



# Gestational Trophoblastic Neoplasia Histopathology Reporting Guide

Family/Last name

Date of birth

DD – MM – YYYY

Given name(s)

Patient identifiers

Date of request

DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are **CORE**. Elements in **grey text** are **NON-CORE**.☐ indicates multi-select values ☐ indicates single select values

SCOPE OF THIS DATASET

**CLINICAL INFORMATION** (Note 1)☐ Information not provided**Age** (years)☐ <40☐ ≥40**Antecedent/causative gestation**

(which may not be the immediate antecedent gestation)

☐ Information not provided☐ Term pregnancy☐ Missed abortion/spontaneous abortion☐ Ectopic (tubal or ovarian) pregnancy☐ Hydatidiform mole (complete or partial)**Interval times from the antecedent/causative gestation**  
(months)☐ Information not provided☐ <4☐ 4-6☐ 7-12☐ >12**Presurgical serum hCG level** (mIU/ml)☐ Information not provided☐ <1,000☐ 1,000-10,000☐ >10,000-100,000☐ >100,000**Previous failed chemotherapy**☐ Information not provided☐ None☐ 1 drug☐ ≥2 drugs**OPERATIVE PROCEDURE** (select all that apply) (Note 2)☐ Not specified☐ Hysterectomy☐ Simple total☐ Simple supracervical/subtotal☐ Radical☐ Type not specified☐ Pelvic exenteration☐ Salpingectomy or salpingo-oophorectomy, *specify*

☐ Lymph nodes, *specify site(s)*

☐ Other, *specify*

**SPECIMEN INTEGRITY** (Note 3)☐ Intact☐ Opened☐ Morcellated/fragmented☐ Other, *specify*

**TUMOUR SITE<sup>a,b</sup>** (select all that apply) (Note 4)☐ Indeterminate☐ Uterine corpus☐ Uterine cervix☐ Fallopian tube☐ Left☐ Right☐ Not specified☐ Ovary☐ Left☐ Right☐ Not specified☐ Broad ligament☐ Vagina☐ Other, *specify*

<sup>a</sup> Involving female genital organs.<sup>b</sup> Where multiple sites are involved, report the primary tumour site.**TUMOUR DIMENSIONS** (Note 5)☐ <30 mm☐ 30-50 mm☐ >50 mm☐ Cannot be assessed, *specify*

**BLOCK IDENTIFICATION KEY** (Note 6)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

**HISTOLOGICAL TUMOUR TYPE** (Note 7)

(Value list based on the World Health Organization Classification of Female Genital Tumours (2020))

- ☐ Invasive hydatidiform mole (complete or partial)  
☐ Gestational choriocarcinoma  
☐ Placental site trophoblastic tumour (PSTT)  
☐ Epithelioid trophoblastic tumour (ETT)  
☐ Mixed trophoblastic tumour, *specify the tumour components and percentage of each component*

  


☐ Other, *specify*

  

**MITOTIC COUNT** (Note 8)

(Only applicable for PSTT and ETT)

- ☐ <5 mitoses/10 HPF  
☐ ≥5 mitoses/10 HPF

**OTHER TISSUE/ORGAN INVOLVEMENT** (select all that apply) (Note 9)

- ☐ Not identified  
☐ Lung  
☐ Spleen  
☐ Kidney  
☐ Gastrointestinal tract  
☐ Liver  
☐ Central nervous system  
☐ Other tissue/organs, *specify*

☐ Indeterminate, *explain reasons*

**SEROSAL EXTENSION**<sup>c</sup> (Note 10)

- ☐ Cannot be assessed  
☐ Not identified  
☐ Identified

<sup>c</sup> Core element for PSTT and ETT; non-core element for invasive mole and choriocarcinoma.

**LYMPHOVASCULAR INVASION** (Note 11)

- ☐ Indeterminate  
☐ Not identified  
☐ Present

**MARGIN STATUS**<sup>c</sup> (Note 12)

- ☐ Cannot be assessed  
☐ Not involved

Distance of tumour from closest margin  mm

Specify closest margin, if possible

- ☐ Involved

Specify margin, if possible

<sup>c</sup> Core element for PSTT and ETT; non-core element for invasive mole and choriocarcinoma.

