Recording and Reporting of Urothelial Tumours of the Urinary Tract

Contents

Introduction

Several studies have shown great variability among registries in the criteria for recording and reporting urinary tract tumours. In addition, following the publication of the last "*Standards and guidelines for cancer registration in Europe*" in 2003, knowledge about the biology and pathology of urinary tract tumours and their classification has varied and increased substantially.

Recording (registration, coding and classification) and reporting (counting in the statistics of incidence and survival) of urothelial tumours requires the application of criteria that should take into account the combination of the following aspects:

- Primary site
- Histological type
- Grade
- Extent of invasion
- Multi-centricity
- Recurrences and the time interval between tumours
- Progressions and the time interval between tumours
- Difficulties in the obtaining of the result of biopsies
- Recording stage
- Existence of tumours diagnosed before the registry's period of recording
- The residence of patients at the time of diagnosis of each tumour
- Standard criteria for multiplicity

It is important to differentiate between **recording** (registration) and **reporting** (counting) tumours. A cancer registry can record several tumours of the urothelium (of different site, grade or invasion) of the same patient but according to international criteria and for the purposes of comparability, only one or a part of them is actually reported.

Entering into force

The new recommendation is published on the website on the 10-06-2022. These recommendations must be applied to all tumours with an incidence date on or after the 1st January 2022.

Recommendations for **recording** urothelial tumours

Principles

These principles apply to all urothelial tumours (transitional cell tumours) (**8120-8131, 8020, 8031, 8082**) regardless of the site of the tumour (renal pelvis, ureter, urinary bladder or urethra –C65 to C68–). Sarcomas and other histological types of cancer (e.g. adenocarcinomas, squamous carcinomas or neuroendocrine tumours) of the urinary tract are **not** included in these recommendations although they appear in the urinary tract and must also be recorded by the registries.

The recording and coding of urothelial tumours include: the date of incidence, topography, morphological type, behaviour and grade. It is, therefore, essential to have access to the pathological examinations (reports).

For the purposes of these recommendations, **synchronous tumours** are considered those that are diagnosed **within four months of each other**. Metachronous tumours are those that are diagnosed more than four months apart.

Rules

Criteria for recording (inclusion) urothelial tumours (see Annex 1 for examples of what should be recorded)

1. **Types to be included**: The following types of tumours arising in the urinary tract must be recorded:
    1. Non-invasive papillary urothelial carcinoma, low-grade
    2. Non-invasive papillary urothelial carcinoma, high-grade
    3. Urothelial carcinoma in situ (Carcinoma in situ)
    4. All invasive carcinomas
    5. Tumour with histologic examination but invasion cannot be assessed
    6. Tumour with cytological examination only (see rule 2.b, page 6)
    7. Tumour with no microscopic confirmation (see rule 2.c, page 6)

Note: Papillary urothelial neoplasms of low malignant potential (PUNLMP) is a papillary urothelial tumour with minimal atypia (code 8130/1), so it is not compulsory to record it. Urothelial papillomas, inverted urothelial papillomas, urothelial proliferation of uncertain malignant potential and urothelial dysplasia are not malignant, therefore recording is not recommended in a cancer registry. However, cancer registries that are interested in any of these entities for any reason may register them if they wish, but they should never be counted in the incidence results.

2. **Multiples sites**: If a patient presents with several (synchronous or metachronous) urothelial tumours in different sites, record all tumours of different three-digit sites (C65-C68) and laterality (if renal pelvis or ureter). If a metachronous tumour is diagnosed in the ureter or urethra after cystectomy, it should not be recorded if it has arisen at the surgical margin because it should be considered as a local recurrence of the removed tumour in the urinary bladder except if it is a progression.

