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 Poche5 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 editions7,8 were published containing new site classifications, and the fourth edition of TNM in 1987.9

In 1993, the project published the TNM Supplement10 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
non-anatomical, at each of the body sites. This was expanded in the second edition in 2001\textsuperscript{16} and the third edition in 2006.\textsuperscript{17}

The current eighth edition of TNM contains rules of classification and staging that correspond with those appearing in the eighth edition of the \textit{AJCC Cancer Staging Manual} (2017).\textsuperscript{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.

\textbf{Note}

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

\textbf{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 facilitating 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

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:

\[ T_0, T_1, T_2, T_3, T_4, N_0, N_1, N_2, N_3, M_0, M_1 \]

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. 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**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1–T4</td>
<td>Increasing size and/or local extent of the primary tumour</td>
</tr>
</tbody>
</table>
**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:

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

**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 N1. These cases should be analysed separately.20 Their classification is as follows.

\[
\begin{align*}
(p)N0 & \quad \text{No regional lymph node metastasis histologically, no examination for isolated tumour cells (ITC)} \\
(p)N0(i–) & \quad \text{No regional lymph node metastasis histologically, negative morphological findings for ITC} \\
(p)N0(i+) & \quad \text{No regional lymph node metastasis histologically, positive morphological findings for ITC} \\
(p)N0(mol–) & \quad \text{No regional lymph node metastasis histologically, negative non-morphological findings for ITC} \\
(p)N0(mol+) & \quad \text{No regional lymph node metastasis histologically, positive non-morphological findings for ITC} \\
\end{align*}
\]

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

\[
\begin{align*}
(p)N0(i–)(sn) & \quad \text{No sentinel lymph node metastasis histologically, negative morphological findings for ITC} \\
(p)N0(i+)(sn) & \quad \text{No sentinel lymph node metastasis histologically, positive morphological findings for ITC} \\
(p)N0(mol–)(sn) & \quad \text{No sentinel lymph node metastasis histologically, negative non-morphological findings for ITC} \\
(p)N0 (mol+)(sn) & \quad \text{No sentinel lymph node metastasis histologically, positive non-morphological findings for ITC} \\
\end{align*}
\]

**pM – Distant Metastasis***

pM1 \quad \text{Distant metastasis microscopically confirmed}

**Note**

* pM0 and pMX are not valid categories.
The category pM1 may be further specified in the same way as M1 (see page 6).

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

**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’.
- Special systems of grading are recommended for tumours of breast, corpus uteri, and prostate.

**Additional Descriptors**

For identification of special cases in the TNM or pTNM classification, the m, y, r, and a symbols may be 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 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.

Optional Descriptors

L – Lymphatic Invasion

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

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.

Pn – Perineural Invasion

PnX Perineural invasion cannot be assessed
Pn0 No perineural invasion
Pn1 Perineural invasion

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 Preface, Reference 3).

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.

Note
* Some consider the R classification to apply only to the primary tumour and its local or regional extent. Others have applied it more broadly to include distant metastasis. The specific usage should be indicated when the R is used.

Stage and Prognostic Groups

The TNM system is used to describe and record the anatomical extent of disease. For purposes of tabulation and analysis it is useful to condense these categories into groups. For consistency, in the TNM system, carcinoma in situ is categorized stage 0; in general, tumours localized to the organ of origin as stages I and II, locally extensive spread, particularly to regional lymph nodes as stage III, and those with distant metastasis as stage IV. The stage 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 stages, if sufficient tissue has been removed for pathological examination to evaluate the highest T and N categories, M1 may be either clinical (cM1) or pathological (pM1). However, if only a distant metastasis has had microscopic confirmation, the classification is pathological (pM1) and the stage is pathological.

Although the anatomical extent of disease, as categorized by TNM, is a very powerful prognostic indicator in cancer, it is recognized that many factors have a significant impact on predicting outcomes. This has resulted in different stage groups. In thyroid cancer there are different stage definitions for different histologies and, new to this edition, in oropharyngeal cancer HPV-related cancer is staged differently from non-HPV-related cancer. Some factors have been combined with TNM in the development of stage groupings; for instance, for different histologies (thyroid), different major prognostic factor groups (age in thyroid), and by aetiology (HPV-related oropharyngeal cancer). In this edition the term stage has been used as defining the anatomical extent of disease while prognostic group for classifications that incorporate other prognostic factors. Historically, age in
differentiated thyroid cancer and grade in soft tissue sarcoma are combined with anatomical extent of disease to determine stage, and stage is retained rather than prognostic group in these two sites.

