



Protocol for the Examination of Specimens From Patients With Primary Gestational Trophoblastic Malignancy

Version: Trophoblast 4.0.0.0

Protocol Posting Date: June 2017

Includes pTNM requirements from the 8th Edition, AJCC Staging Manual and 2015 FIGO Cancer Report

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes hysterectomy with or without oophorectomy and/or salpingectomy
Tumor Type	Description
Malignant gestational trophoblastic tumor	Includes invasive hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Curettage
Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Nongestational trophoblastic tumors (eg, ovarian choriocarcinoma)
Benign trophoblastic tumors (eg, placental site nodule)

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired "Data element: Response" format is NOT considered synoptic.
- The data element must be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
 - Anatomic site or specimen, laterality, and procedure
 - Pathologic Stage Classification (pTNM) elements
 - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e. all required elements must be in the synoptic portion of the report in the format defined above.

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2018*

* Beginning January 1, 2018, the 8th edition AJCC Staging Manual should be used for reporting pTNM.

CAP Trophoblast Protocol Summary of Changes

The following data elements were modified:

Pathologic Staging Classification (pTNM) has been updated per AJCC 8th Edition. Additional revisions to this protocol have been made to support the AJCC 8th Edition elements and prognostic factors important to the treatment of the patient.

Surgical Pathology Cancer Case Summary

Protocol posting date: June 2017

TROPHOBLAST:

Note: This case summary is recommended for reporting curettage specimens, but is not required for accreditation purposes.

Select a single response unless otherwise indicated.

Procedure

- Dilation and curettage
- Simple hysterectomy
- Supracervical hysterectomy
- Radical hysterectomy
- Pelvic exenteration
- Other (specify): _____

+ Hysterectomy Type

- + Abdominal
- + Vaginal
- + Vaginal, laparoscopic-assisted
- + Laparoscopic
- + Laparoscopic, robotic-assisted
- + Other (specify): _____
- + Not specified

+ Specimen Integrity

- + Intact
- + Opened
- + Morcellated
- + Other (specify): _____

Tumor Site

- Uterine corpus
- Uterine cervix
- Other (specify): _____
- Cannot be determined (explain): _____

Tumor Size

- Greatest dimension (centimeters): ____ cm
- + Additional dimensions (centimeters): ____ x ____ cm
- Cannot be determined (explain): _____

Histologic Type (Note A)

- Hydatidiform mole, invasive
- Choriocarcinoma
- Placental site trophoblastic tumor
- Epithelioid trophoblastic tumor
- Malignant trophoblastic tumor, type cannot be determined
- Other histologic type not listed (specify): _____

Other Tissue/Organ Involvement (select all that apply)

Note: Any organ not selected is either not involved or was not submitted.

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

- Not applicable
- Not identified
- Right ovary
- Left ovary
- Ovary (side not specified)
- Right fallopian tube
- Left fallopian tube
- Fallopian tube (side not specified)
- Vagina
- Right broad ligament
- Left broad ligament
- Broad ligament (side not specified)
- Other organs/tissue (specify): _____
- Cannot be determined (explain): _____

Margins

- Cannot be assessed
- Uninvolved by tumor
 - + Distance of tumor from closest margin (millimeters): ____ mm
 - + Specify margin: _____
- Involved by tumor
 - Specify margin(s): _____

Lymphovascular Invasion

- Not identified
- Present
- Cannot be determined

Pathologic Stage Classification (pT, pM, AJCC 8th Edition) (Note B)

Note: Reporting of pT and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

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

- r (recurrent)
- y (posttreatment)

Primary Tumor (pT)

- pTX: Primary tumor cannot be assessed
- pT0: No evidence of primary tumor
- pT1: Tumor confined to uterus
- pT2: Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension

Distant Metastasis (pM) (required only if confirmed pathologically in this case)

- pM1: Distant metastasis
- pM1a: Lung metastasis
- pM1b: All other distant metastasis

Specify site(s), if known (select all that apply)

- Lung
- Spleen
- Kidney
- Gastrointestinal tract
- Liver
- Brain

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

___ Lymph node(s) (specify) #: _____
___ Other (specify): _____

Any lymph node metastasis should be classified as metastatic (M1b) disease.

