core Group 2016

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In addition, the Editors wish to acknowledge the invaluable contributions of:

Head and Neck Cancers	UICC Advisory Committee (see www.uicc.org)
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Cutaneous Squamous Cell Carcinoma	C. Schmults, K. Nehal
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Paediatric Tumours	L. Frazier, J. Aitken
Expert Panel Members	See www.uicc.org
Global Advisory Group Members	See www.uicc.org

Introduction

The History of the TNM System*

The TNM system for the classification of malignant tumours was developed by Pierre Denoix (France) between the years 1943 and 1952.[1]

In 1950, the UICC appointed a Committee on Tumour Nomenclature and Statistics. As a basis for its work on clinical stage classification, it adopted the general definitions of local extension of malignant tumours suggested by the World Health Organization (WHO) Sub-Committee on The Registration of Cases of Cancer as well as Their Statistical Presentation.[2]

In 1958, the Committee published the first recommendations for the clinical stage classification of cancers of the breast and larynx and for the presentation of results.[3]

A second publication in 1959 presented revised proposals for the breast, for clinical use and evaluation over a 5-year period (1960–1964).[4] In 1968, a booklet, the *Livre de Poche*[5] and, a year later, a complementary booklet was published detailing recommendations for the setting-up of field trials, for the presentation of end results, and for the determination and expression of cancer survival rates.[6] The *Livre de Poche* was subsequently translated into 11 languages. In 1974 and 1978, second and third editions[7,8] were published containing new site classifications, and the fourth edition of TNM in 1987.[9]

In 1993, the project published the *TNM Supplement*[10] to promote the uniform use of TNM by providing detailed explanations of the TNM rules with practical examples. Second, third, and fourth editions appeared in 2001, 2003, and 2012.[11–13]

The project also publishes the *TNM Atlas an Illustrated Guide to the TNM Classification of Malignant Tumours*, the sixth edition was published in 2014 as a companion to the seventh edition of the *TNM Classification*.[14]

In 1995, the project published *Prognostic Factors in Cancer*,[15] a compilation and discussion of prognostic factors in cancer, both anatomical and

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non-anatomical, at each of the body sites. This was expanded in the second edition in 2001[16] and the third edition in 2006.[17]

The current eighth edition of TNM contains rules of classification and staging that correspond with those appearing in the eighth edition of the *AJCC Cancer Staging Manual* (2017).[18] While the aim of the UICC and AJCC is to have identical classifications, small differences exist and are identified as footnotes to the text. Wherever possible, the UICC classification is based on published evidence-based recommendation.

To develop and sustain a classification system acceptable to all requires the closest liaison between national and international organizations. As noted, while the classification is based on published evidence, in areas where high-level evidence is not available it is based on international consensus. The continuing objective of the UICC is to present the classification of anatomical extent of cancer globally.

Note

* A more detailed history is available on the website at www.uicc.org

The Principles of the TNM System

The practice of classifying cancer cases into groups according to anatomical extent, termed 'stage', arose from the observation that survival rates were higher for cases in which the disease was localized than for those in which the disease had extended beyond the organ of origin. The stage of disease at the time of diagnosis is a reflection not only of the rate of growth and extension of the neoplasm but also the type of tumour and the tumour–host relationship.

It is important to record accurate information on the anatomical extent of the disease for each site at the time of diagnosis, to meet the following objectives:

1. to aid the clinician in the planning of treatment
2. to give some indication of prognosis for survival
3. to assist in evaluation of the results of treatment
4. to facilitate the exchange of information between treatment centres
5. to contribute to the continuing investigation of human cancer
6. to support cancer control activities.

Cancer staging is essential to patient care, research, and cancer control. Cancer control activities include direct patient care-related activities, the

development and implementation of clinical practice guidelines, and centralized activities such as recording disease extent in cancer registries for surveillance purposes and planning cancer systems. Recording of stage is essential for the evaluation of outcomes of clinical practice and cancer programmes. However, in order to evaluate the long-term outcomes of populations, it is important for the classification to remain stable. There is therefore a conflict between a classification that is updated to include the most current forms of medical knowledge while also maintaining a classification that facilitates longitudinal studies. The UICC TNM Project aims to address both needs.

International agreement on the classification of cancer by extent of disease provides a method of conveying disease extent to others without ambiguity.

There are many axes of tumour classification: for example, the anatomical site and the clinical and pathological extent of disease, the duration of symptoms or signs, the gender and age of the patient, and the histological type and grade of the tumour. All of these have an influence on the outcome of the disease. Classification by anatomical extent of disease is the one with which the TNM system primarily deals.

