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.
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 T1) and N3 (not N3). 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 hemicolecotomy 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 metachronous 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).

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**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].)
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
metastasis an effort to assess N is without clinical significance. In selected pT1 tumours of the colorectum, pNX may be the result of the correct decision to treat by endoscopic polypectomy or local excision. Also, experience shows that – at least in some sites, e.g. colon and rectum – in T1/pT1 tumours of low grade and without lymphatic invasion (L0) the frequency of regional lymph node metastasis as well as of distant metastasis is exceptionally rare and therefore no supplementary efforts are needed to assess the N category and N0 is appropriate. However, if there is a reasonable possibility of nodal metastases and no nodes have been removed pNX is appropriate (for example a thyroidectomy for thyroid carcinoma with no nodes in the specimen). The M is assessed clinically, cM0.

**Stages**

Although the anatomical extent of disease, as categorized by TNM, is a very powerful prognostic indicator in cancer, it is recognized that many other factors can have a significant impact on predicting outcomes (see factors listed in the ‘Prognostic Factors Grid’ supplied in the 8th edition of *TNM Classification of Malignant Tumours* [2]). Some have been incorporated into stages, as has grade in bone and soft tissue sarcomas and age in thyroid cancer. These classifications will be adapted in this edition according to the changes introduced in the 8th edition [2]. In the newly revised classifications for oesophagus carcinomas, stage has been maintained as defining the anatomical extent of disease and new Pathological Prognostic Groups that incorporate other prognostic factors, have been proposed.

1. The term ‘stage’ should be used only for combinations of T, N and M or pT, pN and pM categories. **The expressions ‘T stage’ and ‘N stage’ should be avoided.** It is correct to speak of T categories or N categories.

2. The stage can be determined exclusively according to the clinical classification (cTNM), exclusively according to the pathological classification (pTNM) or based on a combination of clinical and pathological findings (e.g. pT, pN and cM or pT, cN and cM or cT, cN and pM). If available, the pathological classifications are to be used for estimating stage.

**Examples**

Pedunculated polyp of sigmoid colon discovered endoscopically, superficial biopsy: tubular adenoma with carcinoma in situ, endoscopically, no suspicion of invasion, no regional lymph node or distant metastasis. Clinical classification: cTiscN0cM0.

Endoscopic polypectomy: adenocarcinoma arising in a tubular adenoma invading the superficial stalk, with clear deep stalk. No further treatment. Pathological classification: pT1pNXcM0. Summarizing classification: pT1cN0cM0, stage I. This is justified because experience shows that regional lymph node metastasis and distant metastasis in pT1 are very rare.
**Primary tumour of head and neck:** clinical diagnosis of regional lymph node metastasis by CT, no sign of distant metastasis. Treatment by surgical local excision of the primary tumour and radiotherapy of cervical lymph nodes. Clinical classification – cT1cN1cM0. Pathological classification – pT1pNXcM0. Summarizing classification – pT1cN1cM0, stage III (except oropharynx – p16-positive, nasopharynx and thyroid).

3. In the assessment of distant metastases, the entire situation must be considered. If there is only a clinically determined cM1 in an organ that could not be microscopically examined, this finding must be taken into consideration.

**Example**
Colon carcinoma with multiple lung metastases (by radiography). Resection of the colon carcinoma because of stenosis – pT3pN2cM1a. Simultaneously, also local excision of an area suspicious for metastasis in liver, histologically found to be haemangioma. Final classification pT3pN2cM1a, stage IV.

4. In the definitions of stages ‘any T’ includes T0 and TX.

**Example**
Breast carcinoma cT0cN3cM0 = stage IIIC
Malignant melanoma of skin pT0cN1cM0 = stage III

5. If the T or N cannot be determined, stage grouping is possible under the following circumstances:

- Despite TX/pTX, stage can be defined on the basis of N and M or pN and pM findings.
  **Example**
  A firm head of pancreas with one grossly involved peripancreatic lymph node and no signs of distant metastasis at surgery – cTXcN1cM0, stage IIB.

