COLLEGE of AMERICAN PATHOLOGISTS

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

Protocol applies to all gestational trophoblastic malignancies.

Based on AJCC/UICC TNM, 7th edition, and FIGO 2006 Annual Report

Protocol web posting date: October 2013

Procedures

- Dilatation and Curettage
- Resection

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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CAP Trophoblast Protocol Revision History

Version Code

The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Trophoblast 3.0.0.3

Summary of Changes

The following changes have been made since the June 2012 release.

Dilation and Curettage, Resection

Microscopic Tumor Extension

Added data element, "Tumor extends to cervix" as follows:

Microscopic Tumor Extension (select all that apply)

___ Not applicable
___ Tumor confined to uterus
___ Tumor extends outside of the uterus but is limited to genital structures
    ___ Tumor extends to fallopian tube
    ___ Tumor extends to ovary
    ___ Tumor extends to broad ligament
    ___ Tumor extends to vagina
    ___ Tumor extends to cervix
___ Tumor extends to other nongenital organs or structures (specify): _____
Specify organ(s) with separate metastasis: _____

Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

TROPHOBLAST: Dilation and Curettage, Resection

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)
___ Uterus
___ Other (specify): _____
___ Not specified

Procedure
___ Dilation and curettage
___ Hysterectomy
___ Radical hysterectomy
___ Pelvic exenteration
___ Other (specify): _____
___ Not specified

Tumor Site
Specify, if known: _____
___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (See Comment)

Histologic Type (Notes B and C)
___ Hydatidiform mole, complete
___ Hydatidiform mole, partial
___ Hydatidiform mole, invasive
___ Choriocarcinoma
___ Placental site trophoblastic tumor
___ Epithelioid trophoblastic tumor
___ Other (specify type): _____
___ Malignant trophoblastic tumor, type cannot be determined

Microscopic Tumor Extension (select all that apply)
___ Not applicable
___ Tumor confined to uterus
___ Tumor extends outside of the uterus but is limited to genital structures
    ___ Tumor extends to fallopian tube
    ___ Tumor extends to ovary
    ___ Tumor extends to broad ligament
    ___ Tumor extends to vagina
    ___ Tumor extends to cervix
___ Tumor extends to other nongenital organs or structures (specify): _____
Specify organ(s) with separate metastasis: _____

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Margins

___ Cannot be assessed
___ Uninvolved by malignant tumor
    Distance of malignant tumor from closest margin: ___ mm
    Specify margin: _____
___ Involved by malignant tumor
    Specify margin(s): _____

Lymph-Vascular Invasion

___ Not identified
___ Present
___ Indeterminate

Fetal Tissue (Macroscopic or Microscopic)

___ Cannot be determined
___ Not identified
___ Present
    + Specify type: _____

Fetal Anomalies

___ Not applicable
___ Cannot be determined
___ Not identified
___ Present
    + Specify type: _____

Pathologic Staging (pTNM [FIGO]) (Note D)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple)
___ r (recurrent)
___ y (posttreatment)

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

Distant Metastasis (pM)
___ Not applicable
___ pM1a [III]: Lung metastasis
___ pM1b [IV]: All other distant metastasis

Specify number of metastases, if known:
___ 1-4
___ 5-8
___ >8

Specify sites of metastases (select all that apply):
___ Lung
___ Spleen
___ Kidney
___ Gastrointestinal tract
___ Liver
___ Brain

+ Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Implantation site
+ ___ Other (specify): _____

+ Ancillary Studies
+ Specify: _____

+ Clinical History
+ Specify: _____

+ Comment(s)

Explanatory Notes

A. 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.

B. Histologic Type

A modified World Health Organization (WHO) classification of gestational trophoblastic lesions is as follows[1-5]:

Histologic Classification of Gestational Trophoblastic Lesions

Hydatidiform mole
- Complete#
- Partial##

Invasive hydatidiform mole
Choriocarcinoma
Placental site trophoblastic tumor###
Epithelioid trophoblastic tumor[6,###]
Trophoblastic lesions, miscellaneous
- Exaggerated placental site^
- Placental site nodule^^

Unclassified trophoblastic lesions^^^

Usually diploid, 46 chromosomes; most commonly no fetal tissues unless with a twin gestation; villi markedly enlarged, hydropic, central cistern; prominent trophoblastic hyperplasia.

Usually triploid, 69 chromosomes; fetal tissues present; villi scalloped, have stromal trophoblastic inclusions; focal trophoblastic hyperplasia, usually of syncytiotrophoblast.

Malignant tumor of intermediate trophoblast.

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

^^ Retention of nodule(s) 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.[6] 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.[7]

^^^ 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.[6,8] Rarely, a placental site nodule and placental site trophoblastic tumor may co-exist[9]. Rather than specifying the "Histological Type" as "Unclassified," we would recommend classifying composite lesions as "Other," with further annotation of the different components.

