National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gestational Trophoblastic Neoplasia

Version 2.2021 — March 31, 2021

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NCCN Guidelines Version 2.2021
Gestational Trophoblastic Neoplasia

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***Nadeem R. Abu-Rustum, MD Ω/Chair**
Memorial Sloan Kettering Cancer Center

***Catheryn M. Yashar, MD §/Vice Chair**
UC San Diego Moores Cancer Center

Kristin Bradley, MD §
University of Wisconsin
Carbone Cancer Center

Susana M. Campos, MD, MPH, MS †
Dana-Farber/Brigham and Women's
Cancer Center

Hye Sook Chon, MD Ω
Moffitt Cancer Center

Christina Chu, MD Ω
Fox Chase Cancer Center

Lani Clinton, MD, PhD ≠
Duke Cancer Institute

David Cohn, MD Ω
The Ohio State University
Comprehensive Cancer Center -
James Cancer Hospital and
Solove Research Institute

Marta Ann Crispens, MD Ω
Vanderbilt-Ingram Cancer Center

Shari Damast, MD §
Yale Cancer Center/
Smilow Cancer Hospital

Elisabeth Diver, MD Ω
Stanford Cancer Institute

Christine M. Fisher, MD, MPH §
University of Colorado Cancer Center

Peter Frederick, MD Ω
Roswell Park Cancer Institute

David K. Gaffney, MD, PhD §
Huntsman Cancer Institute
at the University of Utah

Robert Giuntoli II, MD Ω
Abramson Cancer Center at
the University of Pennsylvania

Ernest Han, MD, PhD Ω
City of Hope
National Medical Center

Warner K. Huh, MD Ω
O'Neal Comprehensive
Cancer Center at UAB

Jayanthi Lea, MD Ω
UT Southwestern Simmons
Comprehensive Cancer Center

Andrea Mariani, MD Ω
Mayo Clinic Cancer Center

David Mutch, MD Ω
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Larissa Nekhlyudov, MD, MPH Þ
Dana-Farber/Brigham and Women's
Cancer Center

Steven W. Remmenga, MD Ω
Fred & Pamela Buffett Cancer Center

R. Kevin Reynolds, MD Ω
University of Michigan
Rogel Cancer Center

Ritu Salani, MD, MBA Ω
UCLA Jonsson Comprehensive Cancer Center

Rachel Sisodia, MD Ω
Massachusetts General Hospital
Cancer Center

Pamela Soliman, MD, MPH Ω
The University of Texas MD Anderson Cancer Center

Edward Tanner, MD Ω
Robert H. Lurie Comprehensive
Cancer Center of Northwestern University

Todd Tillmanns, MD Ω
St. Jude Children's Research Hospital/
The University of Tennessee Health Science Center

Stefanie Ueda, MD Ω
UCSF Helen Diller Family
Comprehensive Cancer Center

Renata Urban, MD Ω
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Stephanie L. Wethington, MD, MSc Ω
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Emily Wyse ¥
Patient Advocate

NCCN
Nicole McMillian, MS
Angela Motter, PhD

Ω Gynecologic oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocacy
§ Radiotherapy/Radiation oncology
*Discussion Section Writing Committee

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NCCN Guidelines Panel Disclosures

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Gestational Trophoblastic Neoplasia

Gestational Trophoblastic Neoplasia Subcommittee

David Mutch, MD Ω/Lead
Siteman Cancer Center at Barnes-Jewish Hospital
and Washington University School of Medicine

Elisabeth Diver, MD Ω
Stanford Cancer Institute

R. Kevin Reynolds, MD Ω
University of Michigan Rogel Cancer Center

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Ω Gynecologic oncology

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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NCCN Guidelines Version 2.2021
Gestational Trophoblastic Neoplasia

Updates in Version 2.2021 of the NCCN Guidelines for Gestational Trophoblastic Neoplasia from Version 1.2021 include:

MS-1
- **The Discussion has been updated to reflect the changes in the algorithm.**

Updates in Version 1.2021 of the NCCN Guidelines for Gestational Trophoblastic Neoplasia from Version 3.2020 include:

General
- **Principles of Gynecologic Survivorship: This is a new section that discusses the physical and psychosocial effects of gynecologic cancers as well as clinical approaches to managing them. (GTN-C).**
- **Section title changed to *Principles of* Systemic therapy *for GTN*. (GTN-B)**

Hydatidiform Mole (Noninvasive)

HM-1
- **Monitoring: *Contraception (oral contraceptives preferred)* added as a recommendation.**
- **Findings and Additional Evaluation:**
  - **Top pathway; After "Normal hCG levels for 3 consecutive assays": Revised, ~~hCG assay twice in 3-month intervals~~ *hCG assay every 3 months for 6 months***
  - **Bottom pathway: hCG levels indicate postmolar gestational trophoblastic neoplasia (GTN) revised to *Persistent hCG elevation (plateau or rise).***
    - **After Persistent hCG elevation (plateau or rise), revised to Persistent post-molar *gestational trophoblastic neoplasia* (GTN).**
- **Footnote a revised: If chest x-ray positive for metastases, *then perform chest/abdomen/pelvis CT and brain MRI and* manage as GTN after initial uterine evacuation.**
- **Footnote d revised: Hysterectomy with salpingectomy may be considered as initial treatment for hydatidiform mole in patients who ~~are older or~~ do not wish to preserve fertility.**
- **Footnote e revised: *A formal follow-up program allows for early detection of GTN and limits exposure to combination chemotherapy (Sita-Lumsden A, et al. Br J Cancer 2012;107:1810-1814).* See Principles of Pathology (GTN-A).**
- **Footnote f added to page: *Oral contraceptive pills are preferred because they suppress endogenous luteinizing hormone (LH)/ follicle-stimulating hormone (FSH), which may interfere with hCG measurement at low levels.***

HM-2
- **Staging**
  - **First bullet: H&P revised to include *pelvic exam*.**
  - **New bullet added: *Determine FIGO stage and prognostic score*.**
- **Treatment**
  - **No extrauterine disease: *Single-agent systemic therapy as in* GTN-2 added as an option.**
  - **Extrauterine disease: A new bifurcation was added for *Low-risk GTN: (<7 prognostic score)* (See GTN-2) and *High-risk GTN: ≥7 prognostic score or Stage IV* (See GTN-4). Previously chemotherapy on GTN-1 was recommended.**
- **Monitoring for No extrauterine disease: After "hCG assay every 2 weeks until 3 consecutive normal assays, followed by monthly for 6 months" recommendation clarified as Persistent *hCG* elevation (plateau or rise)**
- **Footnote g is new: *See FIGO Staging System for GTN (ST-1)* and *Prognostic Scoring Index for GTN (ST-2)*.**
- **Footnote removed from this page: See Principles of Systemic Therapy (GTN-B) for specific recommendations.**

Continue

Gestational Trophoblastic Neoplasia (GTN)

GTN-1

- Findings; Middle pathway: Revised, High-risk GTN: ~~FIGO stages II–III and~~ ≥7 prognostic score or Stage IV. (Also for GTN-4)
- Footnote c revised: "... consider possibility of *luteinizing hormone (LH) crossover or* phantom hCG. Consult with..."

GTN-2 Low-risk GTN

- New page title added: *Primary Treatment for Low-Risk GTN*
- Response Assessment
  - Top pathway; Normal hCG level: Revised, Continue systemic therapy for ~~2~~ *2–3* treatment cycles ~~(4 weeks total)~~ past hCG normalization.
  - Bottom pathway; Poor response to initial therapy: Revised, "... for 3 treatment cycles ~~(6 weeks total)~~ or hCG level rises (>10% change) for 2 treatment cycles ~~(4 weeks total)~~."
- Follow-up/Surveillance: Second bullet revised, Contraception (oral contraceptive*s* ~~pills~~ preferred).
- Footnote i revised: Regimens are continued until ~~2~~ *2–3* full cycle(s) past normalization of the hCG.
- Footnote l revised: hCG plateau during treatment can be defined as a <10% decrease in hCG over ~~2~~ *3* treatment cycles ~~(4 weeks total)~~.

GTN-3

- New page title added: *Primary Treatment for Persistent GTN*
- Top pathway
  - Revised, Good response to initial therapy followed by hCG level plateau or re-elevation *(hCG <300)*.
- Bottom pathway
  - Revised, Good response to initial therapy followed by rapid rise in hCG level *(hCG ≥ 300)* or Poor response to initial therapy
- Response Assessment
  - The recommendation for Normal hCG levels was revised: Continue systemic therapy for ~~2~~ *2-3 treatment* cycles past normalization.
  - hCG level plateaus: The "weeks" timeframes for the treatment cycles were removed (ie "4 weeks total" and "2 weeks total").
- Footnote removed: ~~hCG level plateaus (<10% change) for 2 treatment cycles (4 weeks total) or hCG level rises (>10% change) for 1 treatment cycle (2 weeks total)~~.
- Footnote removed: Do not start a cycle of methotrexate or dactinomycin if the WBC was <3.0 or the ANC was <1.5 or if there was persistent mucositis >grade 1. CBC and chemistries should not be checked during a chemotherapy cycle; they should only be checked at the start of each cycle.