- Despite NX/pNX, stage can be undertaken when M/pM classification is possible.
  **Example**
  A carcinoma of the pancreas with liver metastasis cT1cNXcM1, Stage IV. Cases with cM1 or pM1 are generally classified as stage IV even in cases of T/pTX and N/pNX.

- Despite NX/pNX, stage grouping is possible when a T category and M0 are provided.
  **Example**
  Squamous cell carcinoma of the oesophagus with invasion of trachea, regional lymph nodes not assessable, no signs of distant metastasis – cT4bcNXcM0, clinical stage IVA.
Note.
There are different stage proposals for squamous cell carcinomas and adenocarcinomas of the oesophagus, both having a clinical stage and a pathological stage.

- Cases of Tis (clinical classification based on biopsy) or pTis (pathological classification based on the examination of the resected specimen) can be classified as stage 0, when combined with NX/pNX and cM0, because by definition no metastasis can be present.
- If substages (A, B, etc.) are designated in the list of stages, in most cases a summarizing definition of the stage is not included. If in such a situation a differentiation between the substages is not possible, often an assignment to the stage is possible and should be performed.

6. After neoadjuvant therapy, if the primary tumour has completely disappeared but lymph node metastasis remained, e.g. oesophagus squamous cell carcinoma, ypT0pN1cM0, the stage can be calculated by assuming that T equals the lowest category and the N essentially determines the stage, therefore pathological Stage IIB.

Note.
The AJCC introduced specific stages after neoadjuvant therapy for both squamous cell carcinomas and adenocarcinomas [3], where the above-mentioned case would be classified as Stage IIIA.

In the 8th edition of the TNM Classification [2], for some tumour entities clinical stages and pathological stages have been introduced with different definitions of the stages. Therefore, it should be clearly documented which stage was calculated. It must be further noted that the clinical stage and the pathological stage may not be comparable for different reasons.

Residual Tumour (R) Classification

TNM and pTNM describe the anatomical extent of cancer in general without considering treatment. The residual tumour (R) classification deals with tumour status after treatment. It reflects the effects of treatment, influences further therapeutic procedures and is a strong predictor of prognosis.

In the R classification, not only is a local-regional residual tumour to be taken into consideration, but also as it was initially described, a distant residual tumour in the form of remaining distant metastasis. Variation in the clinical application of the R classification in different practice settings is discussed below.
R0 corresponds to clinical remission or resection for cure. It is appropriate for cases in which a residual tumour cannot be detected by any diagnostic means. The R0 status, therefore, does not exclude non-detectable residual tumours, which may give rise to tumour recurrence or metastasis during follow-up. R0, in fact, corresponds to no detectable residual tumour and may not be identical to cure.

R1 and R2 should be annotated to indicate which site is positive, e.g. if a colonic polypectomy margin is microscopically positive for cancer, it is R1 (colon). If the patient’s subsequent colectomy margin has no tumour, it would change to R0 (colon) and if a liver metastasis was found at colectomy, and confirmed microscopically (but not removed surgically), it would be R2 (liver).

The R classification can be used following surgical treatment alone, after radiotherapy alone, after chemotherapy alone or following multimodal therapy. After non-surgical treatment, the presence or absence of a residual tumour is determined using clinical methods. Following surgical treatment, the R classification requires close cooperation between the surgeon and pathologist in a two-step process, illustrated in Figure 1.1.

In the R0 group there may be M0 cases as well as M1 cases. In the latter, the distant metastasis as well as the primary tumour must be removed completely.

**Example**
pT3pN1cM1a colon cancer with resection for cure of both the primary tumour and a liver metastasis: R0 (colon); R0 (liver).