**Prognostic Factors Classification**

Prognostic factors can be classified as those pertaining to:

- **Anatomic extent of disease**: describes the extent of disease in the patient at the time of diagnosis. Classically, this is TNM but may also include tumour markers that reflect tumour burden, for instance prostate-specific antigen (PSA) in prostate carcinoma or carcinoembryonic antigen (CEA) in colorectal carcinoma.

- **Tumour profile**: this includes pathological (i.e., grade) and molecular features of a tumour, and gene expression patterns that reflect behaviour. These can be:
  - predictive factors
  - prognostic factors
  - companion diagnostic marker.

- **Patient profile**: this includes terms related to the host of the cancer. These can be demographic factors, such as age and gender, or acquired, such as immunodeficiency and performance status.

- **Environment**: this may include treatment-related and education (expertise, access, ageism, and healthcare delivery) and quality of management.

When describing prognostic factors it is important to state what outcome the factors are prognostic for, and at what point in the patient trajectory. Anatomical extent of disease as described by TNM stage defines prognosis for survival.

In the second edition of the UICC TNM Classification of Malignant Tumours for each tumour site, grids were developed that identified prognostic factors for survival at time of diagnosis and whether they were considered to be essential, additional, or new and promising. The grids were updated for the third edition and have been further updated and incorporated into the ninth edition of the UICC Manual of Clinical Oncology. Essential factors are those that are required in addition to anatomical extent of disease to determine treatment as identified by published clinical practice guidelines. The table is a generic example of the prognostic factors summary grid. The grids from the ninth edition of the UICC Manual of Clinical Oncology are reproduced in this eighth edition. Grids are not available for some of the less common tumours.
Examples of the UICC prognostic factors summary ‘grid’

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Tumour related</th>
<th>Host related</th>
<th>Environment related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential*</td>
<td>Anatomical disease extent</td>
<td>Age</td>
<td>Availability of access to radiotherapy</td>
</tr>
<tr>
<td></td>
<td>Histological type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional</td>
<td>Tumour bulk</td>
<td>Race</td>
<td>Expertise of a treatment at the specific level (e.g., surgery or radiotherapy)</td>
</tr>
<tr>
<td></td>
<td>Tumour marker level</td>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Programmed death 1 (PD-1) receptor and its ligands (PD-L1)</td>
<td>Cardiac function</td>
<td></td>
</tr>
<tr>
<td>New and promising</td>
<td>Epidermal growth factor receptor</td>
<td>Germline p53</td>
<td>Access to information</td>
</tr>
<tr>
<td></td>
<td>Gene expression patterns</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The origin of essential factors as imperatives for treatment decisions are from known and available clinical practice guidelines.


**Essential TNM**

Information on anatomical extent of disease at presentation or stage is central to cancer surveillance to determine cancer burden as it provides additional valuable information to incidence and mortality data. However, cancer registries in low and middle income countries frequently have insufficient information to determine complete TNM data, either because of inability to perform necessary investigations or because of lack of recording of information. In view of this, the UICCTNM Project has with the International Agency for Research in Cancer and the National Cancer Institute developed a new classification system ‘Essential TNM’ that can be used to collect stage data when complete information is not available. To date, Essential TNM schemas have been developed for breast, cervix, colon, and prostate cancer, and are presented in this edition and available for download at www.uicc.org.

**Paediatric Tumours**

Since the fourth edition, the UICC TNM Classification of Malignant Tumours has not incorporated any classifications of paediatric tumours. This decision has stemmed from the lack of an international standard staging system.
Introduction

for many paediatric tumours. To enable stage data collection by population-based cancer registries there needs to be agreement on cancer staging. Recognition of this led to a consensus meeting held in 2014 and resulted in the publication of recommendations on the staging of paediatric malignancies for the purposes of population surveillance. The classifications published are not intended to replace the classifications used by the clinician when treating an individual patient but instead to facilitate the collection of stage by population-based cancer registries.

Related Classifications

Since 1958, WHO has been involved in a programme aimed at providing internationally acceptable criteria for the histological 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. (Information on these publications is at www.iarc.fr).

The WHO International Classification of Diseases for Oncology (ICD-O-3) is 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).

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-3 code be used for storage and retrieval of data.

References
