UNION FOR INTERNATIONAL CANCER CONTROL

TNM Supplement

A Commentary on Uniform Use

Fifth Edition

Edited by
Christian Wittekind, James D. Brierley, Anne Lee and Elisabeth van Eycken

WILEY Blackwell

TNM Supplement

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PREFACE

First published in 1987 [1], and revised in 1992 [2], the fourth edition of the *TNM Classification of Malignant Tumours* was the result of a push from all national TNM committees towards the establishment of a uniform classification system that could be used worldwide. It was, therefore, the first edition of the text in which the featured classification criteria were identical to those detailed in the fourth edition of the AJCC's *Manual for Staging of Cancer of the American Joint Committee on Cancer* [3].

Although the classification system was, by 1987, widely accepted, medical professionals had pointed out that some of its definitions and rules for staging were imprecise and could lead to inconsistency in its application. Discrepant understandings of organ classifications, general rules and, in particular, the requirements of pathological classification (pT, pN) were all potential risks.

In an effort to address these concerns, the TNM Project Committee of the UICC collected and reviewed criticisms and suggestions from the national TNM committees, as well as from registries, oncological associations and individual users. The solution that they found was to complement the fourth edition of the *TNM Classification* [1, 2] with the publication of a new book: the *TNM Supplement* [4]. Designed to provide guidance on the uniform use of the classification system, the first edition of this new text was published in 1993.

By 1997, the *TNM Classification* was in its fifth edition [5], though most descriptions of tumour sites had remained largely unchanged, with only minor additions made so as to reflect new data on prognosis and new methods of outcome assessment. The TNM Project Committee of the UICC was aware that not all classification proposals and updates received could be included in this fifth edition and so the decision was made to produce another *TNM Supplement* within which they may be accommodated [6]. The second edition of the *TNM Supplement* therefore comprised, for the most part, of the first edition's contents, amended to include a number of new items.

Retaining much of its predecessor's content, the sixth edition of the *TNM Classification* [7] again featured only small revisions but was elaborated upon in a third edition of the *TNM Supplement* [8].

The *TNM Classification*'s seventh edition [9] saw the inclusion of several novel tumour classifications. While comments on the new entities and modifications concerned had been published elsewhere [10], it was nevertheless deemed

important to highlight and examine these with a fourth edition of the *TNM Supplement* [11].

In the current, eighth edition of the *TNM Classification* [12], the featured tumour sites are much the same as those found in the book's previous edition. Some hitherto unexamined tumour entities and anatomic sites have, however, been introduced, while others have seen their analyses modified and revised to take account of new data on prognosis and prognosis assessment [13]. This strategy is in accord with the core philosophy of maintaining the classification system's stability over time.

A new approach was adopted in the *TNM Classification*'s seventh edition [9] that helped to distinguish stages from prognostic groupings. This has been expanded upon in the eighth edition, which introduces new clinical and pathological stages for some tumour entities. Additionally, a helpful overview of prognostic factors for different tumour entities has been given. These prognostic factor grids are based on former publications of the UICC and have been expanded to reflect new data [14–16].

This fifth edition of the *TNM Supplement* contains a number of changes. While the previous edition's contents have been largely preserved, feedback from users of the TNM classification and the TNM Help Desk (https://www.uicc.org/tnm-help-desk) has helped to refine and clarify certain elements. Two chapters of 'Explanatory Notes' have, for example, been reworked so that anatomical sites and subsites, regional lymph nodes, and T, N and M categories are more precisely defined. Elsewhere, a chapter discussing 'Pending Questions and Problems' has been added, while the minimum requirements for the pathological classification of individual tumour sites and entities are now described in a chapter on 'Site-Specific Requirements for pT and pN'.