![Figure 1.1](image-url) R classification following surgery.
In a tumour specimen with a formal lymphadenectomy the ‘marginal’ lymph node is the one near the resection line that is most distant from the primary tumour. Involvement of such ‘marginal’ or ‘apical’ nodes or of a sentinel node does not influence the R classification unless an involved lymph node has been transected by the surgeon at the margin.

Difficulties may arise in the case of removal of the tumour in two or more parts and not ‘en bloc’. Without an exact and reliable topographical orientation the pathologist cannot make a definitive assessment of the resection line. In this case the classification ‘RX’ (presence of residual tumour cannot be assessed) is appropriate.

The presence of non-invasive carcinoma (in situ) at the resection margin should be indicated by the suffix (is), e.g. R1(is).

**Example**
Invasive carcinoma of the breast with associated in situ component. Breast preserving surgery, according to the surgeon, was complete. Histology showed:
(a) Invasive carcinoma at the resection margin: R1.
(b) Invasive carcinoma completely removed, but associated in situ component at the resection margin: R1(is).

‘R0-Ablation’ after radiofrequency ablation of liver metastasis: if after radiofrequency ablation of liver metastasis no residual tumour is found by clinical (including imaging) techniques, sometimes ‘R0-ablation’ has been used. Because the diagnosis ‘R0’ requires histopathological examination of a tumour resection specimen (primary tumour and/or distant metastasis) the correct designation in this situation is ‘complete clinical response’.

Patients classified for residual tumour by conventional methods and those classified by new specialized methods cannot be compared. To prevent stage migration by refined diagnostic techniques, the methods used for R classification should be stated in the documentation and be considered in the analysis of treatment results [25].

In the R classification, the serum level of tumour markers is not considered.

Examination of resection specimens is done by conventional methods in histopathological processing of areas marked by the surgeon or areas suspicious by gross inspection. Besides these conventional methods some new techniques have been developed to refine the R classification. Examples of such methods are:

1. Imprint cytology of the resection margin (surface), introduced by Veronesi et al. [9] for breast cancer, but applicable to stomach cancer and other tumour types as well.
2. Cytologic examination of ascites or abdominal lavage fluid to detect metastasis on the peritoneum, which are not grossly recognizable. This was applied to gastric carcinoma [15, 16, 26]. In the R classification R1(cy+) may be used [24, 25].

3. Examination of bone marrow biopsies in patients without evidence of bone metastasis with monoclonal antibodies against cytokeratin. Such investigations have been described by Schlimok et al. [27] for gastric carcinomas and were reviewed by Pantel et al. [28] (see pages 10–12 regarding detection of isolated tumour cells and evidence of tumour by non-morphologic methods).

Although there have been proposals (see below) to code a tumour R1 if the tumour is 1 mm or less from the resection margin, only if the tumour is transected should R1 be used; otherwise it is R0.

According to the data from Erlangen Cancer Center (ECC) and Australia, R1 was only diagnosed if a tumour was demonstrated at the resection margins (tumour transected).

In recent years, an alternative definition of resection margin involvement has gained increasing acceptance, at first for the circumferential resection margin (CRM) in rectal cancer [29–31] but also for other resection margins and other tumour entities. These data strongly supported the following definitions:

1. CRM positive, tumour directly at the CRM or a minimal distance between the tumour and the CRM of ≤ 1 mm.
2. CRM negative, a minimal distance between the tumour and the CRM > 1 mm.

This ‘new’ definition of tumour involvement has gained general acceptance in the United Kingdom [29–33]. It has been supported in the United States [34, 35].

Following a Total Mesorectal Excision (TME) in the management of rectal cancer it is recognized that the circumferential resection margin (CRM) is of great prognostic importance; hence instead of considering tumour within 1 mm of that margin as being R1, it can be classed as CRM positive.

In some practice settings around the world, particularly the USA [36], Canada and the UK, the R classification has been employed only in application to the primary tumour and its local or regional extent. Others have applied it more broadly to include distant metastasis.

