

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 2009 Annual Report

Protocol web posting date: January 2016

Procedures

- Dilatation and Curettage
- Resection

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CAP Trophoblast Protocol Revision History

Version Code

The definition of version control and an explanation of version codes can be found at www.cap.org (search: cancer protocol terms).

Version: Trophoblast 3.1.0.0

Summary of Changes

The following changes have been made since the October 2013 release.

The following data elements were modified:

- Tumor size
- Lymph-Vascular Invasion
- Distant Metastasis (changed to required only if confirmed pathologically)

The following data element was added:

- FIGO Stage (not required)

Surgical Pathology Cancer Case Summary

Protocol web posting date: January 2016

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 (explain): _____

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: _____

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
 Cannot be determined

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) (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: 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)

- pM1a: Lung metastasis
 pM1b: All other distant metastasis
 Specify site(s), if known (select all that apply)
 Lung
 Spleen
 Kidney
 Gastrointestinal tract
 Liver
 Brain
 Other (specify): _____
 Specify number of metastases, if known:
 1-4
 5-8
 >8

+ FIGO Stage

- + ___ 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. 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 follows¹⁻⁶:

Histologic Classification of Gestational Trophoblastic Lesions

Hydatidiform mole

 Complete[#]

 Partial^{##}

Invasive hydatidiform mole

Choriocarcinoma

Placental site trophoblastic tumor^{###}

Epithelioid trophoblastic tumor^{7,###}

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.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 "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.¹¹

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.¹²

[#] Some studies have used cutoff values for p57 staining. In a recent study by McConnell et al,¹¹ semiquantitative assessment of staining in the villous cytotrophoblast and villous stromal cells was performed, with 0% to 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%.¹³

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 Shih¹³ 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 |
| β-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% | |

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.¹⁴

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.⁹

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.¹⁵

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 2009 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 (2009)⁵

| | |
|-----------|--|
| Stage I | Disease confined to the uterus |
| Stage II | Gestational trophoblastic tumor extends outside of 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 Score³⁻⁵

| 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 |

HCG, human chorionic gonadotropin.

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 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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