**LYMPH NODE STATUS** (Note 13)

- ☐ Cannot be assessed  
☐ No nodes submitted or found

**Site 1**

Number of nodes examined

Number of positive nodes

**Site 2**

Number of nodes examined

Number of positive nodes

**COEXISTING NON-NEOPLASTIC TROPHOBLASTIC LESIONS** (Note 14)

- ☐ None identified  
☐ Present (select all that apply)
  - ☐ Exaggerated implantation/placental site (EPS)
  - ☐ Placental site nodule (PSN)
  - ☐ Non molar placental tissue
  - ☐ Hydatidiform mole
  - ☐ Other, *specify*

**ANCILLARY STUDIES** (Note 15)

- ☐ Not performed
- ☐ Performed (select all that apply)

☐ Immunohistochemistry performed for diagnosis, specify test(s) and result(s)


☐ Immunohistochemistry performed for therapeutics (e.g., PD L1), specify test(s) and result(s)


☐ DNA genotyping performed for diagnosis, specify test(s) and result(s)


☐ DNA genotyping performed for risk score assessment, specify test(s) and result(s)


**Representative blocks for ancillary studies, specify those blocks best representing tumour and/or normal tissue for further study**

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**PATHOLOGICALLY CONFIRMED DISTANT METASTASIS** (Note 16)

- ☐ Not identified
- ☐ Present, specify site(s)


**PROVISIONAL PATHOLOGICAL STAGING** (Note 17)**FIGO (2001 edition)<sup>d</sup>**

- ☐ I Gestational trophoblastic tumours strictly confined to the uterine corpus
- ☐ II Gestational trophoblastic tumours extending to the adnexae or to the vagina, but limited to the genital structures
- ☐ III Gestational trophoblastic tumours extending to the lungs, with or without genital tract involvement
- ☐ IV All other metastatic sites

<sup>d</sup> Reprinted from *Int J Gynecol Cancer*, Volume 11(1), Kohorn EI, The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment, pages 73-7, 2001, with permission from BMJ Publishing Group.

**TNM Staging (UICC TNM 8<sup>th</sup> edition 2016)<sup>e</sup>**

**TNM Descriptors** (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post-therapy

**Primary tumour (pT)**

- ☐ TX Primary tumour cannot be assessed
- ☐ T0 No evidence of primary tumour
- ☐ T1 Tumour confined to uterus
- ☐ T2<sup>f</sup> Tumour extends to other genital structures: vagina, ovary, broad ligament, fallopian tube by metastasis or direct extension

<sup>e</sup> Reproduced with permission. Source: *UICC TNM Classification of Malignant Tumours, 8<sup>th</sup> Edition*, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 6<sup>th</sup> October 2020).

<sup>f</sup> Genital metastasis (vagina, ovary, broad ligament, fallopian tube) is classified T2.

## Definitions

### CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence<sup>1</sup>). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the expert committee. An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

### NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the Dataset Authoring Committee.

 [Back](#)

## Scope

The dataset has been developed for the pathology reporting of resection specimens for primary uterine gestational trophoblastic neoplasia (GTN) which includes invasive hydatidiform mole of either complete or partial type, gestational choriocarcinoma, placental site trophoblastic tumour and epithelioid trophoblastic tumour. The dataset should be used primarily for hysterectomy specimens. This dataset may also be used for rare myomectomy specimens but not all elements will be applicable. The dataset is not intended to be used for extrauterine primary lesions.

Non-gestational trophoblastic tumours (germ cell or somatic origin) and metastatic tumours are excluded from this dataset.

The authors of this dataset can be accessed [here](#).

