Thymoma/Thymic Cancer and TNM Classification

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Following this abstract of the article is a review of the TNM system.

Abstract

A TNM classification has been established for various tumors. However, the TNM classification of **thymic** epithelial tumor has not been established yet.

Methods

We received replies to a questionnaire on **thymic** epithelial tumors from 115 institutes. We compiled a database of 1,320 patients with **thymic** epithelial tumor (1,093 thymomas, 186 **thymic** carcinomas, and 41 **thymic** carcinoids) who were treated between 1990 and 1994. We used a tentative TNM classification of thymoma presented by Yamakawa and associates in 1991. The regional lymph nodes of the thymus were classified into three groups: anterior mediastinal lymph nodes (N1), intrathoracic lymph nodes (N2), and extrathoracic lymph nodes (N3).

Results

The rate of lymphogenous metastasis in thymoma, **thymic** carcinoma, and **thymic** carcinoid was 1.8%, 27%, and 28%, respectively. Most tumors with lymph node metastasis metastasized to N1 (thymoma, 90%; **thymic** carcinoma, 69%; **thymic** carcinoid, 91%). The 5-year survival rates of N0, N1, and N2 thymoma were 96%, 62%, and 20%, respectively. The 5-year survival rates of N0, N1, N2, and N3 **thymic** carcinoma were 56%, 42%, 29%, and 19%, respectively. The 5-year survival rates of M0 and M1 thymoma were 95% and 57%. The 5-year survival rates of M0 and M1 **thymic** carcinoma were 51% and 35%. Multivariate analysis demonstrated that survival of

patients with thymoma was dependent on the clinical stage of Masaoka and complete resection. In **thymic** carcinoma, survival was dependent on lymph node metastasis and complete resection.

Conclusions

The N factor was one of the predictors of survival in thymoma and **thymic** carcinoma. However, M factor showed less influence on survival than T or N factors.

THE TNM SYSTEM

Introduction

The TNM system is the most widely used means for classifying the extent of cancer spread. TNM Classification of Malignant Tumours, Sixth Edition provides the new, internationally agreed-upon standards to describe and categorize cancer stages and progression. This guide contains important new and updated organ-specific classifications that oncologists and other professionals who treat patients with cancer must use to adequately classify tumours for prognosis and treatment.

This introduction provides a history of the TNM system, the principles of the classification of cancers and general rules of the TNM system applicable to all sites. Headings used in the TNM system to classify tumours for specific anatomical regions and sites are also provided with definitions.

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 and adopted, as a basis for its work on clinical stage classification, 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 1953, the Committee held a joint meeting with the International Commission on Stage-Grouping in Cancer and Presentation of the Results of Treatment of Cancer appointed by the International Congress of Radiology. Agreement was reached on a general technique for classification by anatomical extent of the disease, using the TNM system.

In 1954, the Research Commission of the UICC set up a special Committee on Clinical Stage Classification and Applied Statistics to "pursue studies in this

field and to extend the general technique of classification to cancer at all sites." 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].

Between 1960 and 1967, the Committee published nine brochures describing proposals for the classification of 23 sites. It was recommended that the classification proposals for each site be subjected to prospective or retrospective trial for a 5-year period.

In 1968, these brochures were combined in 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] were published containing new site classifications and amendments to previously published classifications. The third edition was enlarged and revised in 1982. It contained new classifications for selected tumours of childhood. This was carried out in collaboration with La Société Internationale d'Oncologie Pédiatrique (SIOP). A classification of ophthalmic tumours was published separately in 1985.

Over the years some users introduced variations in the rules of classification of certain sites. In order to correct this development, the antithesis of standardization, the national TNM committees in 1982 agreed to formulate a single TNM. A series of meetings was held to unify and update existing classifications as well as to develop new ones. The result was the fourth edition of TNM[9].

In 1993, the project published the TNM Supplement[10]. The purpose of this work was to promote the uniform use of TNM by providing detailed explanations of the TNM rules with practical examples. It also included proposals for new classifications, and optional expansions of selected categories. A second edition appeared in 2001.[11].

