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

Authors
Blaise A. Clarke, MBBCh, FRCPC*
   Department of Pathology, University of Toronto, Toronto General Hospital, Toronto, Ontario, Canada
Michael T. Deavers, MD, FCAP
   Department of Pathology, University of Texas, MD Anderson Cancer Centre, Houston, Texas
Janice M. Lage, MD, FCAP
   Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, South Carolina
Esther Oliva, MD, FCAP
   Department of Pathology, Harvard University, Massachusetts General Hospital, Boston, Massachusetts
Christopher N. Otis, MD, FCAP
   Department of Pathology, Baystate Medical Center, Springfield, Massachusetts
Kumarasen Cooper, MBChB, DPhil, FRCPath†
   Department of Pathology, University of Vermont, Fletcher Allen Health Care, Burlington, Vermont
For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author. † Denotes senior author. All other contributing authors are listed alphabetically.

Previous contributors: Saeid Movahedi-Lankarani, MD; Donald E. Henson, MD; Enrique Hernandez, MD; Maureen Killacky, MD; Beverly B. Kramer, MD; Rachelle Lanciano, MD; Stanley J. Robboy, MD; Steven G. Ruby, MD; Robert E. Scully, MD; Steven G. Silverberg, MD; Richard Zaino, MD
© 2013 College of American Pathologists (CAP). All rights reserved.

The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) Dictation from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) Copying from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a computerized system for items (1) and (2), provided that the protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from the CAP.

Any public dissemination of the original or modified protocols is prohibited without a written license from the CAP.

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.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.
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 non-genital 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

+ 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.
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:

Histologic Classification of Gestational Trophoblastic Lesions

Hydatidiform mole
  Complete
  Partial

Invasive hydatidiform mole

Choriocarcinoma

Placental site trophoblastic tumor

Epithelioid trophoblastic tumor

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. 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.

^^^^ 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. Rarely, a placental site nodule and placental site trophoblastic tumor may co-exist. 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 (Table 1). 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>
<thead>
<tr>
<th>P57(^{kip2}) nuclear stain</th>
<th>Complete Hydatidiform Mole</th>
<th>Partial Hydatidiform Mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent or very low(^*) in villous cytotrophoblast and villous stromal cells, but is present in intervillous islands and decidualised stromal cells</td>
<td>Strong expression in villous cytotrophoblast and villous stromal cells</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Exaggerated Placental Site</th>
<th>Placental Site Nodule</th>
<th>Placental Site Trophoblastic Tumor</th>
<th>Epithelioid Trophoblastic Tumor</th>
<th>Choriocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mel-Cam (CD146)</td>
<td>75%-100%</td>
<td>0%-2%</td>
<td>75%-100%</td>
<td>0%-2%</td>
<td>6%-75%</td>
</tr>
<tr>
<td>hPL</td>
<td>75%-100%</td>
<td>0%-2%</td>
<td>25%-75%**</td>
<td>0%-2%</td>
<td>Positive in IT and ST</td>
</tr>
<tr>
<td>β-HCG</td>
<td>0%-25%***</td>
<td>0%-25%</td>
<td>0%-25%***</td>
<td>0%-25%</td>
<td>Positive in ST</td>
</tr>
<tr>
<td>P63</td>
<td>Negative</td>
<td>&gt;50%-75%</td>
<td>Negative</td>
<td>&lt;25% up to 75%^</td>
<td>&lt;25%</td>
</tr>
<tr>
<td>Ki-67 (MIB-1)</td>
<td>0%</td>
<td>3%-10%</td>
<td>&gt;10%</td>
<td>&gt;10%</td>
<td>69 ± 20%</td>
</tr>
<tr>
<td>Cyclin E</td>
<td>Focal</td>
<td></td>
<td></td>
<td></td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

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)

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

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 nonvillus trophoblast as placental site trophoblastic tumor.
4. Misdiagnosis of nonvillus 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

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
<tr>
<td>M1a</td>
</tr>
<tr>
<td>M1b</td>
</tr>
</tbody>
</table>

* Genital metastasis (vagina, broad ligament, ovary, fallopian tube) is classified as T2. Direct invasion or metastasis to any non genital 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\(^3,4,5\)

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

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\(^*\)

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>TNM Classification</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any T</td>
<td>M1a</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Any T</td>
<td>M1a</td>
</tr>
<tr>
<td>Stage IIIIB</td>
<td>Any T</td>
<td>M1a</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>M1b</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Any T</td>
<td>M1b</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>M1b</td>
</tr>
</tbody>
</table>

\* 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.

<table>
<thead>
<tr>
<th>RX</th>
<th>Presence of residual tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>No residual tumor</td>
</tr>
<tr>
<td>R1</td>
<td>Microscopic residual tumor</td>
</tr>
<tr>
<td>R2</td>
<td>Macroscopic residual tumor</td>
</tr>
</tbody>
</table>

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.

References