 [Back](#)

## Note 1 – Clinical information (Non-core)

The clinical management of the patient with GTN is primarily based on the 2000 World Health Organization (WHO)/International Federation of Gynecology and Obstetrics (FIGO) risk assessment.<sup>2,3</sup> This requires the following important clinical history: patient age; type of antecedent/causative gestation; intervals between the tumour presentation and the antecedent/causative gestation; presurgical serum human chorionic gonadotropin (hCG) value; and previous response to chemotherapy.<sup>2,3</sup>

It is important to note, that the patient's immediate antecedent pregnancy may not be the causative pregnancy that is pathogenetically linked to the gestational trophoblastic neoplasm. Since the type of and time interval to the causative pregnancy are both critical components of the risk assessment scoring system, molecular genotyping of the neoplasm (and the suspected prior gestation(s) if tissue is available) should be pursued. Genotyping analysis can provide definitive evidence of pathogenetic relationship to a prior hydatidiform mole or a term placenta, and in patients with multiple prior gestations to confirm the time interval between the neoplasm and the causative gestation.<sup>4</sup> Table 1 shows the WHO Prognostic Scoring Index.<sup>2,3</sup>

It is also important to note that although there are four trophoblastic tumour types listed under GTN, invasive mole and choriocarcinoma are by far the most common and they could follow FIGO and Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging, as well as WHO risk scoring system.<sup>2,3,5,6</sup> However, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) are different clinical entities as they are mostly diagnosed months or years after the index gestation and therefore are not part of the post-molar GTN spectrum. PSTT and ETT are tumours that more resemble many somatic malignancies in that they require hysterectomy with or without oophorectomy for management and depending on the pathological staging, the patient may or may not receive post-surgery chemotherapy. The WHO risk scoring system is not appropriate for PSTT and ETT.

**Table 1: World Health Organization Prognostic Scoring Index for invasive mole and choriocarcinoma.**<sup>2,3</sup>

Prognostic Factor	Risk Score				Factor Score
	0	1	2	4	
Age (years)	<40	≥40			
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy		
Interval months from index pregnancy	<4	4–6	7–12	>12	
Pretreatment hCG (IU/mL)	<10 <sup>3</sup>	10 <sup>3</sup> to <10 <sup>4</sup>	10 <sup>4</sup> to <10 <sup>5</sup>	≥10 <sup>5</sup>	
Largest tumour size, including uterus (cm)	<3	3–5	>5		
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver	
Number of metastases identified		1–4	5–8	>8	
Previous failed chemotherapy			Single drug	Two or more drugs	

Note: Low risk score ≤6; high risk score >7.



Back

## Note 2 – Operative procedure (Core)

The type of operative procedure is defined by the operating surgeon predominantly based on the tumour site and extent. It determines the specimen(s) received for pathology evaluation and therefore it is an essential part of the pathology report.

 [Back](#)

## Note 3 – Specimen integrity (Core)

The specimen integrity may have a significant impact on the pathological evaluation and it may also influence the patient's clinical management and outcome. Specimen morcellation/fragmentation could hamper the gross orientation, identification of different anatomic structures, and determination of tumour size and location. In addition, intraoperative morcellation/fragmentation may potentially result in inadvertent tumour spread, which should be taken into account during treatment planning.

 [Back](#)

## Note 4 – Tumour site (Core)

Recording the anatomic site(s) of the tumour is important for FIGO staging.<sup>2,3</sup>

When the tumour is present at multiple sites, determination of the primary tumour site is crucial with regard to tumour staging and identifying the causative antecedent gestational event for WHO risk score assessment.<sup>2,3</sup> Ancillary studies, including immunohistochemistry and DNA genotyping, are recommended whenever possible (see **Note 15 ANCILLARY STUDIES**).

 [Back](#)

## Note 5 – Tumour dimensions (Core)

The largest tumour dimension (<30 millimeters (mm), 30-50 mm and >50 mm) is an integral parameter in the WHO risk scoring algorithm (see **Note 1 CLINICAL INFORMATION**).<sup>2,3</sup>

 [Back](#)

## Note 6 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.

 [Back](#)

## Note 7 – Histological tumour type (Core)

Gestational trophoblastic neoplasia (GTN) (WHO/FIGO)<sup>2,3</sup> is defined by post-molar evacuation serum hCG monitoring or a tissue diagnosis of choriocarcinoma as follows:

- Three or more serum hCG values without significant changes (plateau) over four weeks.
- A rise of serum hCG of 10% or more for two values over three weeks or longer.
- Persistent elevation of serum hCG six months after evacuation of a mole.
- Tissue diagnosis of gestational choriocarcinoma.