GTN-4 High-risk GTN

- New page title added: *Primary Treatment for High-Risk GTN.*
- Treatment; EMA/CO; If brain metastases: Revised, Increase methotrexate dose and ~~folinic acid~~ *leucovorin* dose.
- Footnote q revised: ~~Increase the methotrexate infusion dose in the EMA/CO protocol to 1000 mg/m2 and give folinic acid 30 mg every 12 hours for 3 days starting 32 hours after the infusion begins.~~ *For dosing modifications for brain metastases, See Systemic Therapy for GTN (GTN-B 2 of 6).*

GTN-5 Intermediate trophoblastic tumor: PSTT and ETT

- New page title added: *Primary Treatment for PSTT and ETT.*
- Metastatic pathway; Chemotherapy with a platinum/etoposide-containing regimen,...: Bullet removed, "Use granulocyte colony-stimulating factor (G-CSF) with chemotherapy regimens (See NCCN Guidelines for Hematopoietic Growth Factors)." This recommendation can be found on GTN-B.

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UPDATES

Hydatidiform Mole (Noninvasive) and GTN

GTN-B Systemic Therapy for GTN

- **The dosing and Comments/Considerations throughout this section were extensively revised.**
- **Footnote b is new: *Round filgrastim dose to the nearest vial size by institution-defined weight limits*.**

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- **The "TIP: Paclitaxel, Ifosfamide, Cisplatin" regimen under "Other Recommended Regimens" was moved from page 5 of 6 to page 4 of 6 to clarify that only TIP is recommended for High-Risk GTN: Therapy for Methotrexate-Resistant GTN .**
- **Footnote d regarding VIP is new: For dosing references, See page TEST-E from the NCCN Guidelines for Testicular Cancer.**
- **Footnote e regarding TIP is new: For dosing references, See page TEST-F from the NCCN Guidelines Testicular Cancer.**

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- **Page title revised: High-Risk GTN: ~~Therapy for Methotrexate-Resistant GTN~~ *Additional agents/regimens shown to have some activity in treating multiagent chemotherapy-resistant GTN.***
- **Usefule in Certain Circumstances:**
  - **PD-1/PD-L1 inhibitors: Dosing was added for avelumab, *Avelumab 800 mg IV every 2 weeks***

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Hydatidiform Mole (Noninvasive)

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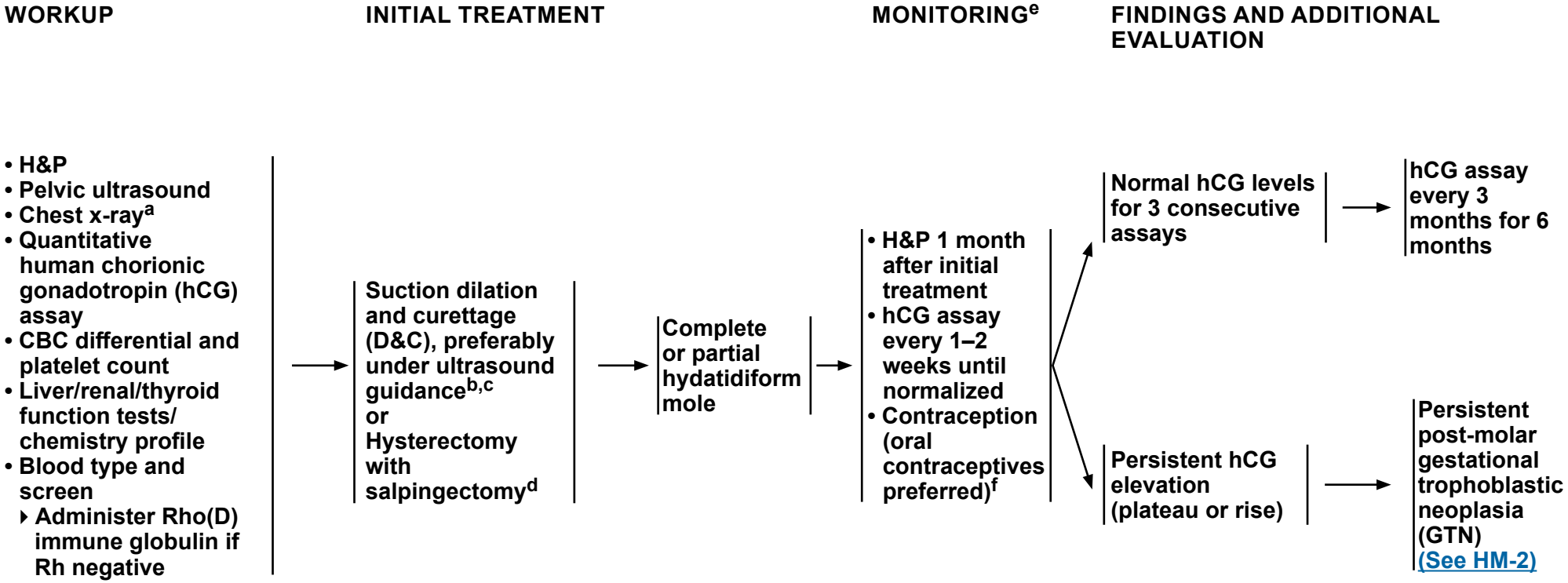
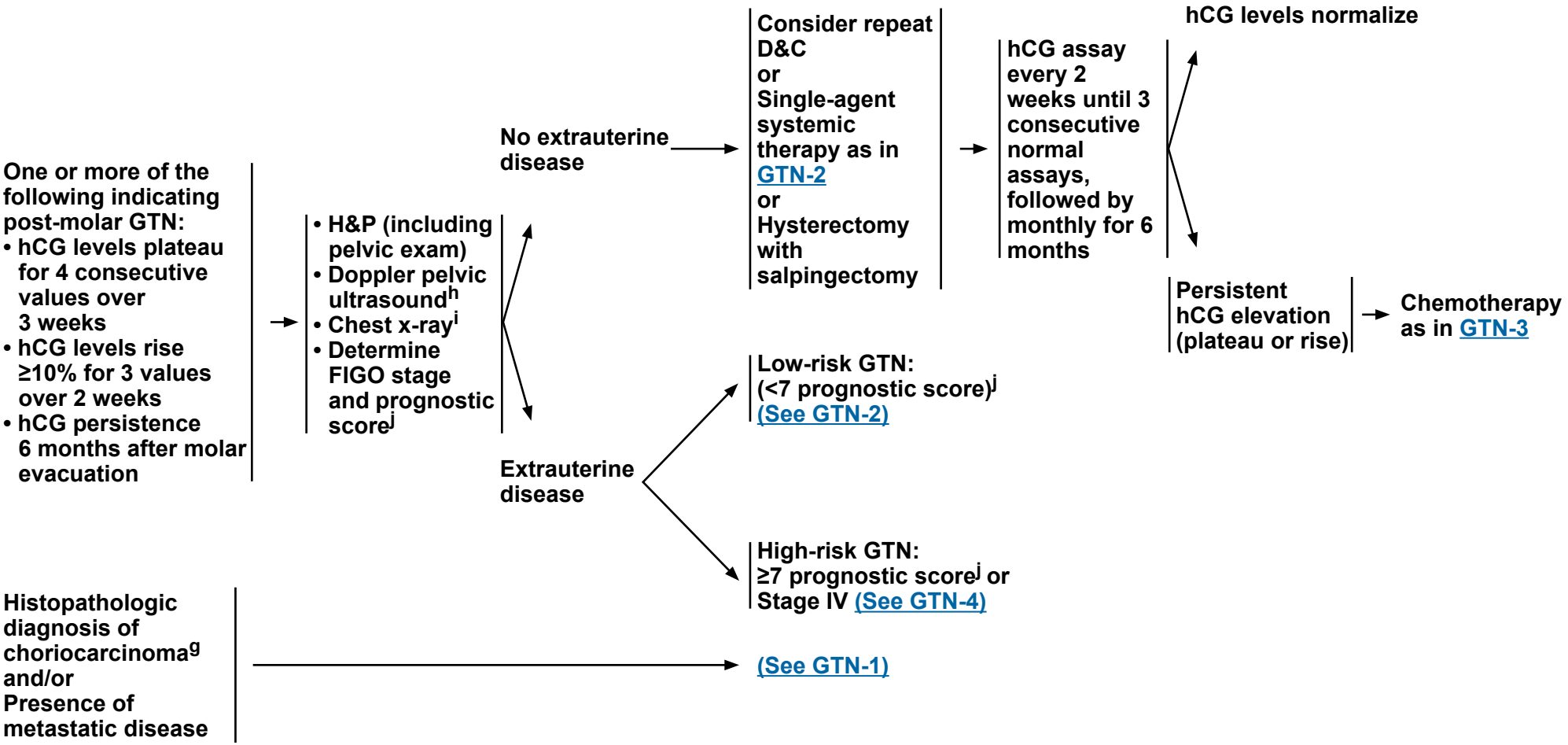