Since the publication of the eighth edition of the *TNM Classification*, the UICC TNM Project Committee has reviewed several recommended changes and amendments, the details of which are outlined in this *TNM Supplement*'s fourth and fifth chapters, entitled 'New TNM Classifications Recommended for Testing and Other Classifications' and 'Optional Proposals for Testing New Subcategories of TNM', respectively. Relevant references have been included wherever data exist to support these recommendations. Where they do not, it may be assumed that such proposals are based on either anecdotal experience or more general considerations. All proposals included are based on the principle of ramification, whereby the T, N and M categories featured in the *TNM Classification*, eighth edition, remain unchanged but optional subdivisions are provided within specific categories. After classifying according to these subdivisions, one may determine to what extent a change of the present categories improves the classification process with respect to prognostic statements or the choice of treatment.

In light of the development of new techniques in molecular biology, the most important and widely used methods of enhancing the accuracy of the TNM classification system have also been presented here. Furthermore, several authors have emphasized that, in the current era of evidence-based medicine, future amendments must be substantiated with data [13, 17]. Others have raised questions regarding the use and interpretation of TNM in specific situations. These, along with informative answers, can be found in the sixth chapter of this supplement: 'Frequently Asked Questions'.

The present stage groupings – as defined in the *TNM Classification*, eighth edition [12] – are generally based on the anatomical extent of disease, represented by T, N and M or pT, pN and pM. For some tumour sites or entities, however, additional factors are included. These are as follows:

Histologic type	Thyroid
Age	Thyroid
Grade	Gastrointestinal neuroendocrine tumours
	Appendix carcinoma
	Bone
	Soft tissues
Mitotic rate	GIST
Tumour markers	Testis

- For oesophageal carcinoma (excluding the anatomical stage), an additional prognostic grouping is provided to encompass squamous cell carcinoma and adenocarcinoma. This group takes into account grade and – for squamous cell carcinoma – location.
- For gestational trophoblastic tumours, a prognostic grouping is provided that considers T/pT, M/pM and relevant risk factors.
- As more non-anatomic prognostic factors become available, this approach may provide a means of separating extent-of-disease staging from prognostic grouping.

Both the AJCC and the TNM Project Committee of the UICC recognize that, in addition to the anatomical extent of disease pre- and post-initial treatment, the residual tumour status after treatment – i.e. the R (residual tumour) classification – and other non-anatomical factors (e.g. host factors, biochemical markers, DNA analysis, oncogenes, oncogene products) may be important when estimating outcome. TNM and R aside, these prognostic factors are currently under investigation and it can be assumed that their roles in treatment planning, analysis of treatment and design of future clinical trials will grow.

The eighth edition of the *TNM Classification* [12] contains rules of classification and staging that correspond to those in the eighth edition of 2017's AJCC *Cancer Staging Manual* [18] and have approval of all national TNM committees.

Institutions and physicians interested in the further development of the TNM system are encouraged to test the recommendations included in this supplement. These may concern the ramification of existing classifications or the classification of new tumour sites and entities. Equally, they may concern methods of enhancing the accuracy of the TNM system over the years to come. Publication of both retrospective and prospective studies is desired. The TNM Project Committee would appreciate receiving relevant information and is available to provide further details and consultation.

The TNM Prognostic Factors Project welcomes comments from TNM users.

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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 Cancer Research
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 renamed the Committee on TNM Classification. With new prognostic factors taken into consideration, the committee was renamed twice more, becoming the TNM Prognostic Factors Project Committee in 1994 and then the TNM Prognostic Factors Core Group in 2003.

UICC TNM Prognostic Factors Core Group: 2018

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ABBREVIATIONS

a	autopsy, p. 23
c	clinical, p. 1
G	histopathological grading, p. 26
ICD-O	International Classification of Diseases for Oncology, 3rd edition, 2000
ITC	isolated tumour cells, p. 10
L	lymphatic invasion, p. 24
m	multiple tumours, pp. 5 and 20
M	distant metastasis, p. 11
N	regional lymph node metastasis, p. 9
p	pathological, p. 1
Pn	perineural invasion, p. 24
r	recurrent tumour, p. 21
R	residual tumour after treatment, p. 15
sn	sentinel lymph node, p. 11
Stage	anatomical Stage, p. 13
T	extent of primary tumour, p. 7
V	venous invasion, p. 24
y	classification after initial multimodality treatment, p. 20

Substantial changes in the 2019 fifth edition compared with the 2012 fourth edition are marked by a bar at the left-hand side of the page.