In 1995, the project published Prognostic Factors in Cancer[12], a compilation and discussion of prognostic factors in cancer, both anatomic and nonanatomic, at each of the body sites. A second edition appeared in 2001.[13].

The present (6th) edition contains rules of classification and staging that correspond exactly with those appearing in the sixth edition of the AJCC Cancer Staging Manual (2002)[14], and have approval of all national TNM committees. These are listed on pages xix-xxiii together with the names of members of the UICC committees who have been associated with the TNM

system.

The UICC recognizes the need for stability in the TNM classification so that data can be accumulated in an orderly way over reasonable periods of time. Accordingly, it is the intention that the classifications published in this booklet should remain unchanged until some major advances in diagnosis or treatment relevant to a particular site require reconsideration of the current classification.

To develop and sustain a classification system acceptable to all requires the closest liaison between national and international committees. Only in this way will all oncologists be able to use a "common language" in comparing their clinical material and in assessing the results of treatment. The continuing objective of the UICC is to achieve common consent in the classification of anatomical extent of disease.

1. The General Rules of the TNM System[1,2]

1.1. General Rule No. 1

All cases should be confirmed microscopically. Any cases not so proved must be reported separately.

Microscopically unconfirmed cases can be staged, but should be analyzed separately.

Microscopic confirmation of choriocarcinoma is not required if the hCG is abnormally elevated.

1.2. General Rule No. 2

Two classifications are described for each site, namely:

a.	*Clinical classification* (Pretreatment clinical classification), designated *TNM* (or cTNM). This is based on evidence acquired before treatment. Such evidence arises from physical examination, imaging, endoscopy, biopsy, surgical exploration and other relevant examinations.
b.	*Pathological classification* (Postsurgical histopathological classification), designated

pTNM. This is based on the evidence acquired before treatment, supplemented or modified by the 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 nodes adequate to validate the absence of regional lymph node metastasis (pN0) and sufficient to evaluate the highest pN category. The pathological assessment of distant metastasis (pM) entails microscopic examination.

TNM is a dual system that includes a clinical (pretreatment) and a pathological (postsurgical histopathological) classification. It is imperative to differentiate between these classifications because they are based on different methods of examination and serve different purposes. The clinical classification is designated TNM or cTNM; the pathological, pTNM. When the abbreviation TNM is used without a prefix, it implies the clinical classification (cTNM). Microscopic confirmation does not in itself justify the use of pTNM. The requirements for pathological classification are described in site-specific Recommendations for pT and pN.

Biopsy provides the diagnosis, including histological type and grade. The clinical assessment of tumour size should not be based on the biopsy.

In general, the cTNM is the basis for the choice of treatment and the pTNM is the basis for prognostic assessment. In addition, the pTNM may determine adjuvant treatment. Comparison between cTNM and pTNM can help in evaluating the accuracy of the clinical and imaging methods used to determine the cTNM. Therefore, it is important to retain the clinical *as well as* the pathological classification in the medical record.

A tumour is primarily described by the clinical classification before treatment or before the decision not to treat. In addition, a pathological classification is performed if specific requirements are met (see Introduction). Therefore, for an individual patient there may be a clinical classification, e.g., T2N1M0 and a pathological classification, e.g., pT2pNXpMX.

1.3. General Rule No. 3

After assigning T, N and M and/or pT, pN and pM categories, these may be grouped into stages. The TNM classification and stage grouping, once established, must remain unchanged in the medical records. The clinical stage is essential to select

and evaluate therapy, while the pathological stage provides the most precise data to estimate prognosis and calculate end results.

The rule that the TNM classification, once established, must remain unchanged in the patient's record applies to the definitive TNM classification determined just before initiation of treatment or before making the decision not to treat. If, for instance, the initial classification T2N0M0 is made in one hospital and is later updated to T2N1M0 after the patient is referred to another center where special imaging techniques are available, then the latter classification, based on a special examination, is considered the definitive one.

After two surgical procedures for a single lesion, the pTNM classification should be a composite of the histological examination of the specimens from both operations.