3. **Progressions**: If a patient presents with several urothelial tumours in the same three-digit topographical site that includes some progression of the disease, **register the first tumour** and then subsequently only those tumours that represent a chronological progression. The following series shows the order that represent a progression:

    Non-invasive, low grade (TaG1) → Non-invasive, high grade (TaG3) → In situ (Tis) → → Invasive, superficial (T1) → Muscle-invasive (T2+)

    Due to the special characteristics of urothelial tumours, the recording of the different stages should be done for these tumours in order to know their progression. Remember that **all known steps of this progression should be recorded**. Therefore, for example, the recording of a T2+ invasive tumour does not replace the recording of a T1 invasive tumour if the latter is known.

4. **Recurrences**: Tumours that represent recurrences (not progressions) with the same or lower level of invasion and degree **do not have to be recorded**.

5. **Synchronous urothelial tumours of the same site and laterality**: If a patient presents with more than one urothelial tumour in the same three-digit topographical site and laterality (if renal pelvis or ureter) in a short period of time (≤4 months – i.e. synchronous–), **record only the most aggressive of them** (based on the progression table in point 3 above) but with the date of diagnosis taken from the first tumour.
   This criterion also applies to tumours whose resection is performed in two phases. In these cases, the temporal course of clinical investigation should also be considered because sometimes initial resections are not complete or the second look is sometimes delayed, particularly in old patients.

6. **Codes of site in synchronous tumours of bladder**: Record synchronous tumours of the bladder using the synchronous tumour rule (rule 5). If the highest level of progression is present in more than one tumour and in more than one subsite (four-digit topography), code the site as C67.8 even if the tumours are not contiguous. If they appear in the same subsite, codify the corresponding subsite.

7. **Synchronous urothelial tumours of different site:** If a patient presents with more than one urothelial tumour in different three-digit topographical sites in a short period of time (≤4 months –synchronous–), record each tumour separately, each one with its corresponding topography, morphology, behaviour codes and incidence date (do not use grouping code C68.9 for registration purpose).

8. **Bilateral tumours**: If a patient presents with several (synchronous or metachronous) urothelial tumours in both sides of the same paired organ (e.g. right and left pelvis or right and left ureter), record all the tumours of each side of each three digit site following rules 3 to 6 (e.g. 1st urothelial carcinoma in right ureter and its progressions, and 1st urothelial carcinoma in left ureter and its progressions).

9. **Mixed situations of multiplicity, progressions and synchronicity/metachronicity**: If a patient presents with a combination of synchronous and metachronous multiple urothelial tumours in the same and/or different three-digit sites, record them according to rules 2 to 8.

10. **First tumour occurring outside the area of registration**: A patient can move from one residence to another, so place of residence should be related to the tumours and not to the patient.

    If information is available showing a patient resident in the coverage area of the registry has been previously diagnosed with a urothelial tumour(s) when resident outside the registration area, record all of them (the ones occurring outside the area of registration and the ones diagnosed being resident in the area of the registry) according to rules 2 to 8 (that enables the tumours to be flagged as 'Extra-regional' for reporting purposes).

The recording of a first tumour diagnosed outside the area of registration allows the registry to know if a subsequent tumour is a recurrence or progression (recorded but not reported as incident).

The recording of this information prevents over-reporting: urothelial tumours tend to recur and progress. If a person had a first tumour whilst resident outside the registration area and the tumour is not recorded, any subsequent recurrences or progressions would be mistakenly considered as the first (reportable) cancer because we do not know that they had a previous cancer.

11. **First tumour occurring before the operation period of the registry**: If information is available showing a patient resident in the coverage area of the registry has been diagnosed with one or more urothelial tumours before the operation period of the registry, record all their tumours (the ones diagnosed before and the one diagnosed after first date of operation of the registry) according to rules 2 to 8.

The recording of tumours diagnosed before the period of operation of the registry allows the registry to know whether subsequent tumours should be recorded as progression or recurrence (recorded but not reported as incident).

The recording of this information also prevents over-reporting in cases of recurrence.

Rules for classification and coding

1) Classification: All urothelial tumours must be coded according to the most recent version of the *International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)* (these classifications are almost equivalents to the WHO classification).

2) Morphology, behaviour and grade

a) Codes of the most frequent categories when histology is available – Specific guidance on grades is in Part e).