[a]If chest x-ray positive for metastases, then perform chest/abdomen/pelvis CT and brain MRI and manage as GTN after initial uterine evacuation.
[b]Use largest curette feasible. Sharp curettage after suction. Use uterotonic drugs after initiating evacuation of uterus. Oxytocin receptors may be absent.
[c]Prophylactic chemotherapy with methotrexate or dactinomycin may be considered at the time of evacuation of a hydatidiform mole in patients at high risk for post-molar GTN (age >40 years, hCG >100,000 mIU/mL, excessive uterine enlargement, and theca lutein cysts >6 cm) when hCG follow-up is unavailable or unreliable (Wang Q, et al. Cochrane Database Sust Rev 2017;9:CD007289).
[d]Hysterectomy with salpingectomy may be considered as initial treatment for hydatidiform mole in patients who do not wish to preserve fertility.
[e]A formal follow-up program allows for early detection of GTN and limits exposure to combination chemotherapy (Sita-Lumsden A, et al. Br J Cancer 2012;107:1810-1814). See Principles of Pathology (GTN-A).
[f]Oral contraceptive pills are preferred because they suppress endogenous luteinizing hormone (LH)/follicle-stimulating hormone (FSH), which may interfere with hCG measurement at low levels.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[g] See Principles of Pathology (GTN-A).
[h] Doppler pelvic ultrasound to confirm absence of pregnancy, measure uterine size, and determine volume and vasculature of tumor within the uterus.
[i] If the chest x-ray is normal, no further imaging is indicated before commencing treatment. If the chest x-ray shows metastases, CT scan of the abdomen/pelvis and MRI of the brain are indicated.
[j] See FIGO Staging System for GTN (ST-1) and Prognostic Scoring Index for GTN (ST-2).

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WORKUP[a]
(unless previously done)

- **H&P**
- **Repeat CBC differential and platelet count**
- **Repeat liver/renal/thyroid function tests/chemistry profile**
- **Imaging**
  - **Chest/abdominal/pelvic CT scan with contrast[b]**
    - ◊ **Brain MRI (preferred) or CT with contrast if pulmonary metastasis**
  - **Pelvic ultrasound or MRI**
- **hCG assay[c,d]**
- **Determine FIGO stage and prognostic score[e]**
- **Histopathologic assessment[f]**

FINDINGS[g]

Low-risk GTN (<7 prognostic score)[e] → **(See GTN-2)**

High-risk GTN: ≥7 prognostic score[e] or Stage IV → **(See GTN-4)**

Intermediate trophoblastic tumor[h]
- **Placental site trophoblastic tumor (PSTT)**
- **Epithelioid trophoblastic tumor (ETT)**

→ **(See GTN-5)**

[a]If visible lesions are seen in lower genital tract, do NOT biopsy due to risk of hemorrhage.
[b]If contrast is contraindicated, other imaging techniques such as MRI may be considered.
[c]If hCG is elevated with no evidence of disease on imaging, consider possibility of LH crossover or phantom hCG. Consult with laboratory medicine/pathology to test for phantom hCG with serial dilution study or comparison of serum to urine hCG.
[d]If hCG is elevated, but hyperglycosylated hCG is normal, quiescent GTN may be diagnosed and not treated.
[e]See FIGO Staging System for GTN (ST-1) and Prognostic Scoring Index for GTN (ST-2).
[f]See Principles of Pathology (GTN-A).
[g]Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.
[h]Prognostic scoring is not valid for intermediate tumors.

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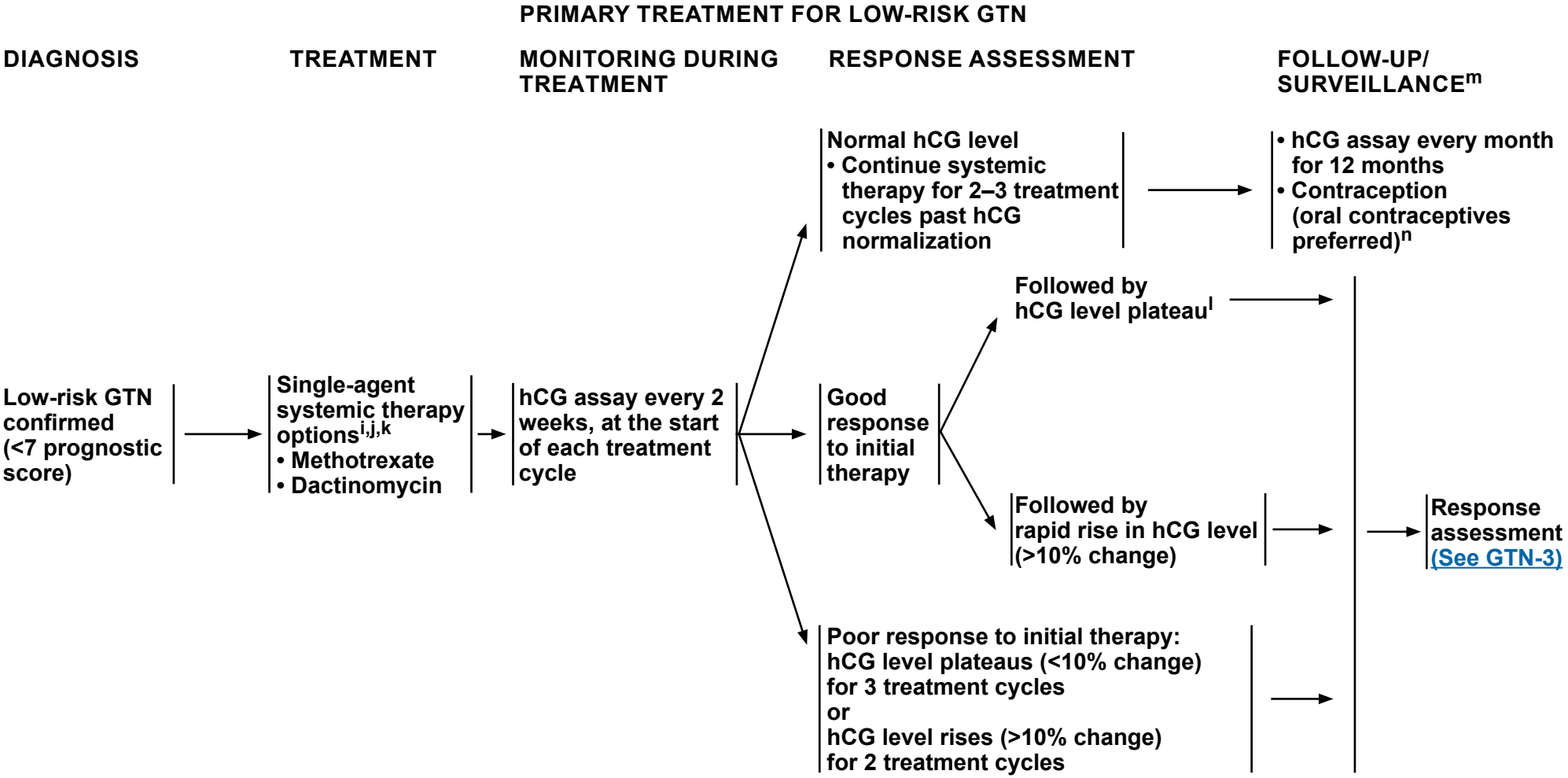
PRIMARY TREATMENT FOR LOW-RISK GTN



[i]Regimens are continued until 2–3 full cycle(s) past normalization of the hCG.
[j]Hysterectomy with salpingectomy may be considered if there is localized disease in the uterus and where fertility preservation is not desired. Leave ovaries in situ, even in presence of theca lutein cysts.
[k]See Systemic Therapy for GTN (GTN-B) for specific recommendations.
[l]hCG plateau during treatment can be defined as a <10% decrease in hCG over 3 treatment cycles.
[m]See Principles of Gynecologic Survivorship (GTN-C).
[n]Oral contraceptive pills are preferred because they suppress endogenous LH/FSH, which may interfere with hCG measurement at low levels.