With regard to the overall prognostic relevance of the R classification, distant metastasis should be included. This is in accordance with the original definition in 1977 [37].

Further confusion results from different definitions of resection margin involvement: direct involvement of the resection margin by a tumour or the minimal distance between a tumour and the resection margin of 1 mm or less.
To avoid confusion a proposal for an expanded uniform R classification has recently been published [24]. This proposal differentiated between the following categories:

- **RX** Presence of residual tumour cannot be assessed
- **R0 > 1 mm** No residual tumour, minimal distance between tumour and resection margin > 1 mm
- **R0 ≤ 1 mm** No residual tumour, minimal distance between tumour and resection margin ≤ 1 mm
- **R1-dir** Microscopic residual tumour, tumour directly at the resection margin (tumour transected)
- **R2a** Local macroscopic residual tumour
- **R2b** Distant macroscopic residual tumour
- **R2c** Macroscopic residual tumour in both sites

Further discussion of the R classification, including its application to leukemias and malignant lymphomas and after non-surgical treatment can be found in Wittekind et al. (2002) [23].

Following neoadjuvant therapy in the R classification only a viable tumour at the resection margin is considered. Scars, fibrotic areas, fibrotic nodules, granulation tissue, mucin lakes, etc., occurring at the resection margin do not qualify as R1.

**Definitions of Completeness of Resection**

**R0(un)**

Concerns have been expressed that the definition of complete resection conferring R0 status is too imprecise and that the application of General Rule No. 4 does not allow one to assess several features that may represent minimal residual disease and have an adverse prognostic influence. The category ‘Uncertain resection’ has been proposed for testing [38].

A new category, ‘R0(un)’, is proposed to document those other features that fall within the proposed category ‘uncertain resection’, i.e. no macroscopic or microscopic evidence of residual disease but any of the following reservations apply:

1. Nodal assessment has been based on less than the number of nodes/stations ordinarily included in a lymphadenectomy specimen.
2. The highest mediastinal node removed/sampled is positive (for lung cancers).

In a recent paper the above proposals have been validated by another institution [39].
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 parenthesis, is used to indicate the presence of multiple primary tumours at a single site. See the TNM Rule No. 5 (page 5).

y Symbol – Classifying Treated Tumours
cTNM is the pre-treatment clinical classification, based on evidence acquired before treatment. pTNM is the post-surgical histopathological classification, based on evidence acquired before treatment, supplemented or modified by additional evidence acquired from surgery and from pathological examination.

After multimodal therapy (neoadjuvant radio- and/or chemotherapy prior to surgery) the pathological assessment may be affected by possible tumour regression or other treatment effects. Thus, such a classification should be identified by the prefix ‘y’ to indicate that this classification has not the same reliability as the pTNM classification after surgery alone. The ypTNM classification deals with the extent of cancer after neoadjuvant therapy. Therefore, the ypTNM should consider only viable tumour cells and not signs of regressed tumour tissue such as necrotic cell debris, scars, fibrotic areas, fibrotic nodules, granulations tissue, mucin lakes, etc.

In analysing results, one should always differentiate between patients treated with primary surgery (cTNM, pTNM) and those treated by surgery following neoadjuvant treatment (ycTNM, ypTNM). Not only for the TNM categories but also for the stage grouping the ‘y’ symbol should be used (Stage yI, Stage yII, ...; Stage ypI, Stage ypII, ...).

After neoadjuvant treatment two additional stages could be used:

Stage y(p)0 = ypT0N0M0 and
Stage y(p)is = ypTisN0M0.

In contrast, after primary surgery, stage 0 is defined as pTisN0M0.

This differentiation is based on:
- the different prognosis of patients with yTNM and ypTNM,
- the different clinical consequences, in particular in the case of yT0, ypT0, stage y0.
After multimodal treatment histological grading may be unreliable and should not be used. It is recommended to add some information on the extent of histologic regression of tumours. For several sites tumour regression scoring systems, mostly semiquantitative, have been published.

