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 analyzed separately.

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

General Rule No. 2
Two classifications are described for each site, namely:
(a) Clinical classification: the pre-treatment clinical classification designated TNM (or cTNM) is essential 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 primary tumour (pT) entails a resection of the primary tumour or biopsy adequate to evaluate the highest pT category. The pathological assessment of the regional lymph nodes (pN) entails removal of the lymph nodes adequate to validate the absence of regional lymph node metastasis (pN0) or sufficient to evaluate the highest pN category. An excisional biopsy of a lymph node without pathological assessment of the primary is insufficient to fully
evaluate the pN category and is a clinical classification. The pathological assessment of distant metastasis (pM1) entails microscopic examination.

TNM is a dual system that includes a clinical (pretreatment or after neoadjuvant radio-/chemo-/radiochemotherapy but before surgery) and a pathological (postsurgical histopathological) classification. It is imperative to differentiate between them as 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 on page 134ff.

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

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

A tumour is primarily described by the clinical classification before treatment or before the decision not to treat. In addition, a pathological classification is performed if specific requirements are met (see Chapter 3, page 134ff.). Therefore, for an individual patient there may be a clinical classification, e.g. T2N1M0 and a pathological classification pT2pNXM0.

**General Rule No. 3**

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

The rule that the TNM classification, once established, must remain unchanged in the patient’s record applies to the definitive TNM classification determined just before initiation of treatment or before making the decision not to treat. If, for instance, the initial classification T2N0M0 is made in one hospital and is later updated to T2N1M0 after the patient is referred to another centre 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 pT1pNXM0; 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: pT0pN1M0. The definitive pTNM classification consists of the results of both operative specimens – pT1pN1bM0 (stage IIIA).

Initial local excision of a rectal carcinoma: pT1pNXM0, R1
Radiotherapy, followed by anterior resection: ypT0pN0M0, R0*
Definitive classification: ypT0pN0M0, R0
* Assignment of the ‘y’ prescript for cases involving multimodality therapy is described on page 18.

For final stage grouping, clinical and pathological data may be combined when only partial information is available in either the pathological classification or the clinical classification. The example on page 2 is expressed as pT2cN1cM0.

‘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 stage grouping.

Example
Sonography of the liver: suspicious lesion but no definitive evidence of metastasis – assign M0 (not M1).
If there are different results from different methods, the classification should be based on the most reliable method of assessment.

Example
Colorectal carcinoma, preoperative examination of the liver: sonography, suspicious, but no evidence of metastasis; computerized tomography (CT), evidence of metastasis. The results of CT determine the classification – M1. If a biopsy is performed and metastases confirmed then it would be classified as pM1. However, if CT were negative, the case would be classified M0.

General Rule No. 5
In the case of multiple simultaneous tumours in one organ, the tumour with the highest T category should be classified and the multiplicity or the number of tumours should be indicated in parentheses, e.g. T2(m)
or T2(5). In simultaneous bilateral cancers of paired organs, each tumour should be classified independently. In tumours of the liver, ovary and fallopian tube, multiplicity is a criterion of T classification.

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

1. Multiple synchronous tumours in one organ may be:
   a) Multiple non-invasive tumours
   b) Multiple invasive tumours
   c) Multiple invasive tumours with associated carcinoma in situ
   d) A single invasive tumour with associated carcinoma in situ

   For (a) the multiplicity should be indicated by the suffix ‘(m)’, e.g. Tis(m). For (b) and (c) the tumour with the highest T category is classified and the multiplicity or the number of invasive tumours is indicated in parentheses, e.g. T2(4) or T2(m).

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

2. For classification of multiple simultaneous tumours in ‘one’ organ, the definitions of one organ listed in Table 1.1 should be applied. 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(m) or T2(5).