Tumour type	Morphology/ Behaviour	Grade
Non-invasive (papillary) urothelial carcinoma, low-grade	8130/2*	1
Non-invasive (papillary) urothelial carcinoma, high-grade		3
Non-invasive (papillary) urothelial carcinoma, grade unknown		9
Urothelial carcinoma (with histologic examination), but invasion cannot be assessed		
- Papillary term mentioned or papillary appearance (exophytic lesion)	8130/2**	1/3/9
- Papillary term not mentioned or no information about appearance	8120/2 ***	
- The clinical impression is of invasive disease	8120/3****	3
Urothelial carcinoma in situ (carcinoma in situ)	8120/2	3*****
Invasive carcinoma, NOS [(1)]	8010/3	3*****
Invasive urothelial carcinoma	8120/3	3*****

[(1)] Although most carcinomas of urinary tract are urothelial, there are also other carcinomas such as squamous or adenocarcinoma. Therefore, if *urothelial* or *transitional cell* is not specified on the pathological

report, code "8010/3". But if non-invasive urothelial carcinoma was previously diagnosed, record (code) as urothelial carcinoma (8120/3), provided that prostate carcinoma invading the urinary bladder is ruled out. Also, if the concept urothelial is in the tumour description, code 8120/3 even if not specified in the final diagnosis.

(*) **When the term "papillary" is not specified in the pathological report but the pathology report indicates an urothelial carcinoma with pTa stage, code 8130/2 (plus grade, if specified)**

(**) In this case, code pTa.

(***) In this case the code pT is **pTX** (and not pTis), so as not to be confused with Carcinoma in situ.

(****) If the clinical impression is of invasive disease, then code with /3 behaviour code and grade 3.

(*****) All in situ and invasive carcinomas must be recorded as high grade. Although the pathology report may indicate "low grade" or not indicate a grade, if it is an in situ or invasive tumour, it must be considered high grade.

b) Codes when only cytological examination is available*:

Cytology results	Morphology* /Behaviour**	Grade
High grade urothelial carcinoma or "suspicious for high-grade urothelial carcinoma" (SHGUC of the Paris classification). (See ANNEX 2, section "Paris System reporting for urine cytology", paragraph "Behaviour of high grade tumours diagnosed by cytology only").	8130/2 (papillary appearance) or 8120/2	3

(*) If you only have cytological examination, try to find out if the tumour has a papillary appearance (8130) or not (8120) by reviewing the imaging.

(**) If the clinical impression (e.g. scans) is of invasive disease, then code with /3 behaviour code.

Note: Non-urothelial malignant cells seen on cytology should be coded according to the pathology report and clinical information.

If the topography of the tumour is highlighted on radiology/imaging, code the specific site. Otherwise, code the topography C68.9 (urinary tract, NOS).

c) Codes when only non-microscopic confirmation is available (histo/cytopathological evidence unavailable): When histo/cytopathological evidence is unavailable but clinical appearance is confirmed by the clinician, use the following codes**.**

Tumour type	Morphology/Behaviour	Grade
No microscopic confirmation: Tumour clinically malignant	8000/3	9
No microscopic confirmation: Tumour NOS	Do not record*	

(*) If recorded, code: 8000/1 Grade 9

d) Codes of behaviour for unknown level of invasion.

d1) "Subepithelial connective tissue" is not present in resection.

First of all, ask for pathologist assessment. If it is not possible or the pathologist can't give an answer:

- If "Urothelial papilloma": **/0** (there is no recommendation to record this tumour).
- If "Papillary urothelial neoplasm of low malignant potential (PUNLMP)": **/1** (there is no recommendation to record this tumour but if it is recorded, code 8130/1 without

grade and pT) (some pathologists can erroneously code pTa in PUNLMP. pTa should be used only in carcinomas).

- If "Urothelial proliferation of uncertain malignant potential": **/1** (there is no recommendation to record this entity).
- If "Non-invasive papillary urothelial carcinoma" or "Carcinoma in situ": **/2**
- If morphological characteristics are not specified: **/2** (Codify morphology 8120 (no papillary appearance) or 8130 (papillary appearance) depending on the appearance at endoscopy).

d2) "Muscularis propria" is not present in resection.