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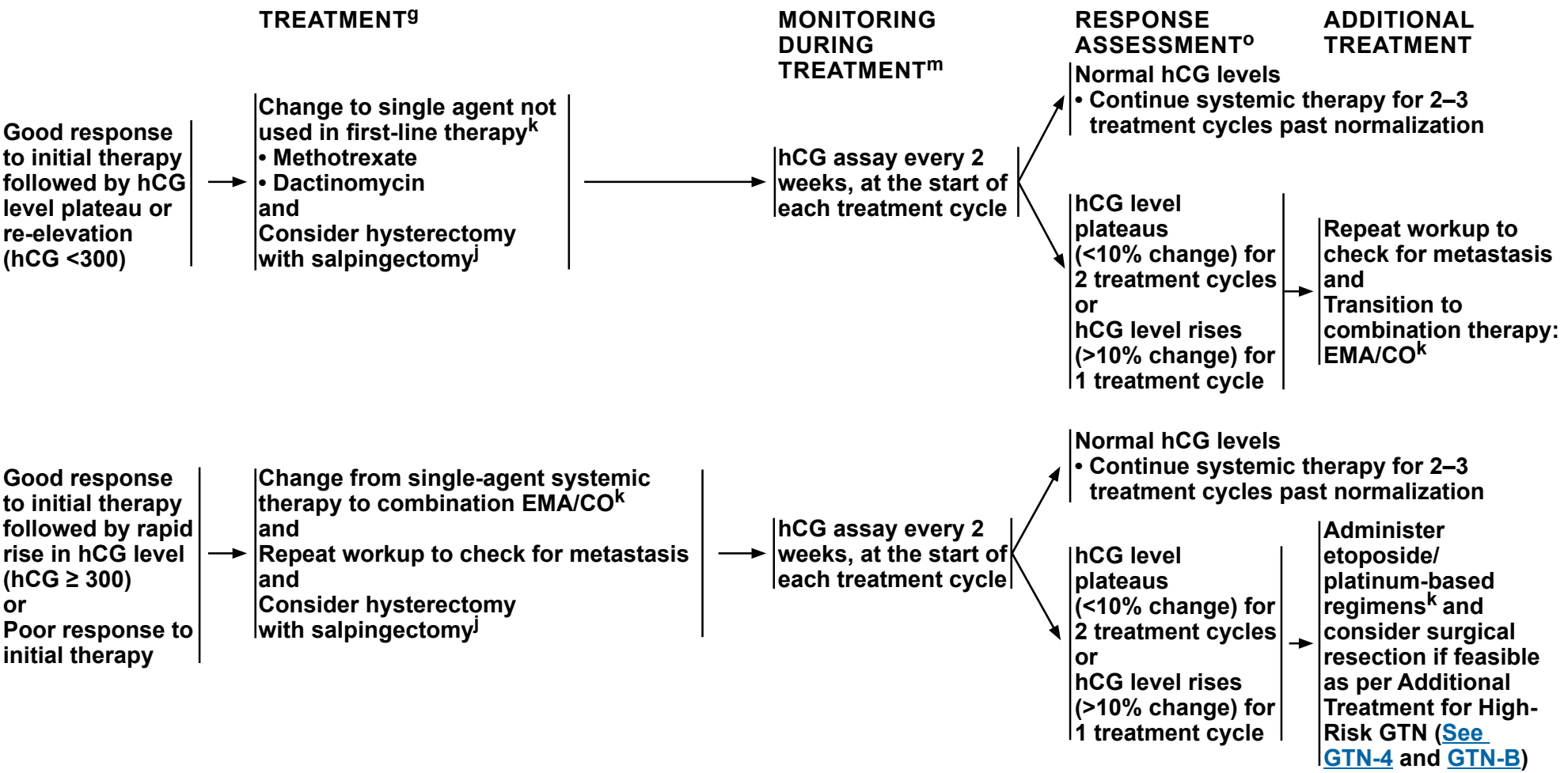
TREATMENT FOR PERSISTENT GTN



[g]Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.

[j]Hysterectomy with salpingectomy may be considered if there is localized disease in the uterus and where fertility preservation is not desired. Leave ovaries in situ, even in presence of theca lutein cysts.

[k]See Systemic Therapy for GTN (GTN-B) for specific recommendations.

[m]See Principles of Gynecologic Survivorship (GTN-C).

[o]Post-treatment imaging is not recommended for follow-up after hCG normalization in patients with post-molar GTN or choriocarcinoma, where hCG is a reliable tumor marker.

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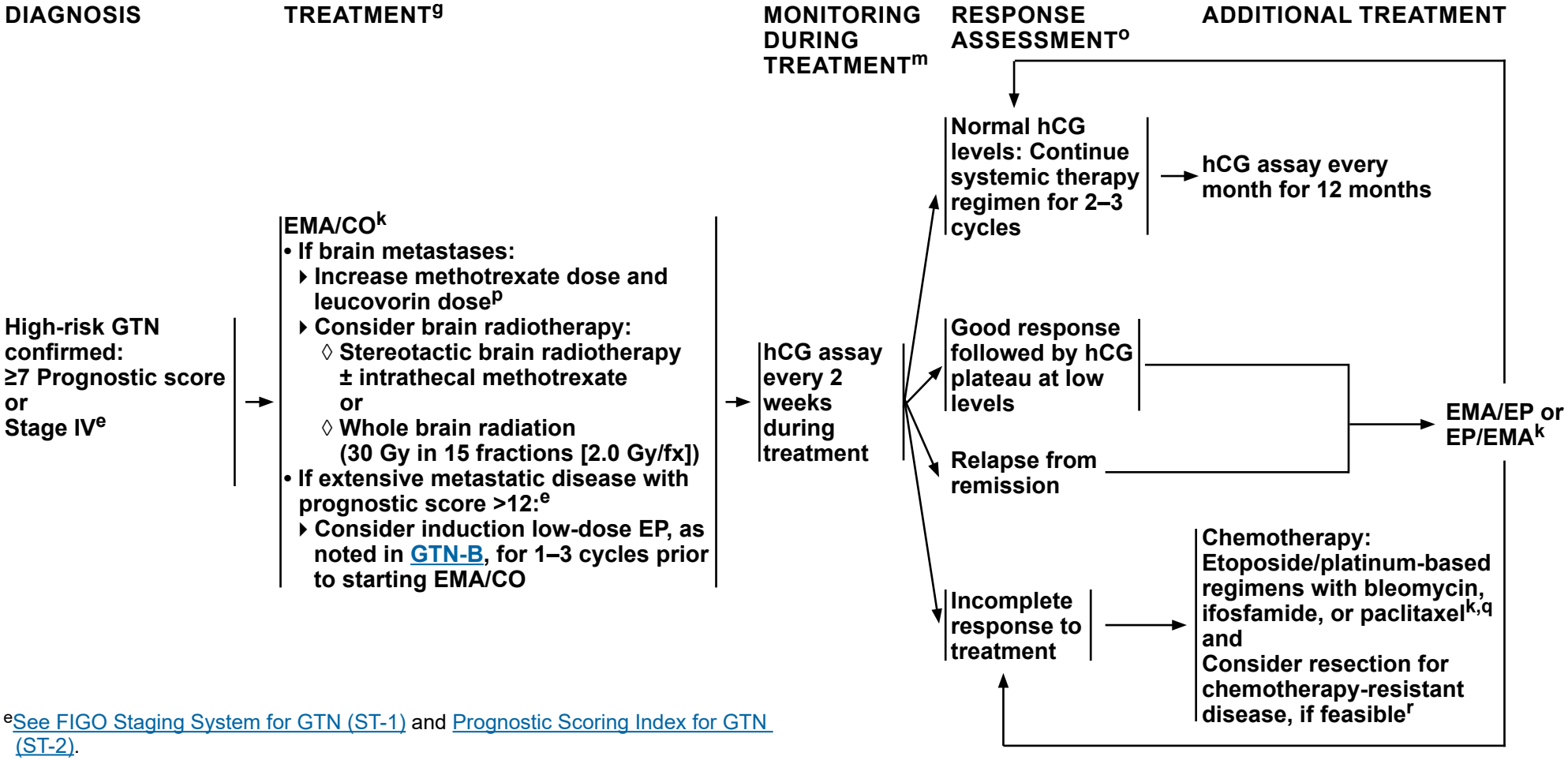
PRIMARY TREATMENT FOR HIGH-RISK GTN



[e] See FIGO Staging System for GTN (ST-1) and Prognostic Scoring Index for GTN (ST-2).
[g] Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.
[k] See Systemic Therapy for GTN (GTN-B) for specific recommendations.
[m] See Principles of Gynecologic Survivorship (GTN-C).
[o] Post-treatment imaging is not recommended for follow-up after hCG normalization in patients with post-molar GTN or choriocarcinoma, where hCG is a reliable tumor marker.
[p] For dosing modifications for brain metastases, See Systemic Therapy for GTN (GTN-B 2 of 6).
[q] Also see Additional Agents Shown to Have Some Activity in Treating Multiagent Chemotherapy-Resistant GTN (GTN-B 5 of 6).
[r] Consider surgery, especially hysterectomy with salpingectomy and pulmonary resection, for chemotherapy-resistant disease.