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

Examples of sites for separate classification of two tumours are:
   • Oropharynx and hypopharynx
   • Submandibular gland and parotid gland
   • Urinary bladder and urethra (separate tumours)
   • Skin carcinoma of eyelid and neck

Examples for classification of the tumour with the highest T category and indication of multiplicity (m symbol) or numbers of tumours:
   • Two separate tumours of the hypopharynx
   • Carcinoma of the caecum and the transverse colon
   • Skin carcinoma of the trunk and the arm
   • Carcinoma of renal pelvis and ureter
   • See item no. 1 of M classification (see page 10)
3. If a new primary cancer is diagnosed within 2 months in the same site, this new cancer is considered synchronous (based on criteria used by the SEER Program of the National Cancer Institute, USA [2]).

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

A tumour in the same organ with a different histological type is counted as a new tumour.

**Table 1.1** Definition of ‘one organ’ for the classification of multiple simultaneous primary tumours: the listed sites/subsites are considered as ‘one organ’

<table>
<thead>
<tr>
<th>Organ/site</th>
<th>ICD-O code [3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip</td>
<td>C00.0, 1, 2, 6</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>C00.3–5, C02.0–3, C03, C04, C05.0, C06</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>C01, C05.1, 2, C09, C10.0, 2, 3</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>C11</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>C12, C13</td>
</tr>
<tr>
<td>Larynx</td>
<td>C10.1, C32.0–2</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>C30.0</td>
</tr>
<tr>
<td>Maxillary sinus</td>
<td>C31.0</td>
</tr>
<tr>
<td>Ethmoid sinus</td>
<td>C31.I</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>C07</td>
</tr>
<tr>
<td>Submandibular (submaxillary) gland</td>
<td>C08.0</td>
</tr>
<tr>
<td>Sublingual gland</td>
<td>C08.1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>C73</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>C15</td>
</tr>
<tr>
<td>Stomach</td>
<td>C16</td>
</tr>
<tr>
<td>Small intestine</td>
<td>C17</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>C18–C20</td>
</tr>
<tr>
<td>Anal canal</td>
<td>C21.1, 2</td>
</tr>
<tr>
<td>Liver*</td>
<td>C22</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>C23</td>
</tr>
<tr>
<td>Extrahepatic bile ducts</td>
<td>C24.0</td>
</tr>
<tr>
<td>Ampulla of Vater</td>
<td>C24.I</td>
</tr>
<tr>
<td>Pancreas</td>
<td>C25</td>
</tr>
<tr>
<td>Lung</td>
<td>C34</td>
</tr>
<tr>
<td>Pleura</td>
<td>C38.4</td>
</tr>
<tr>
<td>Bones</td>
<td>C40, C41</td>
</tr>
<tr>
<td>Soft tissues, peripheral</td>
<td>C47, C49</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>C48</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>C38.1–3</td>
</tr>
<tr>
<td>Skin (subsite(s) only) except eyelid, anal margin and perianal skin</td>
<td>C44.0, 2–4, 6–9</td>
</tr>
</tbody>
</table>
**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 [4] to 3rd edn [5] of the TNM Supplement are any statements concerning the way to measure tumour size for pT classification. According to the AJCC Cancer Staging Manual 2009 [6], ‘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 detected tumour size the clinical measurement should be used also for the pT classification.

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),

<table>
<thead>
<tr>
<th>Organ</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyelid</td>
<td>C44.1</td>
</tr>
<tr>
<td>Anal margin and perianal skin</td>
<td>C44.5</td>
</tr>
<tr>
<td>Breast</td>
<td>C50</td>
</tr>
<tr>
<td>Vulva</td>
<td>C51</td>
</tr>
<tr>
<td>Vagina</td>
<td>C52</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>C53</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>C54</td>
</tr>
<tr>
<td>Ovary*</td>
<td>C56</td>
</tr>
<tr>
<td>Fallopian tube*</td>
<td>C57.0</td>
</tr>
<tr>
<td>Gestational trophoblastic tumours</td>
<td>C58.9</td>
</tr>
<tr>
<td>Penis</td>
<td>C60</td>
</tr>
<tr>
<td>Prostate</td>
<td>C61</td>
</tr>
<tr>
<td>Testis</td>
<td>C62</td>
</tr>
<tr>
<td>Scrotum</td>
<td>C63.2</td>
</tr>
<tr>
<td>Kidney</td>
<td>C64</td>
</tr>
<tr>
<td>Renal pelvis and ureter</td>
<td>C65, C66</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>C67</td>
</tr>
<tr>
<td>Urethra</td>
<td>C68.0</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>C69.0</td>
</tr>
<tr>
<td>Uvea</td>
<td>C69.3, 4</td>
</tr>
<tr>
<td>Retina</td>
<td>C69.2</td>
</tr>
<tr>
<td>Orbit</td>
<td>C69.6</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>C69.5</td>
</tr>
</tbody>
</table>

*In this organ multiplicity is a criterion of T classification.
gallbladder, lung and 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 [7].