First of all, ask for pathologist assessment. If it is not possible or the pathologist can't give an answer:

- If sub-epithelial connective tissue is invaded: **/3**.
- Otherwise, code behaviour **/2** (according to the morphological characteristics).

e) Grade

The recording of grade is especially important for the non-invasive papillary urothelial carcinomas where it is necessary to distinguish between the high-grade (3) and the low-grade (1) tumours.

Codes according to the description in the pathological report:

Description in the pathology report	Code
Grade 1	Low grade (1)
Grade 1/2 (low grade or no grade mentioned)	Low grade (1)
Grade 2 low grade	Low grade (1)
Grade 2 high grade	High grade (3)
Grade 2/3 (high grade or no grade mentioned)	High grade (3)
Grade 3	High grade (3)

As a result, code 2 will no longer be used to code the grade.

3) Codes for urothelial carcinomas with other morphological terms:

a) Urothelial cell carcinoma with epidermoid component (squamous divergent differentiation): 8120

Code **squamous carcinoma** only if it is a **pure** squamous carcinoma: **8070**

"Pure squamous carcinomas" should be registered separately from urothelial carcinomas because they are a different tumour type from urothelial carcinomas and are treated differently ([1,2]), even if the *2004 International Rules for Multiple Primary Cancers* include this two tumours in the same morphology group.

b) Urothelial cell carcinoma with adenocarcinomatous component (glandular divergent differentiation): 8120

Code **adenocarcinoma** only if it is a **pure** adenocarcinoma: **8140**

"Pure adenocarcinomas" should be registered separately from urothelial carcinomas because they are a different tumour type from urothelial carcinomas.

c) **Urothelial cell carcinoma subtypes and ICD-O-3 specific code** (new specific codes may appear in subsequent versions of ICD-O/WHO Classification)**:**
   - Micropapillary: **8131**
   - Lymphoepithelioma-like: **8082**
   - Sarcomatoid: **8122**
   - Giant cell: **8031**
   - Undifferentiated: **8020**

d) **Urothelial cell carcinoma without specific subtype in ICD-O-3 classification (e.g. nested, microcystic, plasmacytoid, signet ring cell, diffuse, lipid-rich, clear-cell)** (some of these may have specific codes in subsequent versions of ICD-O/WHO Classification)**: 8120**

e) **Urothelial cell carcinoma with neuroendocrine component (neuroendocrine differentiation):**
   Always encode neuroendocrine carcinoma **independently of the amount of the neuroendocrine component** (See Annex 2: Comments. Neuroendocrine tumours).
   - Small cell neuroendocrine carcinoma: **8041**
   - Large cell neuroendocrine carcinoma: **8013**
   - Composite small and large cell neuroendocrine carcinoma: **8045**
   - Neuroendocrine carcinoma well-differentiated or low-grade NET: **8240**
   - Neuroendocrine carcinoma moderately-differentiated or high-grade NET: **8249**
   - Neuroendocrine carcinoma, NOS: **8246**

4) **Non-urothelial specific carcinomas[3]:** Non-urothelial tumours of the urinary tract such as (pure) adenocarcinomas, (pure) squamous carcinomas, and neuroendocrine, melanocytic, mesenchymal or lymphoid tumours must be recorded separately from urothelial tumours following the general criteria for other tumours.