The clinician's immediate task when meeting a patient with a new diagnosis of cancer is to make a judgment as to prognosis and a decision as to the most effective course of treatment. This judgment and this decision require, among other things, an objective assessment of the anatomical extent of the disease.

To meet the stated objectives a system of classification is needed:

1. that is applicable to all sites regardless of treatment; and
2. that may be supplemented later by further information that becomes available from histopathology and/or surgery.

The TNM system meets these requirements.

The General Rules of the TNM System[a,b]

The TNM system for describing the anatomical extent of disease is based on the assessment of three components:

T – the extent of the primary tumour

N – the absence or presence and extent of regional lymph node metastasis

M – the absence or presence of distant metastasis.

The addition of numbers to these three components indicates the extent of the malignant disease, thus:

T0, T1, T2, T3, T4, N0, N1, N2, N3, M0, M1

In effect, the system is a 'shorthand notation' for describing the extent of a particular malignant tumour.

The general rules applicable to all sites are as follows:

1. All cases should be confirmed microscopically. Any cases not so proved must be reported separately.
2. Two classifications are described for each site, namely:
   a) *Clinical classification:* the pretreatment clinical classification designated **TNM** (or cTNM) is essential to select and evaluate therapy. This is based on evidence acquired before treatment. Such evidence is gathered from physical examination, imaging, endoscopy, biopsy, surgical exploration, and other relevant examinations.
   b) *Pathological classification:* the postsurgical histopathological classification, designated **pTNM**, is used to guide adjuvant therapy and provides additional data to estimate prognosis and end results. This is based on evidence acquired before treatment, supplemented or modified by additional evidence acquired from surgery and from pathological examination. The pathological assessment of the primary tumour (pT) entails a resection of the primary tumour or biopsy adequate to evaluate the highest pT category. The pathological assessment of the regional lymph nodes (pN) entails removal of the lymph nodes adequate to validate the absence of regional lymph node metastasis (pN0) or sufficient to evaluate the highest pN category. An excisional biopsy of a lymph node without pathological assessment of the primary is insufficient to fully evaluate the pN category and is a clinical classification. The pathological assessment of distant metastasis (pM) entails microscopic examination of metastatic deposit.
3. After assigning T, N, and M and/or pT, pN, and pM categories, these may be grouped into stages. The TNM classification and stages, are established at diagnosis and must remain unchanged in the medical records.
   Only for cancer surveillance purposes, clinical and pathological data may be combined when only partial information is available either in the pathological classification or the clinical classification.
4. If there is doubt concerning the correct T, N, or M category to which a particular case should be allotted, then the lower (i.e., less advanced) category should be chosen. This will also be reflected in the stage.

5. In the case of multiple primary tumours in one organ, the tumour with the highest T category should be classified and the multiplicity or the number of tumours should be indicated in parenthesis, e.g., T2(m) or T2(5). In simultaneous bilateral primary cancers of paired organs, each tumour should be classified independently. In tumours of the liver, ovary and fallopian tube, multiplicity is a criterion of T classification, and in tumours of the lung multiplicity may be a criterion of the M classification.
6. Definitions of the TNM categories and stage may be telescoped or expanded for clinical or research purposes as long as the basic definitions recommended are not changed. For instance, any T, N, or M can be divided into subgroups.

Notes

[a] For more details on classification the reader is referred to the TNM Supplement.

[b] An educational module is available on the UICC website www.uicc.org.

Anatomical Regions and Sites

The sites in this classification are listed by code number of the International Classification of Diseases for Oncology.[19] Each region or site is described under the following headings:

- Rules for classification with the procedures for assessing the T, N, and M categories
- Anatomical sites, and subsites if appropriate
- Definition of the regional lymph nodes
- TNM Clinical classification
- pTNM Pathological classification
- G Histopathological grading if different from that described on page 9
- Stage and prognostic groups
- Prognostic factors grid

TNM Clinical Classification

The following general definitions are used throughout:

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1–T4	Increasing size and/or local extent of the primary tumour

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1–N3	Increasing involvement of regional lymph nodes

M – Distant Metastasis*

M0	No distant metastasis
M1	Distant metastasis

Note

* The MX category is considered to be inappropriate as clinical assessment of metastasis can be based on physical examination alone. (The use of MX may result in exclusion from staging.)