If the diagnostic tissue specimen (biopsy, hysterectomy, etc.) is available, all GTN should be typed based on the most recent edition of the WHO Classification of Tumours of Female Genital Tumours, 5<sup>th</sup> edition, 2020 (Table 2).<sup>7</sup> The International Collaboration on Cancer Reporting dataset includes 5<sup>th</sup> edition Corrigenda, June 2021.<sup>8</sup> The most common histological diagnoses of post-molar GTN include invasive hydatidiform mole (complete or partial) and gestational choriocarcinoma. PSTT and ETT are usually diagnosed months or years after their index gestation (term pregnancy, molar gestation or abortion), which may require ancillary studies to establish their direct relationship.

Invasive hydatidiform mole is generally diagnosed when the molar tissue (complete hydatidiform mole or less often a partial hydatidiform mole) demonstrates direct myometrial invasion without intervening decidual tissue and/or vascular invasion. Grossly the lesion typically appears as an invading hemorrhagic lesion extending from the endometrial surface into the myometrium and hydropic molar villi may be seen grossly. Transmural invasion with uterine perforation or involving the broad ligament is sometimes seen. Diagnosis of invasive hydatidiform mole generally requires a hysterectomy specimen. Metastatic mole usually involves the vagina or pelvic organs.

Based on the 2020 WHO Classification,<sup>7</sup> intraplacental choriocarcinoma is well recognised in term placentas, with aggregates of cytologically malignant trophoblast morphologically resembling choriocarcinoma extending from the chorionic villi into the intervillous space.<sup>9-13</sup> Intraplacental choriocarcinoma is mostly diagnosed in third trimester or postpartum. It may be asymptomatic until metastasis occurs in the patient or even in the infant. Sometimes hydatidiform mole, particularly invasive complete mole, may contain focal or extensive areas of trophoblastic proliferation with marked atypia, qualifying for the presence of ‘emerging/ early’ choriocarcinoma. Such molar-associated/intramolar choriocarcinoma — that is, choriocarcinoma coexisting with complete or invasive hydatidiform mole is increasingly recognised.<sup>13-15</sup>

Fully developed gestational choriocarcinoma typically presents as a bulky, destructive uterine mass with extensive hemorrhage and necrosis. While the tumour most commonly arises in the uterine corpus, it may also arise within the cervix, fallopian tube or other sites possibly involved by ectopic pregnancy. Histologically the tumour consists of diffusely infiltrative or solid destructive growth with proliferating tumour cells recapitulating chorionic villous trophoblast of various types and organised in biphasic to triphasic patterns. Sheets or cords of mononuclear tumour cells (large intermediate trophoblast with abundant amphophilic to eosinophilic cytoplasm and/or smaller cytotrophoblast) rimmed by layers of multinuclear syncytiotrophoblastic cells are typical. Marked cytological pleomorphism, nuclear enlargement and brisk mitotic activity are always present. Frequently, tumour nests display central areas of hemorrhage and necrosis with only viable tumour cells at the periphery. Lymphovascular tumour thrombi are common. Immunohistochemically, neoplastic

syncytiotrophoblastic cells typically show strong and diffuse positivity for hCG and HSD3B1. The intermediate trophoblast expresses Mel-CAM, HLA-G and MUC-4. Tumour cells also stain positive for cytokeratin AE1/AE3, GATA3, inhibin and SALL4. A high Ki-67 proliferation index over 90% is typically observed.<sup>16,17</sup>