Following neoadjuvant therapy, the extent of residual tumour found at resection reflects the response to the preceding therapy. Various proposals of describing the extent of tumour after therapy have been described.

It should be emphasized that there is no generally accepted regression grading system for all tumour entities. Table 1.2 addresses this issue on a site by site basis.

The AJCC has proposed the following to describe the response to neoadjuvant therapy for rectal carcinoma [34]. This scheme in a modified version has been recommended for several tumours of the digestive system.

**Note.**

However, this is a classification of response to treatment and not a stage classification.

<table>
<thead>
<tr>
<th>Description</th>
<th>Tumour Regression Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No viable cancer cells</td>
<td>0 (complete response)</td>
</tr>
<tr>
<td>Single cells or small groups of cancer cells</td>
<td>1 (moderate response)</td>
</tr>
<tr>
<td>Residual cancer outgrown by fibrosis</td>
<td>2 (minimal response)</td>
</tr>
<tr>
<td>Minimal or no tumour kill; extensive residual cancer</td>
<td>3 (poor response)</td>
</tr>
</tbody>
</table>

**Recurrent Tumour, r Symbol**

The prefix ‘r’ is used for classification of recurrent tumours in terms of T, N and M. The use of stages is not appropriate for recurrent tumours. While TNM and pTNM without the prefix ‘r’ always characterize the first manifestation of a tumour, recurrences after curative treatment are described by rTNM or rpTNM. In this way a chronological TNM/pTNM documentation of the course of the disease may be created. An example of such a ‘Pathogram’ is shown in Table 1.3.

For the description of a recurrence in the area of the primary tumour the T categories can be used only in the case of recurrence on the anastomotic suture line after partial or total resection of an organ of the gastrointestinal tract.

It has been suggested that the r symbol can also be used after a period of observation without treatment. For example, it may be described to observe a patient with a cT1ccN0cM0 prostate cancer found on biopsy following identification for an elevated PSA. Subsequently, on restaging after a period of active surveillance, the carcinoma has progressed and now involves more than one half of a single lobe. The classification would be rcT2bcN0cM0.
Table 1.2  Proposed regression grading system

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck squamous</td>
<td>Braun et al. 1989 [40]</td>
</tr>
<tr>
<td>Cell carcinoma</td>
<td>Eich et al. 2008 [41]</td>
</tr>
<tr>
<td></td>
<td>Hermann et al. 2001 [42]</td>
</tr>
<tr>
<td></td>
<td>Wedemeyer et al. 2014 [43]</td>
</tr>
<tr>
<td><strong>For all gastrointestinal sites</strong></td>
<td>Werner and Höfler 2000 [44]</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Japanese Esophageal Society 2017 [45]</td>
</tr>
<tr>
<td></td>
<td>Mandard et al. 1994 [46]</td>
</tr>
<tr>
<td></td>
<td>Baldus et al. 2004 [47]</td>
</tr>
<tr>
<td></td>
<td>Hermann et al. 2006 [48]</td>
</tr>
<tr>
<td>Stomach</td>
<td>Japanese Gastric Cancer Association 1998 [49]</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>Dworak et al. 1997 [52]</td>
</tr>
<tr>
<td></td>
<td>Japanese Society for Classification of Cancer of Colon and Rectum (JSCCR) 1997 [53]</td>
</tr>
<tr>
<td></td>
<td>Wheeler et al. 2002 [54]</td>
</tr>
<tr>
<td></td>
<td>Ryan et al. 2005 [34]</td>
</tr>
<tr>
<td></td>
<td>Williams et al. 2008 [55]</td>
</tr>
<tr>
<td></td>
<td>Bateman et al. 2009 [56]</td>
</tr>
<tr>
<td>Anal canal</td>
<td>Klimpfinger et al. 1994 [57]</td>
</tr>
<tr>
<td>Liver</td>
<td>Adachi et al. 1999 [58]</td>
</tr>
<tr>
<td>Pancreas (ductal adenocarcinoma)</td>
<td>Evans et al. 1992 [59]</td>
</tr>
<tr>
<td>Lung</td>
<td>Junker et al. 2001 [60]</td>
</tr>
<tr>
<td></td>
<td>Langner et al. 2003 [61]</td>
</tr>
<tr>
<td>Bone tumours/osteosarcoma</td>
<td>Salzer-Kuntschick et al. 1983 [62]</td>
</tr>
<tr>
<td></td>
<td>Huvos 1991 [63]</td>
</tr>
<tr>
<td>Soft tissue tumours</td>
<td>Schmidt et al. 1993 [64]</td>
</tr>
<tr>
<td>Breast</td>
<td>Chevallier et al. 1993 [65]</td>
</tr>
<tr>
<td></td>
<td>Sinn et al. 1994 [66]</td>
</tr>
<tr>
<td></td>
<td>Sataloff et al. 1995 [67]</td>
</tr>
<tr>
<td></td>
<td>Fisher et al. 2002 [68]</td>
</tr>
<tr>
<td></td>
<td>Ogston et al. 2003 [69]</td>
</tr>
<tr>
<td></td>
<td>Symmans et al. 2007 [70] (RCB System)</td>
</tr>
</tbody>
</table>
Example