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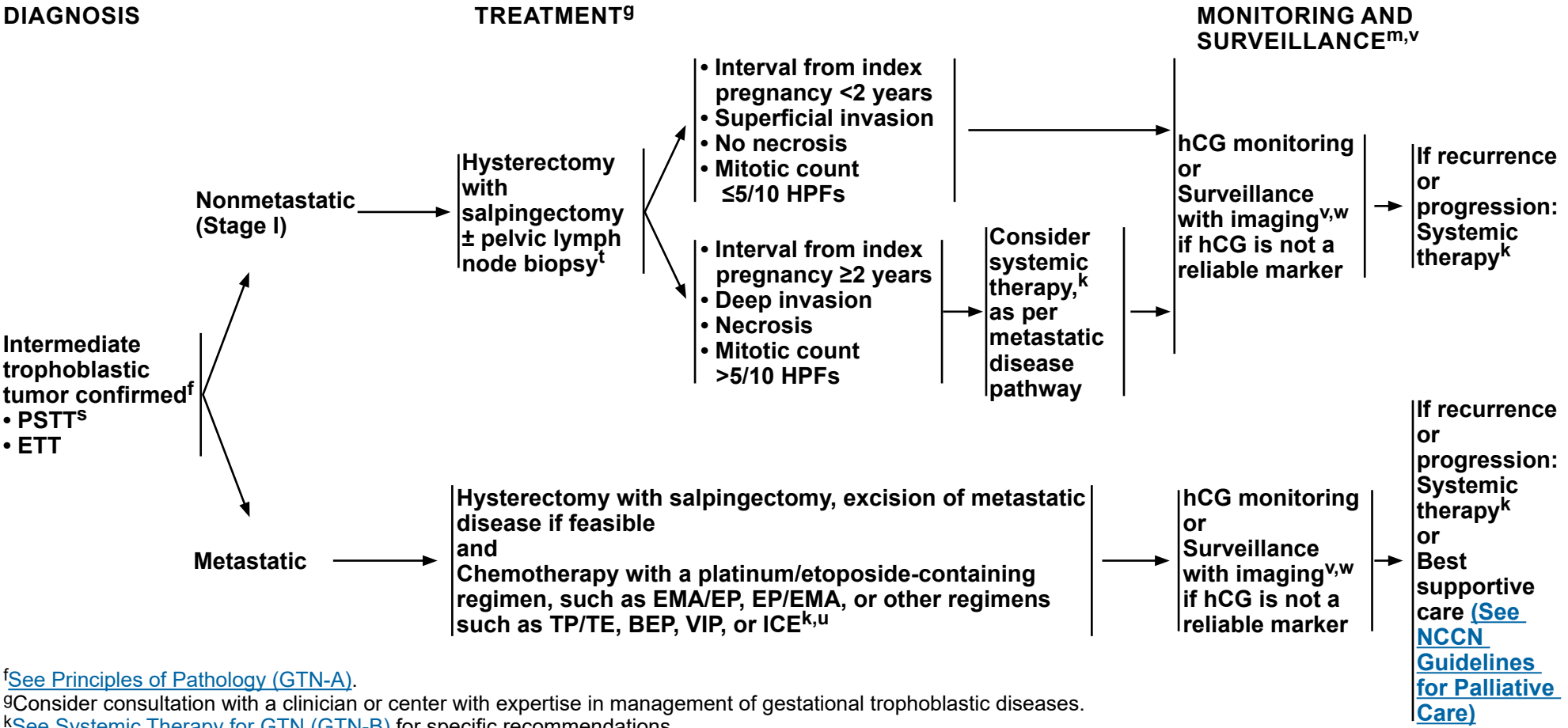
PRIMARY TREATMENT FOR PSTT AND ETT



[f] See Principles of Pathology (GTN-A).
[g] Consider consultation with a clinician or center with expertise in management of gestational trophoblastic diseases.
[k] See Systemic Therapy for GTN (GTN-B) for specific recommendations.
[m] See Principles of Gynecologic Survivorship (GTN-C).
[s] Reported poor prognostic factors in PSTT are high miotic rates (>5/10 high-power fields [HPFs]), deep myometrial invasion, extensive coagulative necrosis, lymphovascular space invasion (LVSI), and interval since last pregnancy >2 years. (Baergen RN, et al. Gynecol Oncol 2006;100:511-520.)
[t] The incidence of pelvic lymph node metastasis in PSTT/ETT is estimated to be between 5% and 15% in clinical stage I tumors. Therefore, pelvic lymph node biopsy should be considered at the time of hysterectomy with salpingectomy, especially with large, deeply invasive tumors.
[u] Also see Additional Agents Shown to Have Some Activity in Treating Multiagent Chemotherapy-Resistant GTN (See GTN-B 6 of 6).
[v] Post-treatment imaging is indicated for follow-up after treatment of PSTT and ETT, where hCG is a less reliable tumor marker.
[w] Consider PET/CT for follow-up at the completion of chemotherapy and then every 6–12 months for 2–3 years.

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PRINCIPLES OF PATHOLOGY

Procedure
- **D&C**
- **Hysterectomy**
- **Pelvic exenteration**
- **Other**

Pathologic Diagnosis of Benign, Noninvasive Hydatidiform Mole[2]

	Gross Examination	Chorionic Villi	Trophoblastic Hyperplasia	Cytologic Atypia	Villous Stroma	p57 IHC	DNA Genotyping
Complete Mole	Diffuse hydropic villi; fetus absent	Diffusely enlarged	Marked, often circumferential	May be marked	Marked edema with cisterns and trophoblast inclusions; blood vessels absent; nucleated red blood cells (RBCs) absent	Absent nuclear staining in cytotrophoblasts and villous stromal cells	Diploid diandric genome
Partial Mole	Patchy hydropic villi; fetal tissue may be present	Dual population of villi composed of enlarged villi and small, fibrotic villi	Mild	Mild	May have cisterns; trophoblastic pseudoinclusions; blood vessels present; nucleated RBCs present	Nuclear staining present in cytotrophoblasts and villous stromal cells	Triploid diandric-monogynic genome

- **Report histologic type only.**
- **If myometrial or vascular invasion is present (ie, invasive mole), use pathologic assessment for malignant GTN below.**

Continued

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PRINCIPLES OF PATHOLOGY

Pathologic Assessment for Malignant Gestational Trophoblastic Tumor[a]

- **Tumor site (ie, uterine corpus, cervix, other, cannot be determined)**
- **Tumor size (measured in cm)**
- **Histologic type**
  - **Hydatidiform mole, invasive**
  - **Choriocarcinoma**
  - **Placental site trophoblastic tumor**
  - **Epithelioid trophoblastic tumor**
  - **Malignant trophoblastic tumor, type cannot be determined**
- **Tissue/organ involvement (list all organs submitted for evaluation involved by tumor)**
- **Specimen margin status (where applicable; when negative, may also include closest margin and distance to closest margin)**
- **Lymphovascular space invasion**

Immunohistochemical Markers for Differential Diagnosis of GTN[1,2,3]

	Mel-CAM (CD146)	hPL	β-HCG	p63	Cyclin E	Ki-67
PSTT	+	+	–	–		>10%
ETT	–	–	–	+	>50%	>10%
Choriocarcinoma	+/-	+	+	–		High, usually >90%

Mel-CAM: melanoma cell adhesion molecule; hPL: human placental lactogen; β-HCG: beta-human chorionic gonadotropin

Footnotes

[a]Benign trophoblastic tumors/lesions (ie, exaggerated placental site, placental site nodule) are benign and should NOT be reported using these principles.

References

[1]College of American Pathologists: Protocol for the Examination of Specimens From Patients With Primary Gestational Trophoblastic Malignancy. 2017. Available at: https://documents.cap.org/protocols/cp-trophoblast-17protocol-4000.pdf.

[2]Kurman RJ, Carcangiu ML, Herrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs, Fourth Edition. Vol. 6; 2014:155-168.

[3]Chi DS, Berchuck A, Dizon DS, et al. Table 26.2: Immunohistochemical Markers for Differential Diagnosis of GTD. Principles and Practice of Gynecologic Oncology 2017:745.