4. The microscopic presence of tumour in lymphatic vessels or veins does not qualify as local spread of tumour as defined by the T classification (except for liver, testis and penis). Tumour in perineural spaces at the primary site is considered part of the T classification, but can also be recorded separately as Pn1, 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 2010 [8], page 21) can be used to record lymphatic and venous involvement.

5. 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 distant metastasis; in contrast, direct spread of the primary tumour into regional lymph nodes is classified as lymph node metastasis.

6. 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.

Example
Retroperitoneal soft tissue sarcoma, 5 cm or less in size with invasion of the ureter: pT2b.

7. Tumour spillage during surgery is considered a criterion in the T classification of tumours of ovary. For all other tumours, tumour spillage does not affect the TNM classification, stage grouping or R classification.

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 as those of the primary site for N classification.

**Example**
Carcinoma of the sigmoid colon or ovary with direct extension into an adjacent small bowel loop: pericolic lymph nodes or regional lymph nodes of ovary, respectively, are tumour-free, but metastases are found in two mesenteric lymph nodes in the vicinity of the invaded small bowel – this is classified as pT4bpN1bM0 (stage IIIc) for sigmoid carcinoma or pT2bpN1M0 (stage IIIC) for cancer of the ovary, respectively.

**N/pN Classification**
1. The clinical category N0 (‘no regional lymph node metastasis’) includes lymph nodes not clinically suspicious for metastases 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 imaging changes. The term ‘adenopathy’ is not precise enough to indicate lymph node metastasis.
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 the 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), i.e. macro- or microscopic nests or nodules, in the lymph drainage area of a primary carcinoma without histological evidence of residual lymph node in the nodule, may represent discontinuous spread (classified in the T category), venous invasion (V1/2) or a totally replaced lymph node. If a nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour), it should be recorded as a positive lymph node, and each such nodule should be counted separately as a lymph node in the final pN determination.
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 (e.g. 0/4) characterizes the reliability of this 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 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 prostatic 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 tumour deposits 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 immuno-histochemistry. An additional criterion has been proposed to include a cluster of fewer than 200 cells in a single histological cross-section [8]. The same applies to cases with findings suggestive of tumour cells or their components by non-morphological techniques such as flow cytometry or DNA analysis. 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 appeared in the TNM 6th edn [9] and has been published more than 10 years ago [10]. These cases should be analyzed separately.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis histologically, no examination for isolated tumour cells (ITC)</td>
</tr>
<tr>
<td>pN0(i−)</td>
<td>No regional lymph node metastasis histologically, negative morphological findings for ITC</td>
</tr>
<tr>
<td>pN0(i+)</td>
<td>No regional lymph node metastasis histologically, positive morphological findings for ITC</td>
</tr>
<tr>
<td>pN0(mol−)</td>
<td>No regional lymph node metastasis histologically, negative non-morphological findings for ITC</td>
</tr>
<tr>
<td>pN0(mol+)</td>
<td>No regional lymph node metastasis histologically, positive non-morphological findings for ITC</td>
</tr>
</tbody>
</table>

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 not likely to contain tumour. Occasionally, there is more than one sentinel lymph node.

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

- \( pN0 \) (\( sn \)) Sentinel lymph node metastasis
- \( pN0 \) (\( sn \)) No 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. c\( N1(sn) \).

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

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

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) [6, 8].

\( pM0 \) is only to be used after autopsies.
\( pMX \) is no longer 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 primary tumours, for example those with obvious mucosal origin; the synchronous tumours are categorized as multiple primary tumours, e.g. \( T2( m) \).
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. lymphangic spread in the lung from prostatic carcinoma.