Placental site trophoblastic tumour (PSTT) generally grossly involves the endomyometrium as a relatively well-circumscribed solid mass with deep myometrial invasion. Perforation may occur with extension into the broad ligament and adnexa in rare cases. The cut surface of the tumour is usually solid and fleshy with white-tan to light yellow colour. Histologically, the tumour consists of relatively large, polyhedral to round, predominately mononuclear intermediate trophoblastic cells forming cords, nests or sheets. At the tumour border, the tumour cells characteristically infiltrate and separate myometrial smooth muscle fibres. Vascular involvement is common in the form of tumour cells replacing the entire vessel wall except the pre-existing endothelial cells. Cytologically, the tumour cells have abundant amphophilic, eosinophilic or clear cytoplasm and variably sized and shaped nuclei. Large convoluted nuclei with marked hyperchromasia, nuclear grooves and nuclear pseudo-inclusions are present in most cases. Scattered multinucleated cells resembling syncytiotrophoblast are common. Nucleoli are generally present and may be prominent. Mitotic count is usually between 2 to 4 per 2 mm<sup>2</sup>, equivalent to 10 high power fields (HPF) (if field diameter is 0.55 mm; i.e., depending on the design of the microscope). PSTT typically expresses human placental lactogen (hPL), hCG, MUC-4, HSD3B1, CD10, HLA-G, GATA3, inhibin and Mel-CAM (CD146). The staining of hPL is generally strong and diffuse. In contrast, hCG and inhibin are positive only in scattered multinucleated tumour cells. Epithelial markers including cytokeratin CK AE1/AE3 and CK18 are strongly expressed. Ki-67 is expressed in 10 to 30% of tumour cells.<sup>18</sup> PSTT recurs or metastasizes in about 25-30% of the cases with a mortality of 6.5 -27%.<sup>7</sup>

Epithelioid trophoblastic tumour (ETT) generally forms a discrete nodule or a cystic hemorrhagic mass deeply invading the surrounding structures and frequently arises in the cervix or lower uterine segment. The tumour cut surface is white-tan to brown, with varying amounts of hemorrhage and necrosis. Ulceration and fistula formation may be seen. Histologically ETT shows a nodular, expansile growth with sharply circumscribed tumour border. The tumour cells form nests, cords or large sheets. They are uniform, medium sized epithelioid cells with a moderate amount of finely granular, eosinophilic to clear cytoplasm, distinct cell borders, and round nuclei with small nucleoli. Eosinophilic hyaline-like material is characteristically present in the centre of some tumour nests, simulating keratin formation. Extensive or 'geographic' necrosis is often present. Most of the tumours have a mitotic count ranging from 0-9 per 2 mm<sup>2</sup>, equivalent to 10 HPFs (if field diameter is 0.55 mm; i.e., depending on the design of the microscope) but it may be as high as 48 per 2 mm<sup>2</sup>. The tumour cells typically diffusely express HSD3B1, HLA-G, p63, GATA 3, p40, cyclin E, inhibin, EMA and cytokeratins (CK18, CAM5.2, AE1/3). Mel-CAM and hPL are expressed only in individual cells and the Ki-67 proliferation index is over 10%. ETT may mimic cervical squamous cell carcinoma, due to frequent eosinophilic 'keratin-like' material within the tumour nests and the ability to colonise the cervical mucosal surface or glandular epithelium, therefore, simulating high-grade squamous intraepithelial lesion. ETT metastasizes in about 25-30% of the cases with a mortality of 10-24%.<sup>6</sup>

Mixed trophoblastic tumours consist of discrete areas of two or more components of choriocarcinoma, PSTT, and/or ETT, with characteristic histomorphology of each type as described above. The most common mixed trophoblastic tumour is mixed choriocarcinoma and ETT; less common forms are mixed choriocarcinoma and PSTT, and mixed ETT and PSTT. The least common subtype is mixed choriocarcinoma, ETT, and PSTT.<sup>19,20</sup> The choriocarcinoma component often dictates the tumour recurrence.



Placental site nodule (PSN) is a non-neoplastic proliferation of chorion laeve type intermediate trophoblast and is usually an incidental finding in a curettage specimen. PSN consists of single to multiple, well-circumscribed, oval nodules or plaques of typically less than 5 mm in size. Variable numbers of intermediate trophoblastic cells are haphazardly arranged in cords or nests embedded in abundant hyalinised matrix. Zonation is usually present, with higher cellularity in the periphery and a central hyalinised, paucicellular area. Lymphocytic infiltrate is common at the lesional periphery. Mitotic activity is very low.