Example. Initial endoscopic polypectomy of a carcinoma of the ascending colon is classified pT1pNXpMX; the subsequent right hemicolectomy contains two lymph nodes with tumour, and a suspicious metastatic focus in the liver, later found to be a haemangioma, is excised-pT0pN1pM0. The definitive pTNM classification consists of the results of both operative specimens-pTlpN1pM0 (stage III).

For final stage grouping clinical and pathological data may be combined when only partial information is available in either the pathological classification or the clinical classification. The example on p. 2 is expressed as pT2cN1cM0 (stage III). For further discussion on the meaning and application of X (e.g. NX, MX).

1.4. General Rule No. 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 grouping.

Example. Sonography of the liver: suspicious lesion but no definitive evidence of metastasis-assign M0 (not M1).

If there are different results from different methods, the classification should be based on the most reliable method of assessment.

Example. Colorectal carcinoma, preoperative examination of the liver: sonography, suspicious, but no evidence of metastasis; CT, evidence of metastasis. The results of CT determine the classification-Ml. However, if CT were negative, the case would be classified M0.

1.5. General Rule No. 5

In the case of multiple simultaneous 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 parentheses, e.g., T2(m) or T2(5). In simultaneous bilateral cancers of paired organs, each tumour should be classified independently. In tumours of the thyroid, liver, ovary, and fallopian tube, multiplicity is a criterion of T classification.

The following apply to *grossly* recognizable multiple primary simultaneous carcinomas at the same site. They do not apply to one grossly detected tumour associated with multiple separate microscopic foci.

1. Multiple synchronous tumours in one organ may be:

a.	Multiple noninvasive tumours
b.	Multiple invasive tumours
c.	Multiple invasive tumours with associated carcinoma in situ
d.	A single invasive tumour with associated carcinoma in situ

For (a) the multiplicity should be indicated by the suffix "(m)", e.g. Tis(m).

For (b) and (c) the tumour with the highest T category is classified and the multiplicity or the number of invasive tumours is indicated in parentheses, e.g., T2(m) or T2(4).

For (c) and (d) the presence of associated carcinoma in situ may be indicated by the suffix "(is)", e.g., T3(m, is) or T2(3, is) or T2(is).

2. For classification of multiple simultaneous tumours in "one organ", the definitions of one organ listed in Table 1 should be applied. The tumours at these sites with the highest T category should be classified and the multiplicity or the number of tumours should be indicated in parentheses, e.g., T2(m) or T2(5).

Combining multiple carcinomas of skin should be done only within subsites (C44.1,2, etc). A carcinoma of the skin in subsite C44.3 and a synchronous one in subsite C44.6 and C44.7 should be classified as separate synchronous tumours.

Examples of sites for separate classification of two tumours are:

·	Oropharynx and hypopharynx

·	Submandibular gland and parotid gland
·	Urinary bladder and urethra (separate tumours)
·	Skin carcinoma of eyelid and neck

Examples for classification of the tumour with the highest T category and indication of multiplicity (m symbol) or numbers of tumours:

·	Two separate tumours of the hypopharynx
·	Carcinoma of the caecum and the transverse colon
·	Skin carcinoma of the trunk and the arm
·	Carcinoma of renal pelvis and ureter
·	See item No. 1 of M classification

3. If a new primary cancer is diagnosed within 2 months in the same site this new cancer is considered synchronous (based on criteria used by the SEER Program of the National Cancer Institute, USA).

Table 1. Definition of "one organ" for the classification of multiple simultaneous primary tumours: the listed sites/subsites are considered as "one organ"

	ICD-O Code[a]
Lip	C00.0,1,2,6
Oral cavity	C00.3-5, C02.0-3, C03, C04, C05.0, C06
Oropharynx	C01, C05.1,2, C09, C10.0,2,3
Nasopharynx	C11
Hypopharynx	C12, C13
Larynx	C10.1, C32.0-2
Maxillary sinus	C31.0
Ethmoid sinus	C31.1
Parotid gland	C07
Submandibular (submaxillary gland)	C08.0