Summary table of main criteria of inclusion (according to invasion, grade and existence of progression):

STEPS of **PROGRESSION** →				
1. Non-invasive low grade/grade unknown	**2. Non-invasive high-grade or Invasion cannot be assessed**	**3. In Situ**	**4. Invasive (T1)**	**5. Invasive (T2+)**
8130/2 G1 or 8130/2 G9	**8130/2 G3 or 8120 or 8130/2 G3 or 8120/2 G3**	**8120/2 G3**	**8010/3 G3 or 8120/3 G3 or 8000/3 G9**	**8010/3 G3 or 8120/3 G3 or 8000/3 G9**
Non-Invasive Papillary Carcinoma, Low Grade	Non-Invasive Papillary Carcinoma, High Grade or	Urothelial Carcinoma In Situ	Invasive carcinoma NOS or	Invasive carcinoma NOS or

or Non-invasive papillary carcinoma grade unknown	High grade urothelial carcinoma on cytology or Suspicious for high grade urothelial carcinoma on cytology	or Urothelial carcinoma with histologic examination but invasion cannot be assessed	Invasive urothelial carcinoma or No microscopic confirmation: Tumour clinically malignant	Invasive urothelial carcinoma or No microscopic confirmation: Tumour clinically malignant

For each site (right and left pelvis, right and left ureter, bladder and urethra), this table summarises, which tumours should be registered by application of rules 2 to 8. In summary: after recording the first tumour (/2 or /3) of each site, only record subsequent tumours that represent progression, according to the grouping of categories (columns 1, 2, 3, 4 and 5).

Coding the Basis of Diagnosis

- Histology (Biopsy or surgical resection or autopsy specimen) ……7
- Cytology only (urine) ……5
- Only imaging or cystoscopy without biopsy or autopsy without a tissue diagnosis ……2
- Death certificate only …… 0

In case of doubt, see the ENCR Recommendations on Basis of Diagnosis.

Coding stage

Record "TNM-stage" [1, 4] whenever possible and, at least the "T-category".
This is important to allow Tis tumours to be easily distinguished from other tumours with behaviour /2.

Recommendations for **reporting** urothelial tumours

1. The most important fact to highlight is that **recommendations for recording (registration) (Chapter 2 of these guidelines) provides the raw data which can be subsequently analysed.**

2. **ENCR recommends following IARC/IACR rules to calculate incidence** and therefore you should include only the first urothelial tumour regardless of the behaviour code (/2 or /3) at each site (according to the *"International Rules for Multiple Primary Cancers"*).

3. Data from cancer registry databases can be used to perform multiple analyses as part of local cancer surveillance and service assessment or can be transmitted for National, European or International projects.

The "data call protocol" from international projects should define very accurately the criteria for inclusion of the data to be submitted and should also explain in detail how the data will be analysed for incidence and survival estimations.

Examples:

1. In calculating the incidence of urinary bladder cancer, will a patient's first urothelial tumour be counted regardless of whether it is invasive or non-invasive, or will only urothelial invasive tumours be counted? Will non-urothelial bladder tumours also be included in the calculation?
2. In calculating the survival of urinary bladder cancer, will any patient's first tumour be included in the analysis regardless of its behaviour or will only invasive tumours be considered?

Annex 1: Examples on inclusion criteria for recording

Rule 2: Multiples sites: If a patient presents with several (synchronous or metachronous) urothelial tumours in different sites, record all tumours of different three-digit topography sites (CXX).

Examples:

A patient with a *"Non-invasive High-grade carcinoma" of bladder (1)* followed by an *"In situ carcinoma" of right renal pelvis (2)* followed by an *"Invasive carcinoma" of urethra (3)*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Right renal pelvis			2	
Left renal pelvis				
Right ureter				
Left ureter				
Bladder		1		
Urethra				3

Action: All cases should be recorded.

A patient with a *"Non-invasive High-grade carcinoma" of bladder (1)* synchronous with an *"Invasive carcinoma" of left ureter (2)*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Right renal pelvis				
Left renal pelvis				
Right ureter				
Left ureter				2
Bladder		1		
Urethra				

Action: All cases should be recorded. Do not use the grouping code (C68.9).

Rule 3: Progressions: If a patient presents with several urothelial tumours in the same three-digit topography site that includes some progression of the disease, record/register the first tumour and those tumours that represent a chronological progression. The following series shows the order that represent a progression:

Non-invasive, low grade (TaG1) → Non-invasive, high grade (TaG3) → In situ (Tis) → → Invasive, superficial (T1) → Muscle-invasive (T2+)

Although in many cases non-invasive high grade papillary carcinomas do not follow the same pathway as in situ carcinomas, they sometimes cross and in situ carcinomas are usually more aggressive than non-invasive high-grade papillary carcinomas.