Immunohistochemically, similar to ETT, the lesional cells typically express hPL, inhibin, p63, cytokeratins (CAM5.2, AE1/3) and epithelial membrane antigen (EMA). Vimentin is also strongly positive in most cases. However, Ki-67 proliferation index is less than 5%.<sup>18</sup> Atypical placental site nodule (APSN) is a recently reported trophoblastic lesion<sup>21,22</sup> which is included in the 2020 WHO Classification,<sup>7</sup> with morphologic features intermediate between typical PSN and ETT. Histological features of APSN include larger size of the nodule (5-10 mm), increased cellularity, marked nuclear atypia, increased mitotic activity and Ki-67 proliferation index between 5-10%. APSN has been proposed as an immediate precursor lesion to gestational trophoblastic tumours (ETT and PSTT). However, definitive diagnostic criteria have not been established. It is clinically relevant that patients with APSN should undergo imaging studies to rule out an underlying mass lesion and require clinical follow-up including serial serum hCG measurement.

‘Other’ may cover rarer scenarios, for example, APSN or unclassifiable trophoblastic tumour.

**Table 2: World Health Organization classification of gestational trophoblastic disease.<sup>7</sup>**

Putative Trophoblastic Cells of Origin		Gestational Trophoblastic Disease Classification		Genetic Features	ICD-0 codes <sup>a</sup>
Chorionic Villous Trophoblast		<ul style="list-style-type: none"><li>• <b>Hydatidiform Mole</b></li></ul>	<ul style="list-style-type: none"><li>• <b>Complete Hydatidiform Mole</b></li></ul>	Androgenic paternal-only genome in sporadic cases. Inherited mutations of NALP7 or KHDC3L in familial biparental complete moles	9100/0
			<ul style="list-style-type: none"><li>• <b>Partial Hydatidiform Mole</b></li></ul>	Diandric-monogynic triploidy in most cases	9100/0
			<ul style="list-style-type: none"><li>• <b>Invasive Hydatidiform Mole</b></li></ul>	Depending on the prior mole	9100/1
		<ul style="list-style-type: none"><li>• <b>Atypical Villous Lesions</b></li></ul>		Unknown in most cases	
Intermediate Trophoblast	Villous Intermediate Trophoblast	<ul style="list-style-type: none"><li>• <b>Gestational Choriocarcinoma</b></li></ul>		Androgenetic XX genome following complete moles in most cases	9100/3
	Implantation Site Intermediate Trophoblast	<ul style="list-style-type: none"><li>• <b>Placental Site Trophoblastic Tumour</b></li></ul>		Preferential requirement of paternal X chromosome	9104/1
		<ul style="list-style-type: none"><li>• <b>Exaggerated Implantation Site Reaction</b></li></ul>		Unknown	
	Chorionic Type Intermediate Trophoblast	<ul style="list-style-type: none"><li>• <b>Epithelioid Trophoblastic Tumour</b></li></ul>		Preferential requirement of paternal X chromosome	9105/3
		<ul style="list-style-type: none"><li>• <b>Placental Site Nodule/Atypical Placental Site Nodule</b></li></ul>		Unknown	
	Mixed Intermediate Trophoblast	<ul style="list-style-type: none"><li>• <b>Mixed Trophoblastic Tumours</b></li></ul>		Unknown	9101/3

<sup>a</sup> These morphology codes are from the International Classification of Diseases for Oncology, Third Edition, second revision (ICD-O-3.2).<sup>23</sup> Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Incorporates all relevant changes from the 5<sup>th</sup> Edition Corrigenda June 2021.

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 **Back**

## Note 8 – Mitotic count (Non-core)

For selecting high risk patients with PSTT or ETT for adjuvant chemotherapy, the following are relevant parameters:  $\geq 4$  years of interval from antecedent gestation; deep myometrial invasion; uterine serosal extension; or high mitotic counts of  $\geq 5$  mitoses per  $2 \text{ mm}^2$ , equivalent to 10 HPFs (if field diameter is 0.55 mm; i.e., depending on the design of the microscope).<sup>24,25</sup>

Due to a lack of data this element has not been required but is highly encouraged so that data is collected moving forward. This is particularly important for PSTT and ETT.

 [Back](#)

## Note 9 – Other tissue/organ involvement (Core)

Precise recording of the tumour involvement of non-genital organs is important for GTN FIGO<sup>2,3</sup> and TNM<sup>5,6</sup> staging.