Previous total gastrectomy, without remaining local-regional residual tumour. Local recurrence at the oesophagojejunostomy involving mucosa, submucosa, muscularis propria and perimuscular tissue: rT3.

In other cases, the recurrence in the area of the primary tumour may be indicated by ‘rT+’.

Example

Local recurrence after simple mastectomy, 2 cm in greatest dimension, with or without invasion of skin or chest wall: rT+.

a Symbol

The prefix ‘a’ indicates that classification is first determined at autopsy. Tumours that have been clinically diagnosed and then classified, based on autopsy findings can be recorded in two ways:

- Recurrence after a disease-free interval: rpTNM
- Other cases: pTNM

It should be emphasized that assignment of pM0 by pathological assessment is possible only at autopsy.

Table 1.3 ‘Pathogram’ of a patient with rectal carcinoma

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
<th>TNM/pTNM</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2012</td>
<td>Initial local excision of rectal carcinoma</td>
<td>pT1pNXM0</td>
<td>R1</td>
</tr>
<tr>
<td>July 2012</td>
<td>Radiotherapy, followed by anterior resection</td>
<td>ypT0pN0M0</td>
<td></td>
</tr>
<tr>
<td>October 2012</td>
<td></td>
<td>cT0cN0cM0</td>
<td></td>
</tr>
<tr>
<td>January 2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>April 2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>July 2013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January 2014</td>
<td></td>
<td>cT0cN0cM0</td>
<td></td>
</tr>
<tr>
<td>April 2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>July 2014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>October 2016</td>
<td>Liver tumour resection</td>
<td>rcT0cN0cM1 (liver)</td>
<td>R0</td>
</tr>
<tr>
<td>January 2018</td>
<td></td>
<td>cT0cN0cM0</td>
<td></td>
</tr>
<tr>
<td>Last contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>March 2018</td>
<td></td>
<td>cT0cN0cM0</td>
<td></td>
</tr>
</tbody>
</table>
Optional Descriptors

Lymphatic Invasion (L Classification)
Lymphatic vessels include those within and at the margins of the primary tumour as well as afferent and efferent lymphatics. Invasion of small lymphatic vessels requires the demonstration of tumour cells (single or groups) within channels that are unequivocally lined with endothelium. If spaces around tumour nests caused by shrinkage during tissue processing cannot be distinguished from lymphatic invasion, L0 is selected (General Rule No. 4). The categories of the L classification are:

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

Venous Invasion (V Classification)
Venous invasion (V1 or V2) can be diagnosed if there is tumour invasion in the vessel wall. V1 or V2 does not necessarily require demonstration of tumour cells in the lumen of the vessels. The categories of the V classification are:

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

There is no classification for invasion of arteries, which is very rare. These cases should be documented separately.