Sublingual gland	C08.1
Thyroid[b]	C73
Oesophagus	C15
Stomach	C16
Small intestine	C17
Colon and rectum	C18-C20
Anal canal	C21.1,2
Liver[b]	C22
Gallbladder	C23
Extrahepatic bile ducts	C24.0
Ampulla of Vater	C24.1
Pancreas	C25
Lung	C34
Pleura	C38.4
Bones	C40, C41
Soft tissues, peripheral	C47, C49
Retroperitoneum	C48
Mediastinum	C38.1-3
Skin (subsite(s) only) except eyelid, anal margin, and perianal skin	C44.0,2-4, 6-9
Eyelid	C44.1
Anal margin and perianal skin	C44.5
Breast	C50
Vulva	C51
Vagina	C52
Cervix uteri	C53
Corpus uteri	C54
Ovary[b]	C56
Fallopian tube[b]	C57
Gestational trophoblastic tumours	C58.9
Nose	C60
Prostate	C61
Testis	C62
Scrotum	C63.2

Kidney	C64
Renal pelvis and ureter	C65, C66
Urinary bladder	C67
Urethra	C68.0
Conjunctiva	C69.0
Uvea	C69.3,4
Retina	C69.2
Orbit	C69.6
Lacrimal gland	C69.5

[a]ICD-O Topography code, 3rd edition, 2000, WHO, Geneva

[b]In this organ multiplicity is a criterion of T classification

2. The Principles of the TNM System

The practice of dividing cancer cases into groups according to so-called stages arose from the fact 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. These groups were often referred to as early cases and late cases, implying some regular progression with time. Actually, the stage of disease at the time of diagnosis may be a reflection not only of the rate of growth and extension of the neoplasm but also of the type of tumour and of the tumour-host relationship.

The staging of cancer is hallowed by tradition, and for the purpose of analysis of groups of patients it is often necessary to use such a method. The UICC believes that it is important to reach agreement on the recording of accurate information on the extent of the disease for each site, because the precise clinical description of malignant neoplasms and histopathological classification may serve a number of related objectives, namely

1. To aid the clinician in the planning of treatment
2. To give some indication of prognosis
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

The principal purpose to be served by international agreement on the classification of cancer cases by extent of disease is to provide a method of conveying clinical experience to others without ambiguity.

There are many bases or axes of tumour classification: for example, the anatomical site and the clinical and pathological extent of disease, the reported duration of symptoms or signs, the gender and age of the patient, and the histological type and grade. All of these bases or axes represent variables that are known to have an influence on the outcome of the disease. Classification by anatomical extent of disease as determined clinically and histopathologically (when possible) is the one with which the TNM system primarily deals.

The clinician's immediate task 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. In accomplishing this, the trend is away from "staging" to meaningful description, with or without some form of summarization.

To meet the stated objectives a system of classification is needed

1. whose basic principles are applicable to all sites regardless of treatment; and
2. which may be supplemented later by information that becomes available from histopathology and/or surgery.

The TNM system meets these requirements.

3. The General Rules of the TNM System

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:

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 (Pre-treatment clinical classification), designated TNM (or cTNM). This is based on evidence acquired before treatment. Such evidence arises from physical examination, imaging, endoscopy, biopsy, surgical exploration, and other relevant examinations.

(b) Pathological classification (Post-surgical histopathological classification), designated pTNM. This is based on the evidence acquired before treatment, supplemented or modified by the 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 nodes adequate to validate the absence of regional lymph node metastasis (pN0) and sufficient to evaluate the highest pN category. The pathological assessment of distant metastasis (pM) entails microscopic examination.

3. After assigning T, N, and M and/or pT, pN, and pM categories, these may be grouped into stages. The TNM classification and stage grouping, once established, must remain unchanged in the medical records. The clinical stage is essential to select and evaluate therapy, while the pathological stage provides the most precise data to estimate prognosis and calculate end results.

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 grouping.

5. In the case of multiple simultaneous 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 parentheses, e.g., T2 (m) or T2 (5). In simultaneous bilateral 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.

6. Definitions of TNM categories and stage grouping may be telescoped or expanded for clinical or research purposes as long as basic definitions recommended are not changed. For instance, any T, N, or M can be divided into subgroups.

4. Anatomical Regions and Sites

The sites in this classification are listed by code number of the International Classification of Diseases for Oncology[15].