 [Back](#)

## Note 10 – Serosal extension (Core)

Serosal extension is an adverse prognostic indicator for PSTT and ETT.<sup>24</sup>

 [Back](#)

## Note 11 – Lymphovascular invasion (Non-core)

The role of lymphovascular invasion in clinical prognosis is undefined and currently plays no role in the GTN staging or risk scoring algorithm. Due to a lack of data this element is not a core element, but it is highly encouraged to record this so that data is collected prospectively. This is particularly important for PSTT and ETT. Lymphovascular invasion should not be recorded if it is within the main tumour mass but just at the periphery or outside the confines of this.

A value of 'indeterminate' should be used sparingly and only in cases where there is genuine doubt and after immunostaining for endothelial markers; in such cases, it may be useful to state the reason for a response of 'indeterminate' on the report.

 [Back](#)

## Note 12 – Margin status (Core)

While tumour margin involvement by invasive mole and gestational choriocarcinoma is not essential for patient risk scoring, surgical margin assessment may be important for the clinical management of PSTT and ETT.<sup>26</sup>

 [Back](#)

## Note 13 – Lymph node status (Core)

Lymph node metastasis, regardless of anatomic site and size of the metastatic tumour, is considered M1b.<sup>24,27</sup> The size of the lymph node metastasis and extracapsular extension are of no proven prognostic significance due to lack of data at the current time. However, it may be useful to collect this data since this may be informative for future studies. In patients with PSTT, retroperitoneal lymph node involvement, particularly para-aortic lymph node, is the most common site of metastasis. Lymph node metastasis is generally associated with a poor prognosis.<sup>27</sup>

↑ Back

## Note 14 – Coexisting non-neoplastic trophoblastic lesions (Non-core)

Placental site nodule (PSN) is considered a benign counterpart of ETT and APSN has been recently established as an immediate precursor lesion to ETT/PSTT.<sup>21,22</sup> If available, DNA genotyping may be used to establish the link between a non-neoplastic trophoblastic lesion (APSN and hydatidiform mole) and the primary tumour.

‘Other’ may cover rarer scenarios, for example, abnormal villous morphology in differential diagnosis with partial mole. DNA genotyping may be required for definitive interpretation.

↑ Back

## Note 15 – Ancillary studies (Non-core)

Recent publications have highlighted the most common diagnostic errors in trophoblastic lesions as follows:<sup>4,28</sup>

1. Misinterpretation of early complete hydatidiform mole as partial mole.
2. Overdiagnosis of hydatidiform mole in tubal pregnancy because of florid appearance of normal early first-trimester trophoblastic proliferation.
3. Misdiagnosis of exaggerated implantation site associated with hydatidiform mole or non-molar gestation as PSTT or choriocarcinoma.
4. Misinterpretation of non-gestational (germ cell or somatic) choriocarcinoma as gestational choriocarcinoma.
5. Errors in assignment of incorrect antecedent gestation to GTN.

DNA genotyping is performed for diagnosis to separate gestational trophoblastic tumours from non-gestational trophoblastic tumours. DNA genotyping is also performed for risk score assessment to determine the nature of the antecedent/causative gestation and the time interval between the causative gestation and the onset of tumour.<sup>29</sup>

Choriocarcinoma can be either gestational or non-gestational in origin. Those arising from a complete hydatidiform mole are purely androgenetic, whereas the intraplacental (non-molar) form of gestational choriocarcinoma is biparental. The rare non-gestational choriocarcinoma is unrelated to pregnancy and can be of germ cell origin or somatic (genetically related to the patient (tumour DNA matching patient DNA)), arising as a component of a carcinoma. Gestational and non-gestational choriocarcinomas have distinct clinical behavior, sensitivity to chemotherapy, and prognosis. Gestational choriocarcinoma has a favorable prognosis when appropriately treated, whereas non-gestational choriocarcinoma is less sensitive to chemotherapy and has a poor prognosis. Two of the