+ Number of Metastasis

- + ___ 1-4
- + ___ 5-8
- + ___ >8

+ FIGO Stage (2015 FIGO Cancer Report)

- + ___ I: Disease confined to the uterus
- + ___ II: Gestational trophoblastic tumor extends outside of the uterus, but limited to the genital structures (adenexa, vagina, broad ligament)
- + ___ III: Gestational trophoblastic tumor extends to the lungs, with or without known genital tract involvement
- + ___ IV: All other metastatic sites

+ **Additional Pathologic Findings (select all that apply)**

- + ___ None identified
- + ___ Implantation site
- + ___ Other (specify): _____

+ **Ancillary Studies**

+ Specify: _____

+ **Clinical History**

+ Specify: _____

+ **Comment(s)**

Explanatory Notes

A. Histologic Type

Previous History

Previous slides should be reviewed by the pathologist if it is deemed necessary by the gynecologist or pathologist for optimal evaluation of the specimen.

Histologic Classification

A modified World Health Organization (WHO) classification of gestational trophoblastic lesions is as follows¹⁻⁶:

Histologic Classification of Gestational Trophoblastic Lesions

Invasive hydatidiform mole

Choriocarcinoma

Placental site trophoblastic tumor[#]

Epithelioid trophoblastic tumor^{7,#}

Unclassified trophoblastic lesions^{##}

[#] Malignant tumor of intermediate trophoblast.

Exaggerated placental site composed of seemingly increased intermediate trophoblast at the implantation site, is most commonly seen in uterine curettage specimens. These lesions are benign and do not require staging.

Placental site nodules are of benign intermediate trophoblast. These lesions are generally benign and do not require staging. However, placental site nodules have been described in association with epithelioid trophoblastic tumors.⁷ Furthermore, there is a morphological continuum, and atypical placental site nodules present with equivocal morphological features, being larger and showing greater cellularity than is typically seen in a placental site nodule, but having insufficient features for a diagnosis of epithelioid trophoblastic tumor. Cyclin E is useful in the distinction of placental site nodule and epithelioid trophoblastic tumor, with the former showing focal weak nuclear staining, whereas the latter typically shows diffuse (>50% of tumor nuclei) intense staining. Atypical placental site nodules may show elevated cyclin E staining.⁸

^{##} Composite or mixed trophoblastic lesions are recognized. Epithelioid trophoblastic tumors have been described coexistent with placental site nodule and with placental site trophoblastic tumor and choriocarcinoma either alone or in combination.^{7,9} Rarely, a placental site nodule and placental site trophoblastic tumor may co-exist.¹⁰ Rather than specifying the "Histologic Type" as "Unclassified," we would recommend classifying composite lesions as "Other," with further annotation of the different components.

Immunohistochemistry in Diagnosis of Gestational Trophoblastic Disease

Immunohistochemistry in the Distinction of, Placental Site Nodule, Placental Site Trophoblastic Tumor, Epithelioid Trophoblastic Tumor, and Choriocarcinoma^{11,12} by Kurman and Shih¹² has dissected the subpopulations of trophoblast that give rise to trophoblast tumors and tumor-like lesions. It is proposed that exaggerated placental site and placental site trophoblastic tumor arise from implantation site intermediate trophoblast, whereas placental site nodule and epithelioid trophoblastic tumor arise from chorionic-type intermediate trophoblast. A panel of immunohistochemical stains (Tables 1 and 2) is recommended to distinguish these entities.

Table 1. Immunohistochemical Studies in Placental Site Nodule, Placental Site Trophoblastic Tumor, Epithelioid Trophoblastic Tumor, and Choriocarcinoma

		Placental Site Nodule	Placental Site Trophoblastic Tumor	Epithelioid Trophoblastic Tumor	Choriocarcinoma
Mel-Cam (CD146) (membranous) [#]		0%-2%	75%-100%	0%-2%	6%-75%
HPL		0%-2%	25%-75% ^{##}	0%-2%	Positive in IT and ST
β-HCG		0%-25%	0%-25% ^{###}	0%-25%	Positive in ST
P63		>50%-75%	Negative	<25% up to 75% [^]	<25%
Ki-67 (MIB-1)		3%-10%	>10%	>10%	69 ± 20%
Cyclin E		Focal		>50%	

HPL human placental lactogen; IT, intermediate trophoblast; ST, syncytiotrophoblast; β-HCG, human chorionic gonadotrophin.

[#] Mel-CAM, melanoma cell adhesion molecule, is a marker of intermediate trophoblast of implantation site origin. Percentages refer to percentage of immunopositive cells.

^{##} 12% of cases reported by Kalhor showed no staining for HPL.⁹

^{###} Mainly in multinucleate intermediate trophoblast.