Examples:

A patient with a "*Non-invasive high-grade carcinoma" of bladder (1)* followed by an *"Invasive carcinoma" of bladder (2)*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Bladder		1		2

Action: All cases should be recorded.

A patient with a "*Non-invasive High-grade carcinoma" of bladder (1)* followed by an *"Invasive urothelial carcinoma" of bladder (2)* followed by an *"In situ carcinoma" of bladder (3)*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Bladder		1		2

Action: Only the first and the second (progression) should be recorded. The third one (CIS) is not a progression of the second one (invasive carcinoma).

A patient with a "*Non-invasive high-grade carcinoma" of bladder (1)* followed by an *"In situ carcinoma" of bladder (2)* followed by an *"Invasive carcinoma" of bladder (3)*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Bladder		1	2	3

Action: All cases should be recorded because the second one is a progression of the first one and the third one is a progression of the second one.

A patient with a "*Non-invasive low-grade carcinoma" of bladder (1)* followed by a *"Non-invasive high-grade carcinoma" of bladder (2)*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Bladder	1	2		

Action: All cases should be recorded because the second one is a progression of the first one.

A patient with a "*Non-invasive Low-grade carcinoma" of bladder (1)* followed by an *"In situ carcinoma" of right renal pelvis (2)* followed by an *"Non-Invasive High grade carcinoma" of right renal pelvis (3)* followed by an *"Invasive carcinoma" of bladder (4)* followed by a *"Non-Invasive high-grade carcinoma" of urethra (5)*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Right renal pelvis			2	
Left renal pelvis				
Right ureter				
Left ureter				
Bladder	1			4
Urethra		5		

Action:
- The first should be recorded.
- The second should be recorded because it has a different site than the first.
- The fourth should be recorded because it is a progression of the first
- The fifth should be recorded because it has a different site than the first and the second.
- The third should not be recorded because it is not a progression of the second.

Rule 4: Recurrences: If a patient presents with an urothelial tumour followed by one or several urothelial tumours of the same three-digit site that are recurrences (not progressions) (same or lower level of invasion and degree) of the disease, record/register only the first tumour and not the recurrences.

Example:
A patient with an *"In situ carcinoma" of bladder (1) followed by a "Non-invasive high-grade carcinoma" of bladder (2)* followed by a *"Non-Invasive high-grade carcinoma" of bladder (3)* followed by an *"In situ carcinoma" of bladder (4) and* followed by a *"Non-Invasive high-grade carcinoma" of bladder (5)*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Bladder			1	

Action: Only the first should be recorded. All other are recurrences, no progressions.

Rule 5: Synchronous tumours of the same site: If a patient presents with two or more urothelial tumours in a same three-digit site in a short period of time **(≤4 months –i.e. synchronous–)**, register only the most aggressive of them (with its histological type, behaviour and grade) **but with the date of diagnosis of the first one.**

Examples:
A patient with a "*Non-invasive low-grade carcinoma" of bladder NOS (1)* followed by a synchronous *"Invasive carcinoma" of bladder NOS (2).*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Bladder				2 (with the date of the "*Non-invasive Low-grade carcinoma" -1-)*

Action: Record the invasive carcinoma with the date of the non-invasive low-grade carcinoma.

A patient with an "*Invasive urothelial carcinoma" of anterior wall bladder (C67.3) (1)* followed by a synchronous *"Invasive urothelial carcinoma" of bladder dome (C67.1) (2).*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Bladder				1 (with the date of the "First-*invasive carcinoma" -1-)*

Action: Record as an invasive urothelial carcinoma with the date of the first invasive carcinoma and with the code C67.8 (Overlapping lesion of bladder).