Pn – Perineural Invasion
In the 7th edition of the TNM Classification [71] perineural invasion was introduced as a new and optional parameter. The findings of the Pn classification have no impact on the T classification or stage but have been shown to be an additional prognostic factor for many tumour entities [72]. The categories of the Pn classification are:

- PnX Perineural invasion cannot be assessed
- Pn0 No perineural invasion
- Pn1 Perineural invasion
Symbols for Describing Methods of Staging
Because of interest in the differentiation between imaging methods such as ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI), prefixes have been proposed for the clinical staging of rectal carcinoma by Schaffzin et al. 2004 [73] and Moran et al. 2007 [74]:
– Ultrasound: ‘u’, e.g. uT2 or uN1
– CT: ‘ct’, e.g. ctT3 or ctN0
– MRI: ‘mr’, e.g. mrT4 or mrN2

Unknown Primary
In the absence of a primary tumour, the presence of metastasis can be coded as T0 plus the assessment of the N and M.

In the head and neck a chapter with an unknown primary and the presence of cervical nodes has been introduced assuming that the primary tumour is located somewhere in the head and neck region with regional cervical lymph nodes. In those cases with cervical lymph nodes that are positive with squamous cell carcinoma and no evidence of a primary tumour the coding is cT0cN2cM0, Stage IVA. In cases without a primary and positive cervical lymph node metastasis occurs as well as distant metastasis: cT0cN2cM1, Stage IVC.

If there is evidence of HPV positivity or EB virus positivity the lymph node is staged as if the primary is from the oropharynx or nasopharynx, respectively.

If the lung contains multiple nodules of malignant melanoma with no primary site identified, the coding would be cT0cNXcM1, Stage IV.

Staging of Tumours for Which No TNM Classification is Provided
Staging according to the rules of the SEER Program [75] is recommended if no TNM classification is provided (see website link: https://training.seer.cancer.gov/staging/systems/summary/). Staging is based on the concept of local, regional and distant.

• In situ (non-invasive, intraepithelial)
• Localized (confined to the organ of origin)
● Regional, direct extension
● Regional, lymph nodes
● Regional, direct extension and lymph nodes
● Distant, direct extension or metastasis
● Distant, lymph nodes

These cases should be analysed separately.

In addition, the 8th edition of *TNM Classification of Malignant Tumours* [2] offers an essential TNM for cancer registries in low- and middle-income countries frequently having insufficient information to determine complete TNM data. In view of this, the UICC TNM Project has developed with the International Agency for Research in Cancer and the National Cancer Institute a new classification system ‘Essential TNM’ that can be used to collect stage data when complete information is not available. Essential TNM schemes have been developed for breast, cervix, colon and prostate cancer, and are presented in the 8th edition and are available for download at www.uicc.org.

### Histopathological Grading

The following applies only to the TNM classification and not to the ICD-O morphology code.

Histopathological grading of tumours of the same histological type is performed to provide some indication of their aggressiveness, which may in turn relate to prognosis or treatment. Grading should follow the recommendations of the WHO Classification of Tumours. For histopathological grading of invasive breast carcinoma see Elston and Ellis [76].

For most sites, histopathological grading consists of four grades:

- **G1** Well differentiated
- **G2** Moderately differentiated
- **G3** Poorly differentiated
- **G4** Undifferentiated

In the event that there are different degrees of differentiation in a tumour, one should assign the tumour to the least favourable grade of G1–G4.

**Example**

Partially well differentiated, partially moderately differentiated adenocarcinoma of the colon – G2.