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SYSTEMIC THERAPY FOR GTN

Regimens for Low-Risk GTN

Preferred Regimens	Comments/Considerations
Methotrexate 0.4 mg/kg/day (max 25 mg/day) IV (preferred) or IM daily x 5 days; Repeat every 14 days (category 1) OR 1 mg/kg IM every other day x 4 days (Days 1, 3, 5, and 7) Alternating every other day with leucovorin 0.1 mg/kg rounded up to the nearest 5-mg dose increment or 15 mg PO (preferred) or IM 30 hours after each methotrexate dose on Days 2, 4, 6, and 8; Repeat every 14 days (category 1)	• A multiday methotrexate regimen is typically used as first-line therapy for low-risk GTN. Due to its toxicity profile, 5-day dactinomycin has most often been used as secondary therapy for patients with methotrexate toxicity or effusions contradicting the use of methotrexate. **NOT RECOMMENDED** • Methotrexate 30–50 mg/m^2 IM weekly OR Methotrexate infusion (eg, 300 mg/m^2 over 12 hours/leucovorin) due to lesser efficacy.
Dactinomycin 10–12 mcg/kg (or 0.5 mg flat dose) IV daily x 5 days; Repeat every 14 days (category 1) OR 1.25 mg/m^2 (max 2 mg) IV pulse; Repeat every 14 days (category 1)	• Dactinomycin pulse regimen should not be used as secondary therapy for methotrexate-resistant disease nor as primary therapy in patients with choriocarcinoma.

Continued

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SYSTEMIC THERAPY FOR GTN

High-Risk GTN: Primary Therapy Options[a]

Preferred Regimens	Comments/Considerations
EMA/CO: Etoposide, Methotrexate, Dactinomycin/Cyclophosphamide, Vincristine **(Repeat every 2 weeks until hCG normalizes, then continue for an additional 6–8 weeks)** • **Etoposide 100 mg/m^2/day IV on Days 1 and 2** • **Dactinomycin 0.5 mg IV push on Days 1 and 2** • **Methotrexate 300 mg/m^2 IV infusion over 12 hours on Day 1** • **Leucovorin 15 mg PO (preferred) or IM every 12 hours for 4 doses starting 24 hours after the start of methotrexate infusion** • **Cyclophosphamide 600 mg/m^2 IV on Day 8** • **Vincristine 1 mg/m^2 (maximum of 2 mg) IV over 5–10 minutes on Day 8**	• **Consider low-dose induction chemotherapy with etoposide 100 mg/m^2/day IV and cisplatin 20 mg/m^2/day IV on Days 1 and 2 every 7 days for 1–3 courses prior to starting EMA/CO in patients with widely metastatic disease (prognostic score >12) who are at significant risk for pulmonary, intraperitoneal, or intracranial hemorrhage.** • **For secondary prophylaxis of neutropenic fever, or for treatment delay: Filgrastim, 5 mcg/kg 3–4 days/wk [ie, on days 4–6(7) and 10–12(13)] of each EMA/CO cycle.[b]** • **For patients with brain metastases, increase the methotrexate infusion dose in the EMA/CO protocol to 1000 mg/m^2 and extend the infusion from 12 to 24 hours; give leucovorin 15 mg PO every 6 hours for 12 doses starting 32 hours after the start of the methotrexate infusion.**

[a]Use granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis with etoposide/cisplatin or etoposide/carboplatin-based regimens. See NCCN Guidelines for Hematopoietic Growth Factors.
[b]Round filgrastim dose to the nearest vial size by institution-defined weight limits.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

SYSTEMIC THERAPY FOR GTN

High-Risk GTN: Primary Therapy Options[a] – Continued

For highest-risk patients, consider: EMA/EP or EP/EMA
- **EMA/EP (or EP/EMA) regimen is considered the most appropriate therapy for patients who have responded to EMA/CO but have plateauing low hCG levels or have developed re-elevation of hCG levels after a complete response to EMA/CO.**

Preferred Regimens	Comments/Considerations
EMA/EP: Etoposide, Methotrexate, Dactinomycin/Etoposide, Cisplatin[c] **(Repeat every 2 weeks alternating EMA with EP weekly through 6–8 weeks post-serologic remission)** • **Etoposide 100 mg/m^2/day IV on Day 1** • **Methotrexate 300 mg/m^2 IV infusion over 12 hours on Day 1** ▸ **Leucovorin 15 mg PO (preferred) or IM every 12 hours for 4 doses beginning 24 hours after the start of the methotrexate infusion** • **Dactinomycin 0.5 mg IV push on Day 1** • **Etoposide 150 mg/m^2 IV on Day 8** • **Cisplatin 75 mg/m^2 IV on Day 8** • **Filgrastim 5 mcg/kg SC on Days 9–14[b]**	• **Consider low-dose induction chemotherapy with etoposide 100 mg/m^2/day IV and cisplatin 20 mg/m^2/day IV on Days 1 and 2 every 7 days for 1–3 courses prior to starting EMA/EP or EP/EMA in patients with widely metastatic disease (prognostic score >12) who are at significant risk for pulmonary, intraperitoneal, or intracranial hemorrhage.** • **For patients with brain metastases, increase the methotrexate infusion dose in the EP/EMA or EMA/EP protocol to 1000 mg/m^2 and extend the infusion from 12 to 24 hours; give leucovorin 15 mg PO every 6 hours for 12 doses starting 32 hours after the start of the methotrexate infusion.**
EP/EMA: Etoposide, Cisplatin/Etoposide, Methotrexate, Dactinomycin[c] **(Repeat every 2 weeks alternating EP with EMA weekly through 6–8 weeks post-serologic remission)** • **Etoposide 150 mg/m^2 on Day 1** • **Cisplatin 75 mg/m^2 IV on Day 1** • **Etoposide 100 mg/m^2 IV on Day 8** • **Methotrexate 300 mg/m^2 IV infusion over 12 hours on Day 8** ▸ **Leucovorin 15 mg PO (preferred) or IM every 12 hours for 4 doses beginning 24 hours after the start of the methotrexate infusion** • **Dactinomycin 0.5 mg IV on Day 8** • **Filgrastim 5 mcg/kg SC on Days 3–6 and 10–13[b]**	

[a]Use G-CSF as primary prophylaxis with etoposide/cisplatin or etoposide/carboplatin-based regimens. See NCCN Guidelines for Hematopoietic Growth Factors.
[b]Round filgrastim dose to the nearest vial size by institution-defined weight limits.
[c]Dosing schedules also apply to the Intermediate Trophoblastic Tumor (PSTT and ETT) regimens listed on GTN-B 6 of 6.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC THERAPY FOR GTN
High-Risk GTN: Therapy for Methotrexate-Resistant GTN[a]

Preferred Regimens	
TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide (Repeat every 2 weeks)[c] • Paclitaxel 135 mg/m^2 IV infusion on Day 1 • Cisplatin 75 mg/m^2 IV on Day 1 **Alternating every 2 weeks with:** • Paclitaxel 135 mg/m^2 IV infusion on Day 15 • Etoposide 150 mg/m^2 IV on Day 15 • Pegfilgrastim 6 mg SC on Days 2 and 16	**VIP: Etoposide, Ifosfamide, Cisplatin** (Repeat every 3 weeks)[c,d] • Etoposide 75 mg/m^2/day IV on Days 1–5 • Ifosfamide 1200 mg/m^2/day IV on Days 1–5 with mesna protection ▸ Mesna 120 mg/m^2/day IV bolus 15 minutes prior to ifosfamide, then 1200 mg/m^2/day IV infusion over 12 hours after ifosfamide dose on Days 1–5 • Cisplatin 20 mg/m^2/day IV on Days 1–5 • Pegfilgrastim 6 mg SC on Day 5; OR Filgrastim 5 mcg/kg SC on Days 6–14[b]
BEP: Bleomycin, Etoposide, Cisplatin (Repeat every 3 weeks)[c,d] • Bleomycin 30 units IV weekly on Days 1, 8, and 15 or Days 2, 9, and 16 • Etoposide 100 mg/m^2/day IV on Days 1–5 • Cisplatin 20 mg/m^2/day IV on Days 1–5 • Pegfilgrastim 6 mg SC on Day 8; OR Filgrastim 5 mcg/kg SC on Days 6–14[b] **Comments/Considerations** • Lifetime dose of bleomycin should not exceed 270 units. • Pulmonary function testing should be performed prior to initiation of therapy and every fourth dose thereafter.	**ICE: Ifosfamide, Carboplatin, Etoposide** (Repeat every 3 weeks)[c] • Ifosfamide 1.2 g/m^2/day IV on Days 1–3 with mesna protection ▸ Mesna 120 mg/m^2/day IV bolus 15 minutes prior to ifosfamide, then 1200 mg/m^2/day IV infusion over 12 hours after ifosfamide dose on Days 1–3 • Carboplatin AUC 4 IV on Day 1 • Etoposide 75 mg/m^2/day IV on Days 1–3 • Pegfilgrastim 6 mg SC on Day 4; OR Filgrastim 300 mcg SC on Days 6–14

Other Recommended Regimens
TIP: Paclitaxel, Ifosfamide, Cisplatin (Repeat every 3 weeks)[e] • Paclitaxel 250 mg/m^2 IV on Day 1 • Ifosfamide 1500 mg/m^2/day IV on Days 2–5 with mesna protection ▸ Mesna 300 mg/m^2 IV 15 minutes prior to ifosfamide, then at 4 hours and 8 hours from the start of each ifosfamide dose on Days 2–5 • Cisplatin 25 mg/m^2/day IV on Days 2–5