[^] 20% of cases reported by Kalhor showed no staining for p63.⁹

Adapted from Tsui-Lien M et al,⁸ Kalhor N et al,⁹ Shih IM et al.¹³

Immunohistochemistry in the Distinction of Intermediate Trophoblastic Tumors, Choriocarcinoma, and Cervical Carcinoma

Table 2. Immunohistochemical Staining Results for Intermediate Trophoblastic Tumors (ITT), Primary Cervical Carcinomas (CA), and Choriocarcinomas (CC)

	CD10 (%)	CD146 (%)	CK5/6 (%)	hCG (%)	p16 (%)	Inhibin (%)	hPL (%)	P63 (%)	CEA (%)	Pan-K (%)
ITT	100	73	13	87	53	40	60	40	33	100
CA	20	20	100	10	100	20	0	80	80	100
CC	100	70	---	100	---	85	45	70	---	100

The percentages refer to the number of cases expressing the marker.

Pan-K, Pankeratin (AE1/AE3); CEA, carcinoembryonic antigen

Adapted from Kalhor N et al.⁹

Additional Notes on Table 2

CD10: variable expression in ITTs and choriocarcinoma: 1% to 100% of cells staining.

P16: Cervical carcinomas showed diffuse nuclear staining for this marker. About half the ITTs had variable staining (1% to 75% of cells), mainly cytoplasmic.

CK5/6: All cervical carcinomas were positive, staining 26% to 100% of cells. Two cases of ITT were focally positive (<25% of cells).

General

A recent review has highlighted the most common diagnostic errors in trophoblastic lesions.¹⁴

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 exuberant placental site nonvillous trophoblast as placental site trophoblastic tumor.

4. Misdiagnosis of nonvillous trophoblast, often seen in the context of complete hydatidiform mole, as choriocarcinoma or placental site trophoblastic tumor.

B. Pathologic Stage Classification

The 8th edition of the TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC)^{3,4} and the corresponding updated staging system of the International Federation of Gynecology and Obstetrics (FIGO),⁵ are recommended, as shown below. Both are based not only on the anatomic extent of the tumor, but on additional factors, including clinical and laboratory findings.

According to AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible. Gestational trophoblastic tumors do not have an N classification (see below).

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically infeasible) and if the highest T category or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor before multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

Additional Descriptors

Residual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

T Category Considerations

Lymphovascular Invasion

Lymphovascular invasion (LVI) indicates whether microscopic lymphovascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymphovascular invasion. According to AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

N Category Considerations

There is no regional nodal designation (N classification) in the staging of gestational trophoblastic tumors. Nodal involvement in these tumors is rare but has an extremely poor prognosis. Nodal metastases should be classified as metastatic M1b disease.

M Category Considerations

Genital metastasis (vagina, broad ligament, ovary, fallopian tube) is classified as T2. Direct invasion or metastasis to any nongenital structure is classified using the M classification.

The score on the FIGO-modified World Health Organization (WHO) Prognostic Scoring Index given below is used to stratify women with gestational trophoblastic neoplasia in addition to the stage group. The risk score is appended to the anatomic FIGO stage. The current FIGO classification includes an anatomic stage designated by Roman numeral I, II, III, or IV, followed by the risk factor score expressed in Arabic numerals (eg, stage II: 4, stage IV: 9).

Prognostic Scoring Index for Gestational Trophoblastic Tumors³⁻⁵

Prognostic Factor	Prognostic Score			
	0	1	2	4
Age	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4 – 6	7 – 12	>12
Pretreatment serum HCG (IU/L)	<10 ³	10 ³ – <10 ⁴	10 ⁴ – <10 ⁵	≥10 ⁵
Largest tumor size (including uterus)	<3 cm	3 – 5 cm	>5 cm	–
Sites of metastasis	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastasis	–	1 – 4	5 – 8	>8
Previous failed chemotherapy	–	–	Single drug	2 or more drugs

Low risk is a score of 6 or less. High risk is a score of 7 or greater. HCG, human chorionic gonadotropin.

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 T and M categories are defined to correspond to the FIGO stages.

In determining the risk score, the following factors are not surgical pathology and are not considered required elements:

- Antecedent pregnancy
- Months from index pregnancy
- Pretreatment serum human chorionic gonadotropin (hCG)
- Previous failed chemotherapy

In summary, the following factors should be considered and noted in reporting:

1. Prior chemotherapy for known gestational trophoblastic tumors should be reported.
2. Benign placental site lesions (exaggerated placental site and placental site nodule) should be reported separately and are not staged.
3. Histologic verification of disease is not required when the HCG is abnormally elevated.
4. TNM and FIGO staging applies to choriocarcinoma, invasive hydatidiform mole, placental site trophoblastic tumor, and epithelioid trophoblastic tumor.
5. In contrast to other sites, an N classification (regional lymph node status) does not apply to gestational trophoblastic tumors. Any lymph node metastasis should be classified as metastatic (M1b) disease.

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