4. Positive cytology using conventional staining techniques from the peritoneal cavity based on laparoscopy or laparotomy before any other surgical procedure, is classified M1, except for ovarian primary tumours, 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 [11, 12, 13, 14, 15]. Thus, it seems important to analyze 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. M1(cy+). In the R classification, R1(cy+) may be used [10, 16].

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. M0(i+). For non-morphological findings, ‘mol’ is used in addition to M0, e.g. M0(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 grouping rest with a designated individual 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. 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 at some sites, e.g. colorectum or anal canal – 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 need be made to assess the N category and N0 is appropriate. However, if there is reasonable possibility of nodal metastases and no nodes have been removed, pNX is appropriate (e.g. a thyroidectomy for thyroid carcinoma with no nodes in the specimen). The M is assessed clinically, cM0.

The MX category is considered to be inappropriate as clinical assessment of metastasis can be based on physical examination alone.
Stage Grouping

Although the anatomical extent of disease, as categorized by TNM, is a very powerful prognostic indicator in cancer, it is recognized that many factors have significant impact on predicting outcomes. Some have been incorporated into stage grouping, as has grade in bone and soft tissue sarcomas and age in thyroid cancer. These classifications will be unchanged in this edition. In the newly revised classifications for oesophagus and prostate carcinomas, *stage grouping* has been maintained as defining the anatomical extent of disease and new *prognostic groupings* 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 (TNM), exclusively according to the pathological classification (pTNM) or based on a combination of clinical and pathological findings (e.g. pT, pN and M or pT, N and M or T, N and pM). If available, the pathological classifications are to be used for stage grouping.

**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: TisN0M0.

Endoscopic polypectomy: adenocarcinoma arising in a tubular adenoma invading the superficial stalk, with clear deep stalk. No further treatment. Pathological classification: pT1pNXM0. Summarizing classification: pT1N0cM0 or pT1N0M0, 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 – T1N1M0. Pathological classification – pT1pNXM0. Summarizing classification – pT1N1M0 or pT1cN1cM0, stage III (except nasopha-rynx and thyroid).

3. In the assessment of distant metastases, the entire situation must be considered. If there is only a clinically determined M1 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 – pT3pN2cM1. Simultaneously, also local excision of an area suspicious for metastasis in liver, histologically found to be haemangiomma. Final classification pT3pN2M1, stage IV.
4. In the definitions of stage groups ‘any T’ includes T0.

**Example**

- Breast carcinoma T0N3M0 = Stage IIIC
- Malignant melanoma of skin pT0N1M0 = Stage III

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

- Despite TX/pTX, stage grouping can be undertaken on the basis of N and M or pN and pM findings.
  **Example**
  A firm head of pancreas with a grossly involved peripancreatic lymph node and no signs of distant metastasis at surgery – TXN1M0, stage IIB.

- Despite NX/pNX, stage grouping can be undertaken when M/pM classification is possible.
  **Example**
  A carcinoma of the pancreas with liver metastasis T1NX M1, stage IV. Cases with M1 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**
  Carcinoma of the oesophagus with invasion of trachea, regional lymph nodes not assessable, no signs of distant metastasis – T4aNXM0, stage III.

- Cases of Tis (clinical classification based on biopsy) or pTis (pathological classification based on the examination of the resected specimen) are always classified as stage 0, when combined in the NX/pNX and M0, because by definition no metastasis can be present.

- If substages (A, B, etc.) are designated in the list of stage grouping, 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.
  **Example**
  Oesophageal carcinoma: T4aNX – stage IIIA or stage IIIC: should be classified as stage III NOS (not otherwise specified), not as unknown.

6. After neoadjuvant therapy, if the primary tumour has completely disappeared but lymph node metastasis remained, e.g. oesophagus, ypT0 pN1 M0, the stage can be calculated by assuming that T equals the lowest number and the N essentially determines the stage, therefore stage IIIB.
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 traditional R classification, not only is local-regional residual tumour to be taken into consideration, but also distant residual tumour in the form of remaining distant metastasis. Variation in 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 residual tumour cannot be detected by any diagnostic means. R0 classification, therefore, does not exclude non-detectable residual tumour, 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, 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 residual tumour is determined using clinical methods. Following surgical treatment, the R classification requires a 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

pT3pN1M1 colon cancer with resection for cure of both the primary tumour and a liver metastasis: R0 (colon); R0 (liver)

In tumour specimens with 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 arise in cases 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 these cases the classification RX (presence of residual tumour cannot be assessed) is appropriate.
The presence of non-invasive carcinoma at the resection margin should be indicated by the suffix (is).