G1 and G2 may be grouped together as low grade (G1–G2) and G3 and G4 as high grade (G3–G4). In some tumour sites, no differentiation is made between
G3 and G4 and therefore the category G3–G4 is used. This is valid for carcinomas of the penis, renal pelvis, ureter, urinary bladder and urethra.

In prostate carcinomas the use of the WHO grade group has been introduced as below:

<table>
<thead>
<tr>
<th>WHO grade group</th>
<th>Gleason score</th>
<th>Gleason pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤6</td>
<td>≤3+3</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>3+4</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>4+3</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>4+4, 3+5, 5+3</td>
</tr>
<tr>
<td>5</td>
<td>9–10</td>
<td>4+5, 5+4, 5+5</td>
</tr>
</tbody>
</table>

In the 7th edition, special staging criteria have been introduced with the TNM classification of gastrointestinal stromal tumour (GIST). Grading for GIST is dependent on the mitotic rate [71] and has been kept in the 8th edition [2].

A grading system has been proposed for well-differentiated neuroendocrine tumours (carcinoids) and well-differentiated neuroendocrine carcinomas. The grading system depends on the mitotic count and Ki-67 index [2].

Only three grades (G1–G3) are used for all gynaecological sites except gestational trophoblastic tumours.

Grading is not applicable for the following tumour entities:

- Malignant melanoma of the upper aerodigestive tract
- Carcinoma of the thyroid
- Pleural mesothelioma
- Thymic tumours
- Malignant melanoma of the skin
- Merkel cell carcinoma
- Uterine sarcomas
- Gestational trophoblastic tumours
- Germ cell tumours of the testis
- Adrenal gland carcinoma
- Malignant melanoma of the uvea
- Retinoblastoma

For undifferentiated carcinomas of the oesophagus, stomach, small intestine, colorectum, gallbladder and pancreas the category G4 is appropriate. By definition, an adenocarcinoma of these organs can be classified only as G1, G2 or G3. When, in an adenocarcinoma of these organs, there are undifferentiated areas
next to areas with glandular differentiation, the tumour is classified as a poorly
differentiated adenocarcinoma. The same applies for squamous cell carcinoma
with undifferentiated areas.

In some sites the WHO classification does not list ‘undifferentiated carcinoma’
as a specific tumour type, e.g. in the lung and breast. In those cases the category
G4 is not applied [77].

In the absence of an assigned grade the following can be considered G4:

- Undifferentiated carcinoma
- Small cell carcinoma
- Large cell carcinoma of the lung
- Ewing sarcoma of bone and soft tissue
- Rhabdomyosarcoma of soft tissue

In grading, different methods may be appropriate for the various tumour entities
(type and site). For example, in gastrointestinal adenocarcinomas the growing
edge of a tumour should not be assessed as it may appear to be of a high grade
[78, 79]. In contrast, grading that considers the histologically invasive edge is
appropriate for predicting the prognosis of oral squamous cell carcinoma [80].

The pathologist should indicate the grading system used in the report.

Grading is generally performed by a combined evaluation of various histologi-
cal and cytological features, including similarity to tissue of origin, cell arrange-
ment, cellularity, differentiation, cellular and nuclear pleomorphism, mitotic
activity and necrosis. Grading is a semiquantitative, sometimes subjective proce-
dure, which requires considerable experience by the pathologist. To reduce indi-
vidual variability and to increase reproducibility of grading, semiquantitative
methods have been proposed. Various morphological parameters have been
scored from 1 to 3 or 1 to 4, with the scores for each variable added into a total
malignancy score for each tumour. A high malignancy score suggests a poorly
differentiated tumour.

References


[2] UICC (Union for International Cancer Control) TNM Classification of Malignant
Tumours, 8th edn, Brierley JD, Gospadarowicz MK, Wittekind C (eds). Oxford: Wiley
Blackwell; 2017.

[3] American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edn,