C. Immunohistochemistry in Diagnosis of Gestational Trophoblastic Disease

Immunohistochemistry in the Distinction of Partial and Complete Hydatidiform Moles
The complete hydatidiform mole is an androgenic conceptus, having either 46, XX or 46, XY chromosomes. Due to lack of maternal DNA, only gene products derived from paternal DNA are expressed. $P57^{kip2}$ is a paternally (differentially) imprinted, maternally expressed gene and thus shows differential expression in trophoblastic disease (Table1). The gene resides on chromosome 11p15. In a complete hydatidiform mole, $P57^{kip2}$ expression is absent or expressed at low levels in villous cytotrophoblast and villous stromal cells. Intermediate trophoblastic cells and decidualised stromal cells will be positive and are useful as positive internal controls. Rare cases of complete hydatidiform mole with aberrant (retained) p57 expression, attributable to trisomy of chromosome 11, have been described.[10]

In a partial hydatidiform mole, $P57^{kip2}$ is strongly expressed in villous cytotrophoblast and villous stromal cells.

Table 1. $P57^{kip2}$ in Partial and Complete Hydatidiform Moles

	Complete Hydatidiform Mole	Partial Hydatidiform Mole
$P57^{kip2}$ nuclear stain	Absent or very low# in villous cytotrophoblast and villous stromal cells, but is present in intervillous islands and decidualised stromal cells	Strong expression in villous cytotrophoblast and villous stromal cells

Adapted from Lage et al.[11]

Some studies have used cutoff values for p57 staining. In a recent study by McConnell et al,[10] semiquantitative assessment of staining in the villous cytotrophoblast and villous stromal cells was performed, with 0%-10% regarded as negative, >10% but <50% as equivocal, and a positive result was reported when >50% of these cells were positive. They emphasized that most cases were readily interpreted as positive or negative. Three equivocal cases were encountered that were shown to be partial hydatidiform moles by molecular genotyping. Although uncommon, they recommend ancillary testing when an equivocal staining pattern is encountered.

The molar implantation site may have a Ki-67 index of 5.2% ± 4%.[12]

Immunohistochemistry in the Distinction of Exaggerated Placental Site Reaction, Placental Site Nodule, Placental Site Trophoblastic Tumor, Epithelioid Trophoblastic Tumor, and Choriocarcinoma
Work by Kurman and Shih [12]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 (Table 2) is recommended to distinguish these entities.

Table 2. Immunohistochemical Studies in Exaggerated Placental Site Reaction, Placental Site Trophoblastic Tumor, Epithelioid Trophoblastic Tumor, and Choriocarcinoma

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

IT, intermediate trophoblast; ST, syncytiotrophoblast; hPL human placental lactogen; 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.[8]

Mainly in multinucleate intermediate trophoblast

^ 20% of cases reported by Kalhor showed no staining for p63.[8]

Adapted from Tsui-Lien M et al,[7] Kalhor N et al,[8] Shih IM et al. [13]

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

Table 3. 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 (AE1AE3); CEA, carcinoembryonic antigen
Adapted from Kalhor N et al.[8]

Additional Notes on Table 3
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.

D. TNM and Stage Groupings

The 7th 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 2006 edition of the 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.

AJCC/UICC TNM Classification for Trophoblastic Tumors[3,4]

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to uterus
T2	Tumor extends to other genital structures (vagina, ovary, broad ligament, fallopian tube) by metastasis or direct extension

Regional Lymph Nodes (N)

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.

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Lung metastasis#
M1b	All other distant metastasis#

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.

FIGO Staging for Gestational Trophoblastic Tumors (2006)[5]

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

Note: Stages I to IV are subdivided into A (low risk) and B (high risk) according to the prognostic score (see below).

Prognostic Score[3,4,5]

	Prognostic Score			
Prognostic Factor	**0**	**1**	**2**	**3**
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

Risk Categories

Total prognostic score 6 or less is low risk (add "A" to FIGO Stage).
Total prognostic score 7 or more is high risk (add "B" to FIGO Stage).

Stage Groupings#

FIGO Stage	TNM Classification		Risk Category
Stage I	T1	M0	unknown
Stage IA	T1	M0	low
Stage IB	T1	M0	high
Stage II	T2	M0	unknown
Stage IIA	T2	M0	low
Stage IIB	T2	M0	high
Stage III	Any T	M1a	unknown
Stage IIIA	Any T	M1a	low
Stage IIIB	Any T	M1a	high
Stage IV	Any T	M1b	unknown
Stage IVA	Any T	M1b	low
Stage IVB	Any T	M1b	high

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

In determining the risk category, 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

TNM Descriptors

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

The "m" suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

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).

Lymph-Vascular Invasion

Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular 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.

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. Histological verification of disease is not required when the human chorionic gonadotropin (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.

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