**Example**

Invasive carcinoma of the breast with associated in situ component. Breast-preserving surgery, according to the surgeon, was complete. Histology shows:

a) Invasive carcinoma at the resection margin: R1

b) Invasive carcinoma completely removed, however, 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 [17].

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:

**Figure 1.1 R classification following surgery**
1. Imprint cytology of the resection margin (surface), introduced by Veronesi et al. [7] for breast cancer, but applicable to stomach cancer and other tumour types as well.

2. Cytological examination of ascites or abdominal lavage fluid to detect grossly non-recognizable metastasis on the peritoneum. This was applied to gastric carcinoma [11, 12, 18]. In the R classification R1(cy+) may be used [16, 17].

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. [19] for gastric carcinomas and are reviewed by Pantel et al. [20] (see pages 9–11 regarding detection of isolated tumour cells and evidence of tumour by non morphological 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 is R1 used, otherwise it is R0.

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

However, in the recent years, an alternative definition of resection margin involvement has gained increasing acceptance, at first for the circumferential resection margin (CRM) in rectal cancer [21, 22, 23] 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 [23, 24, 25, 26]. It has been supported in the USA [27–29].

Following a total mesorectal excision in the management of rectal cancer, it is recognized that the CRM is of great prognostic importance and that rather than referring to tumour within 1 mm of that margin as being R1, it can be classed as CMR positive.

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

With regards to the overall prognostic relevance of the R classification, distant metastasis should be included; this is in accordance with the original definition in 1977 [30].
Further confusion results from different definitions of resection margin involvement: direct involvement of the resection margin by tumour or minimal distance between tumour and resection margin of ≤1 mm. To avoid confusion, a proposal for an expanded uniform R classification recently has been published [16]. This proposal differentiates between the following categories:

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RX</td>
<td>Presence of residual tumour cannot be assessed</td>
</tr>
<tr>
<td>R0 &gt;1 mm</td>
<td>No residual tumour, minimal distance between tumour and resection margin &gt;1 mm</td>
</tr>
<tr>
<td>R0 ≤1 mm</td>
<td>No residual tumour, minimal distance between tumour and resection margin ≤1 mm</td>
</tr>
<tr>
<td>R1-dir</td>
<td>Microscopic residual tumour, tumour directly at the resection margin (tumour transected)</td>
</tr>
<tr>
<td>R2a</td>
<td>Local macroscopic residual tumour</td>
</tr>
<tr>
<td>R2b</td>
<td>Distant macroscopic residual tumour</td>
</tr>
<tr>
<td>R2c</td>
<td>Macroscopic residual tumour in both sites</td>
</tr>
</tbody>
</table>

Further discussion of the R classification, including its application to leukaemias and malignant lymphomas and after non-surgical treatment can be found in Wittekind et al. [31].

Following neoadjuvant therapy in the R classification, only 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 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 [32].

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)
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 TNM Rule No. 5 (page 3ff).

**y Symbol – Classifying Treated Tumours**
In the TNM and pTNM classification the extent of cancer prior to therapy is assessed. 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 does not have the same reliability as the pTNM classification after surgery alone. The ypTNM classification deals with the extent of cancer after neoadjuvant therapy. Therefore, the yTNM/ypTNM should consider only viable tumour cells and not signs of regressed tumour tissue such as necrotic cell debris, scars, fibrotic areas, fibrotic nodules, granulation tissue, mucin lakes, etc.