CHAPTER 1

EXPLANATORY NOTES – GENERAL

The General Rules of the TNM System

General Rule No. 1

All cases should be confirmed microscopically as malignant tumours including histological type. Any cases not so proved must be reported separately.

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

Examples

Microscopic confirmation of choriocarcinoma is not required if the serum/urine βHCG level is abnormally elevated.

Microscopic confirmation of hepatocellular carcinoma is not required if the serum AFP level is abnormally elevated in the presence of characteristic radiological appearance.

General Rule No. 2 (Table 1.1)

Two classifications are described for each site, namely:

(a) *Clinical classification:* the pre-treatment clinical classification designated TNM (or cTNM) is used to select and evaluate therapy. This is based on evidence acquired before treatment. Such evidence is based on physical examination, imaging, endoscopy, biopsy, surgical exploration and other relevant examinations.

(b) *Pathological classification:* the post-surgical histopathological classification, designated pTNM, is used to guide adjuvant therapy and provides additional data to estimate prognosis and calculate end results. This is based on evidence acquired before treatment, supplemented or modified by additional evidence acquired from surgery and from pathological examination.

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Table 1.1 Definitions of various TNM terms

Definitions

1. **Cancer stage** (a noun) – 'the stage'
   The UICC has defined the term 'stage' as the anatomical extent of disease (UICC 8th edition [2, 3]).
2. **Cancer staging** (a verb) – 'to stage'
   It refers to the process of deriving the 'stage'. This includes the investigational work-up, most usually examination and imaging studies, or, alternatively, verifying or consulting the T, N and M category definitions and combinations.
3. **Stage migration**
   The term 'stage migration' describes a change in the proportion of T, N or M categories following introduction of new means of assessing disease extent in populations of patients rather than in individual patients.
4. **Stage shift**
   The term 'stage shift' describes a change in the pattern of stage distribution within a defined population to a lower stage following the introduction of early detection or screening programs, or to a higher stage when access to care becomes limited.
5. **Downstaging/downsizing/upstaging/understaging**
   - The term 'downstaging' is used to describe a reduction in the T or N category after neoadjuvant therapy.
   - The term 'downsizing' is used to describe a reduction in size of the tumour after neoadjuvant therapy.
   - The terms 'upstaging' and 'understaging' are occasionally used, and typically relate to different diagnostic accuracy of various staging investigations. We do not recommend their use.

The pathological assessment of the regional lymph nodes (pN) entails removal of at least one lymph node to validate the absence or presence of cancer. It is not necessary to pathologically confirm the status of the highest N category to assign the pN. The assignment of the regional lymph nodes (pN) requires pathological assessment of the primary tumour (pT), except in cases of an unknown primary (T0).

An excisional biopsy of a lymph node without assessment of the pT category is insufficient to fully evaluate the pN category and is considered a clinical classification.

Example

The examination of axillary lymph nodes (sentinel lymph node or non-sentinel lymph nodes) with only a biopsy diagnosis of the primary tumour in the breast is classified as cN, e.g. cN1, if there are metastases in movable ipsilateral level I, II axillary lymph node(s).

The pathological assessment of distant metastasis (pM1) entails microscopic examination.

TNM is a dual system that includes a clinical (pre-treatment or after neoadjuvant radio-/chemo-/radiochemotherapy but before surgery) and a pathological (post-surgical histopathological) classification. It is imperative to differentiate between them since they are based on different methods of examination and serve different purposes. The clinical classification is designated TNM or cTNM; the pathological, pTNM. When TNM is used without a prefix, it implies the clinical classification (cTNM). Microscopic confirmation does not in itself justify the use of pT. The requirements for pathological classification are described in Chapter 3 on page 157.