[a]Use G-CSF as primary prophylaxis with etoposide/cisplatin or etoposide/carboplatin-based regimens. See NCCN Guidelines for Hematopoietic Growth Factors.
[b]Round filgrastim dose to the nearest vial size by institution-defined weight limits.
[c]Dosing schedules also apply to the Intermediate Trophoblastic Tumor (PSTT and ETT) regimens listed on GTN-B 6 of 6.
[d]For dosing references, see page TEST-E in the NCCN Guidelines for Testicular Cancer.
[e]For dosing references, see page TEST-F in the NCCN Guidelines for Testicular Cancer.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC THERAPY FOR GTN

High-Risk GTN:
Additional Agents/Regimens Shown to Have Some Activity in Treating Multiagent Chemotherapy-Resistant GTN[c,f]

Useful in Certain Circumstances
• PD-1/PD-L1 inhibitors (eg, pembrolizumab, nivolumab, avelumab)[g] ▸ Pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks ▸ Nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks ▸ Avelumab 800 mg IV every 2 weeks
• 5-fluorouracil–based regimens ▸ 5-fluorouracil 1200 mg/m^2/day continuous infusion over 3 days
• Capecitabine-based regimens (repeat cycle every 3 weeks) ▸ Capecitabine 1250 mg/m^2 PO twice daily for 2 weeks on and 1 week off
• Gemcitabine ± carboplatin (Repeat every 3 weeks) ▸ Gemcitabine 600–1000 mg/m^2/day IV on Days 1 and 8 depending on the patient's bone marrow reserves. ▸ Carboplatin AUC 4 or 5 IV on Day 1
• Gemcitabine ± cisplatin (Repeat every 4 weeks) ▸ Gemcitabine 600–800 mg/m^2/day IV on Days 1, 8, and 15 ▸ Cisplatin 25–30 mg/m^2/day IV on Days 1, 8, and 15, repeat every 4 weeks
• High-dose chemotherapy with peripheral stem cell transplant[h]

[c]Dosing schedules also apply to the Intermediate Trophoblastic Tumor (PSTT and ETT) regimens listed on GTN-B 6 of 6.
[f]Recommend referral to center that specializes in the treatment of GTN.
[g]See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[h]Given on clinical trial protocol.

Continued

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC THERAPY FOR GTN

Intermediate Trophoblastic Tumor (PSTT and ETT)[a,i,j]

Preferred Regimens[g]	Other Recommended Regimens[g]	Useful in Certain Circumstances[g]
• EMA/EP: Etoposide, methotrexate, dactinomycin/etoposide, cisplatin • EP/EMA: Etoposide, cisplatin/etoposide, methotrexate, dactinomycin	• TP/TE: Paclitaxel, cisplatin/paclitaxel, etoposide • BEP: Bleomycin, etoposide, cisplatin • VIP: Etoposide, ifosfamide, cisplatin • ICE: Ifosfamide, carboplatin, etoposide	Additional agents/regimens shown to have some activity in treating multiagent chemotherapy-resistant GTN: • PD-1/PD-L1 inhibitors (eg, pembrolizumab, nivolumab, avelumab)[g] • 5-fluorouracil–based regimens • Capecitabine-based regimens • Gemcitabine ± carboplatin • Gemcitabine ± cisplatin • High-dose chemotherapy with peripheral stem cell transplant[h]

[a]Use G-CSF as primary prophylaxis with etoposide/cisplatin or etoposide/carboplatin-based regimens. See NCCN Guidelines for Hematopoietic Growth Factors.
[g]See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[h]Given on clinical trial protocol.
[i]If feasible, perform hysterectomy with salpingectomy and excision of metastatic disease.
[j]For dosing schedules, see High-Risk GTN sections GTN-B 3 of 6, GTN-B 4 of 6, and GTN-B 5 of 6.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF GYNECOLOGIC SURVIVORSHIP

Physical Effects

- Gynecologic cancer treatment typically involves surgery, chemotherapy, hormone therapy, radiation therapy, and/or immunotherapy. These treatments cause acute, short-term, and long-term toxicities.
- Surgical approaches may be extensive and pose risks such as adhesion formation, which may cause pain and may contribute to small bowel obstruction, urinary or gastrointestinal complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a variety of urinary, bowel, and/or sexual effects), and lymphedema.
- Chemotherapy agents vary, though commonly used regimens may pose a significant risk of neurotoxicity, cardiac toxicity, development of hematologic cancers, and cognitive dysfunction.
- Long-term estrogen deprivation may cause symptoms such as hot flashes, vaginal dryness, and bone loss.
- Radiation therapy may cause long-term complications (eg, fibrosis, vulvovaginal atrophy) and may predispose patients to secondary cancers of the subcutaneous tissue, and/or underlying organs that are proximal to the radiation field.
- Immunotherapy use is emerging, and to date, long-term effects of these treatments are unknown.

Psychosocial Effects

- Psychosocial effects after cancer may include psychological (eg, depression, anxiety, fear of recurrence, altered body image), financial (eg, return to work, insurance concerns), and interpersonal (eg, relationships, sexuality, intimacy) effects.

Clinical Approach

- All gynecologic cancer survivors should receive regular general medical care that focuses on chronic disease management, monitoring of cardiovascular risk factors, recommended vaccinations, and encouraging adoption of a healthy lifestyle.
- In order to assess the late and long-term effects of gynecologic cancers, clinicians should comprehensively document the patient's history, conduct a thorough physical examination, and conduct necessary imaging and/or laboratory testing. All women, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness. Referral to appropriate specialty providers (eg, physical therapy, pelvic floor therapy, sexual therapy, psychotherapy) is recommended. As most treatments for gynecologic cancers will cause sexual dysfunction, early menopause, and infertility, special attention to the resultant medical and psychosocial implications is needed.
- Post-radiation use of vaginal dilators and moisturizers is recommended.
- Communication and coordination with all clinicians involved in the care of survivors, including primary care clinicians, is critical. Providing cancer survivors with a summary of their treatment and recommendations for follow-up is recommended.

Additional Guidance

- See NCCN Guidelines for Distress Management
- See NCCN Guidelines for Smoking Cessation
- See NCCN Guidelines for Survivorship

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FIGO STAGING SYSTEM FOR GTN[a]

Stage	Criteria
I	Tumor confined to uterus
II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension
III	Lung metastasis
IV	All other distant metastases

Continued

[a]Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

PROGNOSTIC SCORING INDEX FOR GTN[a]

Prognostic factor	Risk score			
	0	1	2	4
Age (years)	<40	≥40	--	--
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	--
Interval from index pregnancy (months)	<4	4-6	7-12	>12
Pretreatment hCG (IU/L)	$<10^3$	10^3 to $<10^4$	10^4 to 10^5	$\geq 10^5$
Largest tumor size, including uterus (cm)	<3	3-5	>5	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	0	1-4	5-8	>8
Previous failed chemotherapy	--	--	Single drug	Two or more drugs
Total score	--	--	--	--

- The total score for a patient is obtained by adding the individual scores for each prognostic factor.
- FIGO Prognostic Score
  - Low risk: <7
  - High risk: ≥7

[a]Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN Guidelines Version 2.2021
Gestational Trophoblastic Neoplasia

Discussion

This discussion corresponds to the NCCN Guidelines for Gestational Trophoblastic Neoplasia. Last updated: March 31, 2021.

Table of Contents

Overview

Gestational trophoblastic disease (GTD) refers to a group of benign and malignant tumors that develop in the uterus from placental tissue. Pathogenesis of GTD is unique in that maternal tumors arise from gestational tissue that can have locally invasive or metastatic potential. Historical data on incidence of GTD varies widely by region, with higher incidence reported in Asia compared with Europe and North America. These differences are thought to be due at least in part to varying diagnostic criteria, reporting practices, quality of epidemiologic data, and diet and nutrition. In the United States, the reported incidence of GTD is approximately one out of every 1000 pregnancies.[1-3]

The most common form of GTD is hydatidiform mole (HM), also known as molar pregnancy. HMs are considered a benign, premalignant disease. Malignant forms of GTD are collectively referred to as gestational trophoblastic neoplasia (GTN), and include invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). HM encompasses about 80% of all GTD, invasive moles account for 15%, and choriocarcinoma and other rarer types of GTN comprise the remaining 5%.[4] Cure rates are approaching 100%, and treatment typically allows for fertility preservation.[4,5]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Gestational Trophoblastic Neoplasia, an electronic search of the PubMed database was performed to obtain key literature in GTD published since the previous Guidelines update, using the following search terms: gestational trophoblastic OR choriocarcinoma OR intermediate trophoblastic tumor. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Types of Gestational Trophoblastic Disease

HM occurs as a result of abnormal fertilization and is characterized as complete or partial based on differences in morphology, karyotype, and malignant potential. The majority of complete moles (80%) occur as a result of abnormal fertilization of an ovum lacking nuclear DNA, and have two identical paternal chromosome complements derived from duplication of the haploid genome of a single sperm. The remaining 20% occur as a result of dispermy (fertilization by two sperm). Partial moles occur when an ovum retains its nucleus and abnormal fertilization occurs in one of two ways: 1) fertilization by a single sperm with subsequent paternal chromosome duplication; or 2) via dispermy. Partial HMs can contain fetal tissue, but complete moles do not.