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
- Stage grouping
- Summary for the region or site

5. TNM Clinical Classification

The following general definitions are used throughout: **5.1. T - Primary Tumour**

TX. Primary tumour cannot be assessed
T0. No evidence of primary tumour
Tis. Carcinoma in situ
T1, T2, T3, T4. Increasing size and/or local extent of the primary tumour

5.2. N - Regional Lymph Nodes

NX. Regional lymph nodes cannot be assessed
N0. No regional lymph node metastasis
N1. Regional lymph node metastasis

5.3. M - Distant Metastasis

MX. Distant metastasis cannot be assessed
M0. No distant metastasis
M1. Distant metastasis

The categories M1 and pM1 may be further specified according to the following notation:

Pulmonary	PUL	Bone marrow	MAR
Osseous	OSS	Pleura	PLE
Hepatic	HEP	Peritoneum	PER
Brain	BRA	Adrenals	ADR
Lymph nodes	LYM	Skin	SKI

Others	OTH		

6. pTNM Pathological Classification

The following general definitions are used throughout:

6.1. pT - Primary Tumour

pTX. Primary tumour cannot be assessed histologically
pT0. No histological evidence of primary tumour
pTis. Carcinoma in situ
pT1, pT2, pT3, pT4. Increasing size and/or local extent of the primary tumour histologically

6.2. pN - Regional Lymph Nodes

pNX. Regional lymph nodes cannot be assessed histologically
pN0. No regional lymph node metastasis histologically
pN1, pN2, pN3. Increasing involvement of regional lymph nodes histologically

Notes:

1. Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.
2. A tumour nodule in the connective tissue of a lymph drainage area without histologic evidence of residual lymph node is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. A tumour nodule with an irregular contour is classified in the pT category, i.e., discontinuous extension. It may also be classified as venous invasion (V classification).
3. When size is a criterion for pN classification, measurement is made of the metastasis, not of the entire lymph node.
4. 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) or pN2(mi)

6.3. 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:

pNX (sn). Sentinel lymph node could not be assessed
pN0 (sn). No sentinel lymph node metastasis
pN1 (sn). Sentinel lymph node metastasis

6.4. Isolated Tumour Cells

Isolated tumour cells (ITC) are single tumour cells or small clusters of cells not more than 0.2 mm in greatest dimension that are usually detected by immunohistochemistry or molecular methods, but which may be verified with H and E stains. 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-morphologic techniques such as flow cytometry or DNA analysis. These cases should be analysed separately[16]. Their classification is as follows.

pN0. No regional lymph node metastasis histologically, no examination for isolated tumour cells (ITC)
pN0(i-). No regional lymph node metastasis histologically, negative morphological findings for ITC
pN0(i+). No regional lymph node metastasis histologically, positive morphological findings for ITC
pN0(mol-). No regional lymph node metastasis histologically, negative non-morphological findings for ITC
pN0(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:

pN0 (i-)(sn). No sentinel lymph node metastasis histologically, negative morphological findings for ITC
pN0 (i+)(sn). No sentinel lymph node metastasis histologically, positive morphological findings for ITC
pN0 (mol-)(sn). No sentinel lymph node metastasis histologically, negative non-morphological findings for ITC
pN0 (mol+)(sn). No sentinel lymph node metastasis histologically, positive non-morphological findings for ITC

6.5. pM - Distant Metastasis

pMX. Distant metastasis cannot be assessed microscopically
pM0. No distant metastasis microscopically

pM1. Distant metastasis microscopically
The category pM1 may be further specified in the same way as M1 (see M - Distant Metastasis).

Isolated tumour cells found in bone marrow with morphological techniques are classified according to the scheme for N, e.g., M0(i+). For non-morphologic findings "mol" is used in addition to M0, e.g., M0(mol+).

6.6. Subdivisions of pTNM

Subdivisions of some main categories are available for those who need greater specificity (e.g., pT1a, 1b or pN2a, 2b).