Biopsy provides the diagnosis, including histological type and grade (if possible). 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 determines 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 Chapter 3, page 157). Therefore, for an individual patient there should be a clinical classification, e.g. cT2cN1cM0 and a pathological classification pT2pN2cM0.

Note.

The various T, N and M categories as well as the categories of optional classifications like R, L, V, G should be written as common Arabic numerals, not as subscripts, e.g. T1 (not T_1) and N3 (not N_3). Stages are designated by Roman numerals.

General Rule No. 3

After assigning cT, cN and cM and/or pT, pN and pM categories, these may be grouped into stages. The TNM classification and stages, 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 cT2cN0cM0 is made in one hospital and is later updated to cT2cN1cM0 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.

Following 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 pT1pNXcM0; the subsequent right hemicolectomy contains two regional lymph nodes with tumour and a suspicious metastatic focus in the liver, later found to be a haemangioma, is excised: pT0pN1cM0. The definitive pTNM classification consists of the results of both operative specimens: pT1pN1bcM0 (Stage IIIA).

If an initial local excision of a rectal carcinoma is performed and the margins are positive the stage may be pT1pNXcM0, R1.

If radiotherapy is given, followed by anterior resection and there is no residual disease, the stage is ypT0pN0cM0, R0.

The definitive classification is ypT0pN0cM0, R0.

Note.

Assignment of the 'y' as an additional descriptor for cases involving multimodality therapy is described on page 20.

For an estimation of the final stage, clinical and pathological data may be combined when only partial information is available in either the pathological classification or the clinical classification. See examples below.

It is important to note that the category is defined by whether it is determined clinically or pathologically. Stage should not be assigned as is not clinical or pathological.

However, for surveillance purposes stage data are lost if clinical and pathological data are not combined when only partial information is available either in the clinical classification or pathological classification. The term harmonized stage, hTNM, has been proposed.

Example

A CT scan reveals a bladder cancer but there is no evidence of lymph node metastasis and the clinical stage is cT3bcN0cM0, cStage IIIA. A cystectomy is performed and the pT category is pT2 but there are no lymph nodes in the specimen so the pN category is pNX. The stage is therefore pT2bpNXcM0 and a pathological stage cannot be assigned but a combined harmonized stage group can be assigned as hStage II.

'X' denotes the absence or uncertainty of assigning a given category (T or N) when all reasonable clinical or pathological methods of assessment have been

used or are unavailable to assess the patient. 'X' should not be used to simply fill in the blanks when data are unavailable to one individual on the assessment team. For further discussion on the meaning and application of X (e.g. NX) see Greene et al. [1].

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 stages.

Example
Sonography of the liver: suspicious lesion but no definitive evidence of metastasis - assign cM0 (not cM1).

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

Example
Colorectal carcinoma, pre-operative examination of the liver: sonography, suspicious, but no evidence of metastasis; CT, evidence of metastasis. The results of CT determine the classification: cM1. If a biopsy is performed and metastases are confirmed, then it would be classified as pM1. However, if CT were negative, the case would be classified cM0.

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(5) or T2(m). In simultaneous bilateral cancers of paired organs, each tumour should be classified independently. In tumours of the liver (HCC), intrahepatic bile ducts (ICC) as well as 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 non-invasive tumours
   b) Multiple invasive tumours
   c) Multiple invasive tumours with associated non-invasive tumours (carcinoma in situ)

d) A single invasive tumour with an associated non-invasive tumour (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(4) or T2(m).

For (c) and (d) the presence of an 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 tumours at these sites with the highest T category should be classified and the multiplicity of the number of tumours should be indicated in parentheses, e.g. T2(5) or T2(m).