factors used to determine the WHO/FIGO<sup>2,3</sup> prognostic score for patients with gestational choriocarcinoma are the type of antecedent pregnancy and the time interval from the index pregnancy. Gestational choriocarcinoma related to a molar pregnancy has a lower risk than that related to a non-molar abortion or a term pregnancy, and a shorter time interval since the index pregnancy. However, the immediate antecedent or concurrent pregnancy is not always the causative pregnancy of a gestational choriocarcinoma. In addition, patient age, menstrual status, pregnancy history, and tumour location are not necessarily reliable for determining the gestational versus non-gestational nature of a choriocarcinoma. Genetic analysis, in particular DNA-based genotyping via short tandem repeat (STR) analysis performed on formalin-fixed paraffin-embedded tissues, can distinguish gestational and non-gestational choriocarcinomas, determine the molar versus non-molar nature of the gestational tumours, and can identify the causative pregnancy for the gestational tumours when material is available for comparative analysis. Genotyping can also be applied to other trophoblastic neoplasms, including PSTT and ETT, to distinguish them from rare non-gestational variants of either germ cell or somatic origin.<sup>30</sup>

PD-L1 is commonly expressed in GTN and testing for PD-L1 expression by immunohistochemistry may guide potential immunotherapy for patients with chemoresistant tumour recurrence.<sup>31</sup>

 **Back**

## **Note 16 – Pathologically confirmed distant metastasis (Core)**

Documentation of known metastatic disease is an important part of the pathology report. Such information, if available, should be recorded with as much detail as is available including the site, whether the specimen is a histopathology or cytopathology specimen and with reference to any relevant prior surgical pathology or cytopathology specimens. Lung metastasis is considered M1a and metastasis to any other organs, including the lymph node, is considered M1b.

 **Back**

## **Note 17 – Provisional pathological staging (Core and Non-core)**

The pathological staging must be provided on the pathology report and the latest version of FIGO should be used.<sup>2,3</sup> The FIGO system is in widespread use internationally and is the system used in most clinical trials and research studies.

However, UICC or AJCC versions of TNM are used or mandated in many parts of the world and TNM is included as a non-core element.<sup>5,6</sup> With regards to updating of staging systems, there is collaboration between FIGO and those agencies responsible for TNM with an agreement to adopt changes to FIGO staging. Following the introduction of a new FIGO Staging System, this is usually incorporated into TNM (both UICC and AJCC) versions) at a later date. Apart from minor discrepancies in terminology, the UICC and AJCC systems are broadly concurrent.

The term ‘provisional pathological staging’ is used in this dataset to indicate that the stage that is provided may not represent the final tumour stage which should be determined at the multidisciplinary tumour board meeting where all the pathological, clinical and radiological features are available.<sup>2,3,5,6</sup>

A tumour should be staged following diagnosis using various appropriate modalities (clinical, radiological, pathological). While the original tumour stage should not be altered following treatment,

TNM systems allow staging to be performed on a resection specimen following non-surgical treatment (for example chemotherapy, radiotherapy); in such cases, if a stage is being provided on the pathology report (this is optional), it should be prefixed by 'y' to indicate that this is a post-therapy stage.

There is no regional nodal designation in the staging of gestational trophoblastic tumours. Nodal metastases are classified as metastatic M1b disease.

Lymph node metastases are rare in gestational choriocarcinoma and ETT, but occur in approximately 6% of PSTT and have been reported as a poor prognostic parameter.<sup>27</sup>

The WHO risk score<sup>2,3</sup> (Table 1) is appended to the anatomic FIGO stage<sup>2,3</sup> and TNM Classification<sup>5,6</sup> (see Table 3). The current FIGO classification includes an anatomic stage designated by the Roman numeral I, II, III, or IV, followed by the risk factor score expressed in Arabic numerals (e.g., Stage II: 4, Stage IV: 9).<sup>2,3</sup>

**Table 3: Stage Groupings.**

TNM Classification	FIGO stage	Stage with risk score
T1 M0	I	I: risk score
T2 M0	II	II: risk score
Any T M1a	III	III: risk score
Any T M1b	IV	IV: risk score

The reference document TNM Supplement: A commentary on uniform use, 5<sup>th</sup> Edition (C Wittekind et al. editors) may be of assistance when staging.<sup>32</sup>

 **Back**

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