The category M1 may be further specified according to the following notation:

Pulmonary	PUL (C34)	Bone marrow	MAR (C42.1)
Osseous	OSS (C40, 41)	Pleura	PLE (C38.4)
Hepatic	HEP (C22)	Peritoneum	PER (C48.1,2)
Brain	BRA (C71)	Adrenals	ADR (C74)
Lymph nodes	LYM (C77)	Skin	SKI (C44)
Others	OTH		

Subdivisions of TNM

Subdivisions of some main categories are available for those who need greater specificity (e.g., T1a, T1b or N2a, N2b).

pTNM Pathological Classification

The following general definitions are used throughout:

pT – Primary Tumour

pTX	Primary tumour cannot be assessed histologically
pT0	No histological evidence of primary tumour
pTis	Carcinoma in situ
pT1–4	Increasing size and/or local extent of the primary tumour histologically

pN – Regional Lymph Nodes

pNX	Regional lymph nodes cannot be assessed histologically
pN0	No regional lymph node metastasis histologically
pN1–3	Increasing involvement of regional lymph nodes histologically

Notes

- Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.
- Tumour deposits (satellites), i.e., macro- or microscopic nests or nodules, in the lymph drainage area of a primary carcinoma without histological evidence of residual lymph node in the nodule, may represent discontinuous spread, venous invasion (V1/2) or a totally replaced lymph node. If a nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour), it should be recorded as a positive lymph node, and each such nodule should be counted separately as a lymph node in the final pN determination.
- Metastasis in any lymph node other than regional is classified as a distant metastasis.
- When size is a criterion for pN classification, measurement is made of the metastasis, not of the entire lymph node. The measurement should be that of the largest dimension of the tumour.
- Cases with micrometastasis only, i.e., no metastasis larger than 0.2 cm, can be identified by the addition of '(mi)', e.g., pN1(mi).

Sentinel Lymph Node

The sentinel lymph node is the first lymph node to receive lymphatic drainage from a primary tumour. If it contains metastatic tumour this indicates that other lymph nodes may contain tumour. If it does not contain metastatic tumour, other lymph nodes are not likely to contain tumour. Occasionally, there is more than one sentinel lymph node.

The following designations are applicable when sentinel lymph node assessment is attempted:

(p)NX(sn)	Sentinel lymph node could not be assessed
(p)N0(sn)	No sentinel lymph node metastasis
(p)N1(sn)	Sentinel lymph node metastasis

Isolated Tumour Cells

Isolated tumour cells (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest extent that can be detected by routine H and E stains or immunohistochemistry. An additional criterion has been

proposed in breast cancer to include a cluster of fewer than 200 cells in a single histological cross-section. Others have proposed for other tumour sites that a cluster should have 20 cells or fewer; definitions of ITC may vary by tumour site. ITCs do not typically show evidence of metastatic activity (e.g., proliferation or stromal reaction) or penetration of vascular or lymphatic sinus walls. Cases with ITC in lymph nodes or at distant sites should be classified as N0 or M0, respectively. The same applies to cases with findings suggestive of tumour cells or their components by non-morphological techniques such as flow cytometry or DNA analysis. The exceptions are in malignant melanoma of the skin and Merkel cell carcinoma, wherein ITC in a lymph node are classified as N1a (clinically occult) or N2a. These cases should be analysed separately.[20] Their classification is as follows.

(p)N0	No regional lymph node metastasis histologically, no examination for isolated tumour cells (ITC)
(p)N0(i–)	No regional lymph node metastasis histologically, negative morphological findings for ITC
(p)N0(i+)	No regional lymph node metastasis histologically, positive morphological findings for ITC
(p)N0(mol–)	No regional lymph node metastasis histologically, negative non-morphological findings for ITC
(p)N0(mol+)	No regional lymph node metastasis histologically, positive non-morphological findings for ITC

Cases with or examined for isolated tumour cells (ITC) in sentinel lymph nodes can be classified as follows:

(p)N0(i–)(sn)	No sentinel lymph node metastasis histologically, negative morphological findings for ITC
(p)N0(i+)(sn)	No sentinel lymph node metastasis histologically, positive morphological findings for ITC
(p)N0(mol–)(sn)	No sentinel lymph node metastasis histologically, negative non-morphological findings for ITC
(p)N0 (mol+)(sn)	No sentinel lymph node metastasis histologically, positive non-morphological findings for ITC

pM – Distant Metastasis*

pM1	Distant metastasis microscopically confirmed

Note

* pM0 and pMX are not valid categories.