Combining multiple carcinomas of skin should be done only with subsites (C44.5-7 or C63.2) [3]. Carcinomas of the skin of the head and neck should only be combined with carcinomas of the skin of the head and neck. A carcinoma of the skin in subsite C44.3 and a synchronous one in subsites C44.6 and C44.7 should be classified as synchronous tumours.

Examples of sites for separate classifications of two tumours are:

- Oropharynx and hypopharynx
- Submandibular gland and parotid gland
- Urinary bladder and urethra (separate tumours)
- Skin carcinoma of the eyelid and skin carcinoma of the head and neck, since both have their own classifications

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
- Skin carcinoma of the abdominal wall and the back (both part of the trunk)

Cancer Registries have their own rules to decide on multiple tumours in order to improve comparability and uniformity in cancer incidence reporting. These rules should be clearly documented when reporting.

For tumours of the colon or rectum in different localizations it is recommended to classify those tumours separately; e.g. a carcinoma of the ascending colon and one of the sigmoid colon should be classified separately, particularly because the regional lymph nodes are defined differently (see *TNM Classification of Malignant Tumours*, 8th edition [2], pages 73–74).

Second or subsequent primary cancers occurring in the same organ or in different organs after initial treatment are staged independently and are known as metachronuous primary tumours. Such cancers are not staged using the prefix 'y'.

For systemic or multicentric cancers potentially involving many discrete organs, four histological groups – malignant lymphomas, leukemias, Kaposi sarcoma and mesothelioma – are included. They are counted only once in any individual.

A tumour in the same organ with a different histologic type is counted as a new tumour, e.g. lung carcinomas (see page 88).

The TNM Clinical and Pathological Classifications

T/pT Classification

1. When size is a criterion for the T/pT category, it is a measurement of the invasive component. If in the breast, for example, there is a large in situ component (e.g. 4 cm) and a small invasive component (e.g. 0.5 cm), the tumour is coded for the invasive component only, i.e. pT1a.
2. Neither in the TNM Classification nor in the 1st [5] to 4th edition [6–8] of the TNM Supplement are there any statements concerning the way to measure tumour size for pT classification. According to the AJCC *Cancer Staging Manual*, 2017 [3], 'pT is derived from the actual measurement of the unfixed tumour in the surgical specimen. It should be noted, however, that up to 30% shrinkage of soft tissues may occur in the resected specimen'. Thus, in cases of discrepancies of clinically and pathologically measured tumour size, the clinical measurement should also be considered for the pT classification.

   In some cases, especially with those tumour entities where size is important for the pT category, it may be necessary to correlate the macroscopic size (fixed or infixed) with the microscopic size. A thorough calculation of the latter should be the basis for the size calculation.
3. Penetration or perforation of visceral serosa is a criterion for the T classification of some tumour sites, e.g. stomach, colon, rectum, liver (HCC and ICC), gallbladder, lung, ovary. It may be confirmed by histological examination of biopsies or resection specimens or by cytological examination of specimens obtained by scraping the serosa overlying the primary tumour.
4. The microscopic presence of a tumour in lymphatic vessels or veins does not qualify as local spread of the tumour and does not affect the cT/pT category (except for liver (HCC and ICC), testis, kidney and penis). It can be recorded separately (*TNM Classification*, 8th edition, page 10 [2]).

5. A tumour in perineural spaces at the primary site is considered part of the T classification, but can also be recorded separately as Pn1 (*TNM Classification*, 8th edition, [2], page 10), as it may be an independent prognostic factor.

   Example
   In carcinoma of the uterine cervix, direct invasion beyond the myometrium of the uterine cervix qualifies as parametrial invasion with T2a/b, but not if based only on the discontinuous presence of tumour cells in lymphatics of the parametrium. The L (lymphatic invasion) and V (venous invasion) symbols (*TNM Classification*, 8th edition [2], page 10) can be used in this case to record lymphatic and venous involvement.

6. Direct spread of tumour into an adjacent organ, e.g. the liver from a gastric primary, is recorded in the T/pT classification and is not considered to be distant metastasis.