7. Histopathological Grading

In most sites further information regarding the primary tumour may be recorded under the following heading:

G - Histopathological Grading

GX. Grade of differentiation cannot be assessed
G1. Well differentiated
G2. Moderately differentiated
G3. Poorly differentiated
G4. Undifferentiated

Notes:

- Grades 3 and 4 can be combined in some circumstances as "G3-4, Poorly differentiated or undifferentiated."
- The bone and soft tissue sarcoma classifications also use "high grade" and "low grade."
- Special systems of grading are recommended for tumours of breast, corpus uteri, and liver.

8. Additional Descriptors

For identification of special cases in the TNM or pTNM classification, the m, y, r, and a symbols are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis. **m Symbol**. The suffix m, in parentheses, is used to indicate the presence of multiple primary tumours at a single site. See TNM rule no. 5.
y Symbol. In those cases in which classification is performed during or following initial multimodality therapy, the cTNM or pTNM category is identified by a y prefix. The ycTNM or ypTNM categorizes the extent of

tumour actually present at the time of that examination. The y categorization is not an estimate of the extent of tumour prior to multimodality therapy.
r Symbol. Recurrent tumours, when classified after a disease-free interval, are identified by the prefix r.
a Symbol. The prefix a indicates that classification is first determined at autopsy.

9. Optional Descriptors

9.1. L - Lymphatic Invasion

LX. Lymphatic invasion cannot be assessed
L0. No lymphatic invasion
L1. Lymphatic invasion

9.2. V - Venous Invasion

VX. Venous invasion cannot be assessed
V0. No venous invasion
V1. Microscopic venous invasion
V2. Macroscopic venous invasion

Note: Macroscopic involvement of the wall of veins (with no tumour within the veins) is classified as V2.

9.3. C-Factor

The C-factor, or certainty factor, reflects the validity of classification according to the diagnostic methods employed. Its use is optional.

The C-factor definitions are:

C1. Evidence from standard diagnostic means (e.g., inspection, palpation, and standard radiography, intraluminal endoscopy for tumours of certain organs)
C2. Evidence obtained by special diagnostic means (e.g., radiographic imaging in special projections, tomography, computerized tomography [CT], ultrasonography, lymphography, angiography; scintigraphy; magnetic resonance imaging [MRI]; endoscopy, biopsy, and cytology)
C3. Evidence from surgical exploration, including biopsy and cytology
C4. Evidence of the extent of disease following definitive surgery and pathological examination of the resected specimen
C5. Evidence from autopsy

Example: Degrees of C may be applied to the T, N, and M categories. A case might be described as T3C2, N2C1, M0C2.

The TNM clinical classification is therefore equivalent to C1, C2, and C3 in varying degrees of certainty, while the pTNM pathological classification generally is equivalent to C4.

10. Residual Tumour (R) Classification

The absence or presence of residual tumour after treatment is described by the symbol R. More details can be found in the TNM Supplement (see footnote 11).

TNM and pTNM describe the anatomical extent of cancer in general without considering treatment. They can be supplemented by the R classification, which deals with tumour status after treatment. It reflects the effects of therapy, influences further therapeutic procedures and is a strong predictor of prognosis.

The definitions of the R categories are:

RX. Presence of residual tumour cannot be assessed
R0. No residual tumour
R1. Microscopic residual tumour
R2. Macroscopic residual tumour

11. Stage Grouping

Classification by the TNM system achieves reasonably precise description and recording of the apparent anatomical extent of disease. A tumour with four degrees of T, three degrees of N, and two degrees of M will have 24 TNM categories. For purposes of tabulation and analysis, except in very large series, it is necessary to condense these categories into a convenient number of TNM stage groups.

Carcinoma in situ is categorized stage 0; cases with distant metastasis stage IV (except at certain sites, e.g., papillary and follicular carcinoma of thyroid).

The grouping adopted is such as to ensure, as far as possible, that each group is more or less homogeneous in respect of survival, and that the survival rates of these groups for each cancer site are distinctive.

For pathological stage grouping, if sufficient tissue has been removed for pathologic examination to evaluate the highest T and N categories, M1 may be either clinical (cM1) or pathologic (pM1). However, if only a distant metastasis has had microscopic confirmation, the classification is pathologic (pM1) and the stage is pathologic.