In analyzing results differentiation should always be made between patients treated with primary surgery (cTNM, pTNM) and those treated with 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:

\[
\text{Stage } y(p)0 = ypT0N0M0 \\
\text{Stage } y(p)is = ypTisN0M0
\]

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 [33]
- The different clinical consequences, in particular in cases of yT0, ypT0, stage y0

After multimodal treatment, histological grading may be unreliable.
Following neoadjuvant therapy the extent of residual tumour found at resection reflects the response to the preceding therapy. Various ways of describing the extent have been described (see Table 1.2).

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

Table 1.2  Tumour sites and references of neoadjuvantly treated tumour entities

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all gastrointestinal sites</td>
<td>Werner and Höfler 2000 [34]</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Braun et al. 1989 [35]</td>
</tr>
<tr>
<td></td>
<td>Hermann et al. 2001 [36]</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Japanese Society Esophagus Diseases 1990 [37]</td>
</tr>
<tr>
<td></td>
<td>Mandard et al. 1994 [38]</td>
</tr>
<tr>
<td></td>
<td>Baldus et al. 2004 [39]</td>
</tr>
<tr>
<td></td>
<td>Hermann et al. 2006 [40]</td>
</tr>
<tr>
<td>Stomach</td>
<td>Japanese Gastric Cancer Association 1998 [41]</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>Dworak et al. 1997 [44]</td>
</tr>
<tr>
<td></td>
<td>Japanese Society for Classification of Cancer of Colon and Rectum (JSCCR) 1997 [45]</td>
</tr>
<tr>
<td></td>
<td>Wheeler et al. 2002 [46]</td>
</tr>
<tr>
<td></td>
<td>Ryan et al. 2005 [26]</td>
</tr>
<tr>
<td></td>
<td>Williams et al. 2007 [47]</td>
</tr>
<tr>
<td></td>
<td>Bateman et al. 2009 [48]</td>
</tr>
<tr>
<td>Anal canal</td>
<td>Klimpfinger et al. 1994 [49]</td>
</tr>
<tr>
<td>Liver</td>
<td>Adachi et al. 1999 [50]</td>
</tr>
<tr>
<td>Pancreas (ductal adenocarcinoma)</td>
<td>Evans et al. 1992 [51]</td>
</tr>
<tr>
<td>Lung</td>
<td>Junker et al. 2001 [52]</td>
</tr>
<tr>
<td></td>
<td>Langner et al. 2003 [53]</td>
</tr>
<tr>
<td>Bone tumours/osteosarcoma</td>
<td>Huvos 1991 [54]</td>
</tr>
<tr>
<td></td>
<td>Salzer-Kuntschick et al. 1983 [55]</td>
</tr>
<tr>
<td>Soft tissue tumours</td>
<td>Schmidt et al. 1993 [56]</td>
</tr>
<tr>
<td>Breast</td>
<td>Chevallier et al. 1993 [57]</td>
</tr>
<tr>
<td></td>
<td>Sinn et al. 1994 [58]</td>
</tr>
<tr>
<td></td>
<td>Sataloff et al. 1995 [59]</td>
</tr>
<tr>
<td></td>
<td>Fisher et al. 2002 [60]</td>
</tr>
<tr>
<td></td>
<td>Ogston et al. 2003 [61]</td>
</tr>
<tr>
<td></td>
<td>RCB System (Symmans et al. 2007 [62])</td>
</tr>
</tbody>
</table>
The AJCC has proposed the following to describe the response to neoadjuvant therapy for rectal cancer [26]. Table 1.3 addresses this issue.

### Recurrent Tumour, r Symbol

The prefix ‘r’ is used for classification of recurrent tumours (stage grouping is not appropriate for recurrent tumours). Whereas 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 disease may be created. An example of such a ‘pathogram’ is demonstrated in Table 1.4.

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

**Example**

Previous total gastrectomy, without remaining local-regional residual tumour. Local recurrence at the oesophagojejunalostomy 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. On the other hand, 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 noted that assignment of M0 by pathological assessment (pM0) is possible only at autopsy.