Rule 7: Synchronous tumours of different site: If a patient presents with two or more urothelial tumours in different three-digit sites in a short period of time (≤4 months – i.e. synchronous–), register each tumour separately, each one with its corresponding date of diagnosis (**do not use grouping code C68.9**) (see the second example of the Rule 2).

Rule 8: Bilateral tumours: If a patient presents with several (synchronous or metachronous) urothelial tumours in the both sides of the same paired organ (e.g. right and left pelvis or right and left ureter), record the first tumour of each side of each site (CXX) and the corresponding progressions, if any.

Example:
A patient with a "*Non-invasive Low-grade carcinoma" of left ureter (1a)* with a synchronous *"Invasive carcinoma" of right ureter (1b)* followed by an *"In situ carcinoma" of left ureter (2)* followed by a *"Non-Invasive high-grade carcinoma" of right ureter (3).*

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Left ureter	1a		2	
Right ureter				1b

Action: Record tumours 1a, 1b and 2. Tumours 1a and 1b are synchronous and they appeared in two different ureters. The tumour 2 must be recorded because it is a progression of tumour 1a. The third tumour should not be recorded because it represents a simple recurrence of the tumour 1b.

Rule 9: Mixed situations of multiplicity, progressions and synchronicity/metachronicity: If a patient presents with a mixed combination of multiple synchronous and metachronous urothelial tumours in the same and/or different three-digit topographical sites, record/register them according to rules 2 to 8.

Example:
A patient with a "*Non-invasive low-grade carcinoma" of bladder (1)* followed by a synchronous *"Invasive carcinoma" of bladder (2)* followed by an *"In situ carcinoma" of right renal pelvis (3)* followed by a *"Non-Invasive high-grade carcinoma" of right renal pelvis (4)* followed by an *"Invasive carcinoma" of bladder (5).*

	Non-invasive	Non-invasive	In situ	Invasive

	Low grade	High grade		
Right renal pelvis			3	
Bladder				2 (with the date of the "*Non-invasive Low-grade carcinoma" -1-)*

Action: Tumour 1 and tumour 2 are synchronous at the same site but only the invasive should be recorded (with the date of diagnosis of the first tumour). Record tumour 3 because it appeared in a different site. Do not register tumour 4 (recurrence of tumour 3) or tumour 5 (recurrence of tumour 2).

Rule 10: First tumour occurring outside the area of registration: If a patient resident in the coverage area of the registry has been previously diagnosed with one or several urothelial tumours whilst resident outside the registration area, record all of the tumours according to rules 2 to 8. Since a patient can move from one residence to another, place of residence should be related to the tumours and not to the patient.
Note that only incident (first) tumours occurring inside the area registration will potentially be counted in the incidence according to the objective pursued. The registries should therefore have the possibility to flag tumours that occurred outside the incident area of registration.

Examples:
A patient with a "*Non-Invasive high-grade carcinoma" of bladder (1)* **diagnosed outside the area of registration** followed by an *"In situ carcinoma" of left renal pelvis (2)* and an *"Invasive carcinoma" of bladder (3),* both of them **diagnosed within the area of registration**.

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Left renal pelvis			2	
Bladder		1		3

Action: Record tumour 1 to know that the first tumour of this patient was diagnosed when the patient was not yet resident in the registration area. Record tumour 2 (it appeared in another site) and tumour 3 (it represents a progression of tumour 1).

A patient with an *"Invasive carcinoma" of bladder (1)* **diagnosed outside the area of registration** followed by an *"In situ carcinoma" of right renal pelvis (2)* and a *"Non-invasive high grade carcinoma" of bladder (3),* both of them **diagnosed within the area of registration**.

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Right renal pelvis			2	
Bladder				1

Action: Record tumour 1 to know that the first tumour of this patient was diagnosed when the patient was not yet resident in the registration area and tumour 2 (it appeared at another site). Do not record tumour 3 (it is a recurrence of tumour (1).