   Direct spread of the primary tumour into regional lymph nodes is classified as lymph node metastasis.
7. The very uncommon cases with direct extension into an adjacent organ or structure not mentioned in the T definitions are classified as the highest T category.
8. Tumour spillage during surgery is considered a criterion in the T classification of tumours of ovary, Fallopian tube and primary peritoneal carcinoma. For all other tumours, tumour spillage does not affect the TNM classification or stages.

   Note.
   In tumours of the uterus (endometrium) positive cytology should be reported separately without change of the stage.

Regional Lymph Nodes

1. If a tumour involves more than one site or subsite, e.g., contiguous extension to another site or subsite, the regional lymph nodes include those of all involved sites and subsites.

   Example
   Carcinoma of the sigmoid colon involving the small intestine (jejunum): the regional lymph nodes are those for the sigmoid colon, i.e. the sigmoid, left colic, superior rectal (haemorrhoidal), inferior mesenteric and rectosigmoid as well as those for the small intestine, i.e. the mesenteric nodes including the superior mesenteric nodes.

2. In rare cases, one finds no metastases in the regional lymph nodes, but only in lymph nodes that drain an adjacent organ directly invaded by the primary tumour. The lymph nodes of the invaded site are considered regional as those of the primary site for N classification.

Example
Carcinoma of the stomach with direct extension into an adjacent small bowel loop: perigastric lymph nodes are tumour-free, but metastases of 0.5 cm size are found in two mesenteric lymph nodes in the vicinity of the invaded small bowel – this is classified as pT4bpN1M0 (Stage IIIC) for cancer of the stomach.

N/pN Classification

1. The clinical category N0 ('no regional lymph node metastasis') includes lymph nodes not clinically suspicious for metastasis even if they are palpable or visualized with imaging techniques. The clinical category N1 ('regional lymph node metastasis') is used when there is sufficient clinical evidence, such as firmness, enlargement or specific imaging characteristics. The term 'adenopathy' is not precise enough to indicate lymph node metastasis and should be avoided.
2. Size of lymph nodes: in advanced lymphatic spread, one often finds perinodal tumour and the confluence of several lymph node metastases into one large tumour conglomerate. In the definition of the N classification, the perinodal component should be included in the size for isolated lymph node metastasis; for conglomerates, the overall size of the conglomerate should be considered and not only the size of the individual lymph nodes.
3. Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.
4. Tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the lymph drainage area of a primary carcinoma that are discontinuous from the primary carcinoma and without histological evidence of residual lymph node or identifiable vascular or neural structures. If a vessel is identifiable on H&E, elastic or other stains, it should be classified as venous invasion (V1/2) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1). The presence of tumour deposits does not change the T categories of the primary tumour. This rule is to be followed particularly in tumours of the colon and rectum as well as in tumours of the appendix and may be applicable to other tumour sites.
5. The reliability of the pN classification depends on the number of histologically examined regional lymph nodes. Thus, it is recommended to add the number of examined and involved lymph nodes in parentheses to the pN category, e.g. in colorectal tumours pN1b (3/15).

   For the various organs the number of lymph nodes ordinarily included in the lymph node dissection specimen is stated. If the lymph nodes are negative, but the number ordinarily examined is not met, pN0 is classified. The addition of the number of lymph nodes (in colon tumours, e.g. 0/4) characterizes the reliability of the pN classification.