**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).

**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.

Tumour deposits (satellites), i.e. macro- or microscopic nests or nodules, in the lymph drainage area of a primary carcinoma without histological evidence of residual lymph node in the nodule, may represent discontinuous spread, venous invasion (V1/V2) with extravascular spread or a totally replaced lymph node. If a nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour), it should be recorded as a

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### Table 1.4  ‘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 2002</td>
<td>Initial local excision of rectal carcinoma</td>
<td>pT1pNXM0</td>
<td>R1</td>
</tr>
<tr>
<td>July 2002</td>
<td>Radiotherapy, followed by anterior resection</td>
<td>ypT0pN0M0</td>
<td>R0</td>
</tr>
<tr>
<td>October 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>April 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>July 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>April 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>July 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>October 2006</td>
<td>Liver tumour resection</td>
<td>rT0N0M1 (liver)</td>
<td>R0</td>
</tr>
<tr>
<td>January 2008</td>
<td></td>
<td>rT0N0pM1</td>
<td>R0</td>
</tr>
<tr>
<td>Last contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January 2011</td>
<td></td>
<td>T0N0M0</td>
<td></td>
</tr>
</tbody>
</table>
positive lymph node, and each such nodule should be counted separately as a lymph node in the final determination.

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

**Pn – Perineural Invasion**

In the 7th edn of the TNM classification [8], perineural invasion was introduced as a new and optional parameter. The findings of the Pn classification have been shown to be an additional prognostic factor [63]. 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**

The C (certainty) factor, introduced since the 4th edn of TNM [64, 65], is included in the 7th edn [8]. However, for describing the certainty of clinical classification (C1-C3) it is seldom used. Because of interest in the differentiation between imaging methods such as ultrasound, CT and magnetic resonance imaging (MRI), prefixes have been proposed for the clinical staging of rectal carcinoma by Schaffzin et al. [66] and Moran et al. [67]:

- 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. For example: in head and neck where cervical lymph nodes are positive with squamous cell carcinoma and there is no evidence of a primary: T0N2M0, stage III. If the lung contains multiple nodules of malignant melanoma with no primary site identified, the coding would be T0NXM1, stage IV.

**Staging of Tumours for Which No TNM Classification is Provided**

Staging according to the rules of the SEER Program [2] is recommended if no TNM classification is provided. Staging is based on the concept of local, regional and distant.
Explanatory Notes – General

- 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 analyzed separately.

**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 hepatocellular carcinoma see Edmondson and Steiner [68]. For histopathological grading of invasive breast carcinoma see Elston and Ellis [69].

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 (G1-2) and G3 and G4 as high grade (G3-4). In some tumour sites, no differentiation is made between G3 and G4, and therefore the category G3-4 is used. This is valid for carcinoma of the penis, prostate, kidney, renal pelvis, ureter, urinary bladder and urethra.

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

A grading system has been proposed for well-differentiated neuroendocrine tumours (carcinoids) and well-differentiated neuroendocrine carcinomas. The grading system depends on mitotic count and Ki-67 index [8].
Only three grades (G1–G3) are used for all gynaecological sites except gestational trophoblastic tumours.

Grading is not applicable for the following: upper aerodigestive tract malignant melanoma, carcinoma of the thyroid, pleural mesothelioma, malignant melanoma of the skin, Merkel cell carcinoma, uterine sarcomas, gestational trophoblastic tumours, malignant testis tumours, malignant melanoma of uvea and retinoblastoma.

For undifferentiated carcinomas of the oesophagus, stomach, 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 lung and breast. In those cases the category G4 is not applied [70].

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

- Undifferentiated carcinoma
- Small cell carcinoma
- Large cell carcinoma of 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 high grade [71]; in contrast, grading that considers the histologically invasive edge is appropriate for predicting the prognosis of oral squamous cell carcinoma [72].

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

Grading is generally performed by a combined evaluation of various histological and cytological features, including similarity to tissue of origin, cell arrangement, cellularity, differentiation, cellular and nuclear pleomorphism, mitotic activity and necrosis. Grading is a semiquantitative, sometimes subjective procedure, which requires considerable experience by the pathologist. To reduce individual 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, and the scores for each variable added into a total malignancy score for each tumour. A high malignancy score suggests a poorly differentiated tumour.
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.

References


[23] Quirke P. The pathologist, the surgeon and colorectal cancer – get it right because it matters. Prog Pathol 1998; 4:201–213.