12. Site Summary

As an aide-mémoire or as a means of reference, a simple summary of the chief points that distinguish the most important categories is added at the end of each site. These abridged definitions are not completely adequate, and the full definitions should always be consulted.

13. Related Classifications

Since 1958, WHO has been involved in a programme aimed at providing internationally acceptable criteria for the histologic diagnosis of tumours. This has resulted in the International Histological Classification of Tumours, which contains, in an illustrated multivolume series, definitions of tumour types and a proposed nomenclature. A new series, WHO Classification of Tumours-Pathology and Genetics of Tumours, continues this effort. The publications can be ordered online at www.iarc.fr/who-bluebooks/ or by email, iarcpress@who.int.

The WHO International Classification of Diseases for Oncology (ICD-O) (see footnote 15) s a coding system for neoplasms by topography and morphology and for indicating behaviour (e.g., malignant, benign). This coded nomenclature is identical in the morphology field for neoplasms to the Systematized Nomenclature of Medicine (SNOMED)[17].

In the interest of promoting national and international collaboration in cancer research and specifically of facilitating cooperation in clinical investigations, it is recommended that the WHO Classification of Tumours be used for classification and definition of tumour types and that the ICD-O code be used for storage and retrieval of data.

End Notes

1.	Denoix PF: Bull Inst Nat Hyg (Paris) 1944;1:69. 1944;2:82. 1950;5:81. 1952;7:743.
2.	World Health Organization Technical Report Series, number 53, July 1952, pp. 47–48
3.	International Union Against Cancer (UICC), Committee on Clinical Stage Classification and Applied Statistics: Clinical stage classification and presentation of results, malignant tumours of the breast and larynx. Paris; 1958.
4.	International Union Against Cancer (UICC), Committee on Stage Classification and Applied Statistics: Clinical stage classification and presentation of results, malignant tumors of the breast. Paris; 1959.
5.	International Union Against Cancer (UICC): TNM Classification of malignant tumours. Geneva; 1968.
6.	International Union Against Cancer (UICC): TNM General Rules. Geneva; 1969.
7.	International Union Against Cancer (UICC): TNM Classification of malignant tumours. 2nd ed. Geneva; 1974.
8.	International Union Against Cancer (UICC): TNM Classification of malignant tumours. 3rd ed. Harmer MH, ed. Geneva; 1978. Enlarged and revised 1982.
9.	International Union Against Cancer (UICC): TNM Classification of malignant tumours. 4th ed. Hermanek P, Sobin LH, eds. Berlin,

	Heidelberg, New York: Springer Verlag; 1987. Revised 1992.
10.	International Union Against Cancer (UICC): TNM Supplement 1993. A commentary on uniform use. Hermanek P, Henson DE, Hutter RVP, Sobin LH, eds. Berlin, Heidelberg, New York: Springer Verlag; 1993.
11.	International Union Against Cancer (UICC): TNM Supplement. A commentary on uniform use. 2nd ed. Wittekind Ch, Henson DE, Hutter RVP, Sobin LH, eds. New York: Wiley; 2001.
12.	International Union Against Cancer (UICC): Prognostic factors in cancer. Hermanek P, Gospodarowicz MK, Henson DE, Hutter RVP, Sobin LH, eds. Berlin, Heidelberg, New York: Springer Verlag; 1995.
13.	International Union Against Cancer (UICC): Prognostic factors in cancer. 2nd ed. Gospodarowicz MK, Henson DE, Hutter RVP, O'Sullivan B, Sobin LH,Wittekind Ch, eds. New York: Wiley; 2001.
14.	Greene FL, Page D, Morrow M, Balch C, Haller D, Fritz A, Fleming I, eds. AJCC Cancer Staging Manual, 6th ed. New York: Springer; 2002.
15.	Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, eds. WHO International Classification of Diseases for Oncology ICD-O, 3rd ed. Geneva: WHO; 2000.
16.	Hermanek P, Hutter RVP, Sobin LH, Wittekind Ch. Classification of isolated tumor cells and micrometastasis. Cancer 1999;86:2668–2673.
17.	*SNOMED International: The systematized nomenclature of human and veterinary medicine*, Northfield, Ill: College of American Pathologists, `http://snomed.org`

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