6. Metastasis in any lymph node other than regional is classified as a distant metastasis. If there is doubt concerning the correct category to which a particular case should be allotted, then the lower (i.e. less advanced) category should be chosen.
7. When size is a criterion for pN classification, measurement is made of the metastasis, not of an entire lymph node. However, for the cN classification only, the overall size of the lymph node should be considered.
8. Invasion of lymphatic vessels (tumour cells in endothelium-lined channels, so-called lymphangiosis carcinomatosa or lymphangitic spread) in a distant organ is coded as pM1, e.g. lymphangitic spread in the lung from prostate carcinoma or liver cell carcinoma.
9. 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). If deposits of tumour cells are 0.2 mm or smaller they are likely to be considered isolated tumour cells (see below).
10. 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 to include a cluster of fewer than 200 cells in a single histological cross-section [10]. 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. ITCs may be apparent with routine histological stains as well as with immunohistochemical methods. ITCs do not typically show evidence of metastatic activity (e.g. proliferation or stromal reaction) or penetration of lymphatic sinus walls.

    The following classification of isolated tumour cells was published in the 6th edition of the TNM booklet [10] following a communication by the UICC in 1999 [11]. These cases with ITC in regional lymph nodes should be analysed separately since the prognostic importance of those ITC cases is not yet clear.

    Cases with ITC cells in lymph nodes or at distant sites should be classified as cN0 or cM0. The exceptions are in malignant melanoma of the skin [12, 13] and in Merkel cell carcinoma, where ITC in a lymph node are classified as N1/pN1 [3]. These cases should be analysed separately.
    The 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

Note.
This approach is consistent with TNM General Rule No. 4.

Sentinel Lymph Node

Definition

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 unlikely to contain tumour. Occasionally, there is more than one sentinel lymph node.

The following designations are applicable when sentinel lymph node assessment is attempted following resection of the primary tumour:

(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

Excisional biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, e.g. cN1(sn).

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

M Classification

The MX category is considered to be inappropriate in the clinical assessment of TNM if metastasis can be evaluated based on physical examination alone. (The use of MX may result in exclusion from staging [2, 3, 14].)

pM0 is only to be used after autopsies.
pMX is not a valid category.

1. In tumours of the gastrointestinal tract, multiple tumour foci in the mucosa or submucosa ('skip metastasis') are not considered in the TNM classification and should not be classified as distant metastasis. They should be distinguished from synchronous tumours, for example those with obvious mucosal origin. The synchronous tumours are categorized as multiple primary tumours if appropriate, e.g. pT2(m).
2. Metastasis in any lymph node other than regional is classified as distant metastasis.
3. Invasion of lymphatic vessels (tumour cells in endothelium-lined channels, so-called lymphangiosis carcinomatosa or lymphangic spread) in a distant organ is coded as pM1, e.g. lymphangitic spread in the lung from prostatic carcinoma or liver cell carcinoma.
4. Positive cytology using conventional staining techniques from the peritoneal cavity based on laparoscopy or laparotomy before any other surgical procedure is classified as M1, except for primary tumours of the ovary and Fallopian tube, where it is classified in the T category. Data indicate that the worsening of prognosis as indicated by positive lavage cytology may have been overestimated [15–22]. Thus, it seems important to analyse such cases separately. For identification of cases with positive cytology from pleural or peritoneal washings or pleural effusions or ascites as the sole basis for M1, the addition of 'cy+' is recommended, e. g. cM1(cy+). In the R classification R1(cy+) may be used [11, 23, 24]
5. Micrometastasis, i.e. no metastasis larger than 0.2 cm, in viscera (lung, liver, etc.) or bone marrow can be identified by the addition of '(mi)', e.g. pM1(mi).
6. Isolated tumour cells found in bone marrow with morphological techniques are classified according to the scheme for N, e.g. cM0(i+). For non-morphologic findings 'mol' is used in addition to M0, e.g. cM0(mol+).

Who Is Responsible for TNM Coding?

Data for TNM are derived from a variety of sources, e.g. the examining physician, the radiologist, the gastroenterologist, the operating surgeon and the histopathologist. The final TNM classification and/or stage rest with a designated individual physician who has access to the most complete data.

The Significance of X

An X classification of an individual component of TNM or pTNM, e.g. TX or pNX, does not necessarily signify inadequate staging [1]. The practical value of staging in the individual situation is to be considered, e.g. in patients with distant