Rule 11: First tumour occurring before the operation period of the registry: If a patient resident in the coverage area of the registry has been diagnosed with one or several urothelial tumours before the operation period of the registry, record all of their tumours (both the ones diagnosed before and the ones diagnosed after the registry started operating) according to rules 2 to 8.
Note that only incident (first) tumours occurring after the operation period of the registry will potentially be counted in the incidence according to the objective pursued. The registries should therefore have the possibility to flag tumours that occurred before the operation period of the registry.

Example:
A patient with a *"Non-Invasive high-grade carcinoma" of bladder (1)* **diagnosed before the operation period of the registry** followed by an *"In situ carcinoma" of left renal pelvis (2)* and an *"Invasive carcinoma" of bladder (3),* both of them **diagnosed within the operating period of the registry**.

	Non-invasive Low grade	Non-invasive High grade	In situ	Invasive
Left renal pelvis			2	
Bladder		1		3

Action: Record tumour 1 to know that the first tumour of this patient was diagnosed before the operation period of the registry. Record also tumour 2 (it appeared at another site) and tumour 3 (it is a progression of tumour 1).

Annex 2: Comments

This annex contains a brief commentary on the current state of knowledge of three controversial topics and provides justification for the criteria used within these recommendations.

Grade of the invasive urothelial tumours.

The overwhelming majority of invasive urothelial carcinomas are high grade ([1]). However, some variants (large nested variant of urothelial carcinoma) may present a "pseudo-benign" (deceptively bland) appearance, but this appearance is misleading, since this form has a poor outcome ([5, 6, 7]). On this basis, all invasive urothelial tumours should be recorded as 'Grade 3'.

Paris System reporting for urine cytology [8,9,10,11]

Diagnostic categories of the Paris System:

1. Non-diagnostic/Unsatisfactory
2. Negative for high-grade urothelial carcinoma (NHGUC)
3. Atypical urothelial cells (AUC)
4. **Suspicious for high-grade urothelial carcinoma (SHGUC)**
5. **High-grade urothelial carcinoma (HGUC)**
6. Low-grade urothelial neoplasm (LGUN)
7. Other: primary and secondary malignancies and miscellaneous lesion.

Categories 4 and 5 should be considered as high-grade urothelial carcinomas.

Behaviour of high-grade tumours diagnosed by cytology only: In tumours diagnosed by cytological examination only, a consensus has been agreed upon for high-grade urothelial carcinoma to be coded as Behaviour '2' although it was acknowledged there is a limited evidence base to support either this or coding to behaviour code '3'.

Neuroendocrine tumours.

Neuroendocrine carcinoma: The term should be used in all tumours with small or large cell neuroendocrine histology in any proportion of the tumour ([12]). Code:

- **8041** (small cell neuroendocrine carcinoma)
- **8013** (large cell neuroendocrine carcinoma)
- **8045** (small and large cell carcinoma)
- **8240** (neuroendocrine carcinoma well-differentiated or low-grade)
- **8249** (neuroendocrine carcinoma moderately-differentiated or high grade)
- **8246** (neuroendocrine carcinoma, NOS).

Recording the histological tumour type using the 2016 WHO classification is a required element as this parameter is often of prognostic and therapeutic significance. A tumour is classified as an urothelial carcinoma if there is any urothelial differentiation [including associated urothelial carcinoma in situ (CIS)] with any other types present reported with an estimated percentage. Thus, a carcinoma showing

20% urothelial differentiation and 80% glandular differentiation would be reported under the histological tumour type “Urothelial carcinoma”. **An exception to this rule is for cases with any amount of neuroendocrine component** (small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma) **where classification is now in the neuroendocrine tumour category**. Thus, a mixed tumour with 30% small cell neuroendocrine carcinoma and 70% urothelial carcinoma would be reported under the histological tumour type as neuroendocrine tumour (small cell neuroendocrine carcinoma). This is a controversial issue as reflected by the different approaches recommended by WHO 2016 in chapters on the neuroendocrine tumours and urothelial carcinoma variants. ICCR recommends the latter approach but recognises that the percentage of the neuroendocrine component could inform patient management, particularly with newer treatment modalities such as immunotherapy.

Annex 3: References

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Annex 4: Working group members

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