Post-molar GTN, which includes invasive mole and choriocarcinoma, develops in about 15% to 20% of complete moles, but in only 1% to 5% of partial moles.[2,3,6,7] The reported incidence of GTN after molar pregnancy is 18% to 29%.[2,3,8,9] This rate appears to be stable despite the progressively

earlier diagnosis of complete HM.[9] Invasive moles arise from extension of HM into the myometrium via tissue or venous channels. Approximately 15% of invasive moles metastasize to the lung or vagina. Persistent elevated human chorionic gonadotropin (hCG) after evacuation of a molar pregnancy most often leads to the diagnosis of invasive mole.[2] Choriocarcinoma develops from villous trophoblast. Features of these malignant epithelial tumors include abnormal trophoblastic hyperplasia and anaplasia, hCG production, absence of chorionic villi, hemorrhage, and necrosis.[2,3] Choriocarcinoma has been reported to occur with different types of pregnancy events, including HM (50%), term or preterm gestation (25%), and tubal pregnancy or abortion (25%). Approximately 2% to 3% of HMs progress to choriocarcinoma.

Intermediate trophoblastic tumors (ITT), including PSTT and ETT, are rare subtypes of GTN with an incidence of about 1 in 100,000 pregnancies, representing approximately 1% of all GTN cases.[10] Most PSTTs follow nonmolar gestations and present months to years after the antecedent pregnancy. Less often, PSTT develops after evacuation of HM.[4] PSTT arises from interstitial trophoblast at the placental implantation site and consists predominately of mononuclear intermediate trophoblast without chorionic villi, infiltrating in sheets or cords between myometrial fibers. It is associated with less vascular invasion, necrosis, and hemorrhage than choriocarcinoma.

ETT is a rare variant of PSTT that simulates carcinoma. Based on morphologic and histochemical features, it appears to develop from neoplastic transformation of chorionic-type intermediate trophoblast. ETT typically presents years after term delivery.

Hydatidiform Mole

Presentation and Workup

Patients with HM commonly present with vaginal bleeding, typically around 6 to 16 weeks of gestation. Due to widespread ultrasound screening during early pregnancy and accurate hCG testing, most cases of HM are detected prior to the onset of additional signs such as uterine enlargement beyond that expected for gestation date, preeclampsia, hyperemesis, anemia, and theca lutein ovarian cysts.[2-4] Partial HMs tend to grow more slowly and may present later in the first or early second trimester, often with symptoms of incomplete or missed abortion and diagnosis made upon histologic examination of the curettage specimen.[2,3]

Initial determination of suspected HM is often made based on ultrasound findings in combination with clinical symptoms and hCG levels. Due to hyperplastic trophoblastic cells in complete HM, many patients will have marked elevations in hCG, at times greater than 100,000 IU/L. However, such elevations in hCG are observed in less than 10% of patients with partial HM. Characteristic ultrasound findings of complete HM include enlarged uterus with a heterogenous mass (ie, snowstorm appearance). Hydropic/swollen chorionic villi lead to the appearance of small cystic spaces, creating a vesicular pattern. However, these characteristics may not be readily observed with the diagnosis of HM early in the first trimester. As molar pregnancy advances, these cystic spaces become larger and more numerous. Features that may be noted on ultrasound imaging of partial HM include focal cystic spaces within the placenta, gestational sac that is empty or elongated along the transverse axis, and/or fetal anomalies or fetal demise.[2-4,8,11] The NCCN Panel recommends workup of patients with HM to include history and physical; pelvic ultrasound; quantitative hCG assay; complete blood count (CBC) with platelet count; liver, renal, and thyroid function tests; as well as blood type and screen [administer Rho(D) immune globulin if Rh-negative]. Recommended imaging also includes chest x-ray. If chest x-ray is positive

for metastases, perform chest/abdomen/pelvis CT and brain MRI; manage as GTN after initial uterine evacuation.

Treatment

Initial treatment of HM in women who wish to preserve fertility is suction dilation and curettage (D&C), preferably performed under ultrasound guidance to reduce the risk of uterine perforation.[8,12]To reduce the risk of heavy bleeding, uterotonic agents (eg, methylergonovine and/or prostaglandins) should be administered during the procedure and continued for several hours postoperatively.[2,13] For women who do not wish to preserve fertility, hysterectomy with salpingectomy can be considered as an alternative.[14] Histopathologic review and DNA genotyping help confirm the diagnosis of benign, noninvasive HM,[15] and may allow patients at low risk for developing post-molar GTN (ie, those with partial HM) to avoid unnecessary treatment with prophylactic chemotherapy.[16]

Prophylactic chemotherapy at the time of uterine evacuation is controversial and may reduce the incidence of post-molar GTN by 3% to 8%. A Cochrane database review (three randomized controlled trials [RCTs], n = 613) did not conclude sufficient evidence for standard administration of prophylactic chemotherapy to prevent post-molar GTN; however, evidence was suggestive that prophylactic chemotherapy may reduce the risk of progression to GTN among women with complete HM at high risk for malignant transformation.[17] The NCCN Guidelines state that prophylactic methotrexate or dactinomycin can be considered for patients deemed at high risk for post-molar GTN (eg, age >40 years, hCG levels in excess of 100,000 mIU/mL, excessive uterine enlargement, and/or theca lutein cysts larger than 6 cm).[2,8,17,18]

Follow-up

Follow-up with hCG monitoring is essential following initial treatment of HM to ensure that hCG levels return to normal. The hCG molecules associated with GTD are more heterogenous and degraded than those associated with normal pregnancy.[2,19] Therefore, monitoring should be performed with a quantitative assay capable of detecting all forms of hCG, including beta-hCG, core hCG, nicked-free beta, beta core, and hyperglycosylated forms.[4,20,21] Post-molar GTN develops in about 15% to 20% of complete moles, but in only 0.1% to 5% of partial moles. Therefore, careful monitoring can facilitate early detection of persistent GTN. Risk of recurrence is low (<2%) following a single molar pregnancy, but increases significantly for women who experience one or more recurrences.[2,3,6,12,13,22]

Once normalized, recurrent elevation of hCG has been reported in less than 1% of patients.[22,23] The occurrence of GTN following hCG normalization is rare after the recommended 6 months of post-normalization hCG monitoring.[24] A recent study showed that patients with complete HM who normalized beyond 56 days post uterine evacuation had a 3.8-fold higher risk of developing post-molar GTN.[22]

The NCCN Panel recommends hCG assay monitoring every one to two weeks until levels have normalized, defined in the guidelines as three consecutive normal assays. Patients should also use contraception; oral contraceptive pills are preferred because they suppress endogenous luteinizing hormone (LH)/follicle-stimulating hormone (FSH), which may interfere with hCG measurement at low levels. Following initial normalization, hCG should be measured every 3 months for 6 months to ensure levels remain normal. If hCG levels remain persistently elevated (ie, plateau or rise), treat per the post-molar GTN algorithm.

Post-Molar GTN

Post-molar GTN is typically diagnosed by hCG surveillance. The NCCN Guidelines use the FIGO staging criteria for post-molar GTN as meeting one of more of the following criteria after treatment for HM, as indicated by hCG monitoring:[25]

- hCG levels plateau for 4 consecutive values over 3 weeks
- hCG levels rise ≥10% for 3 values over 2 weeks
- hCG persistence ≥6 months after molar evacuation

Assessment and staging of post-molar GTN should include history and physical examination (including pelvic exam), FIGO stage and prognostic score, Doppler pelvic ultrasound, and chest x-ray to assess for metastatic disease. Doppler pelvic ultrasound is used to confirm the absence of pregnancy, measure uterine size, and to delineate the volume and vasculature of the tumor. If chest x-ray reveals no evidence of metastatic disease, no further imaging is recommended prior to treatment. If the chest x-ray suggests metastases, CT scan of the abdomen/pelvis and MRI of the brain are indicated.

Repeat D&C, hysterectomy with salpingectomy, or single-agent systemic therapy can be considered for persistent post-molar GTN with no evidence of extrauterine disease.[26-28] An observational study conducted over a period of 10 years examined 544 women who underwent second uterine evacuation for persistent GTD.[28] Following repeat curettage, 68% had no further evidence of disease or chemotherapy requirements. However, chemotherapy requirement was more likely for patients with a histologic confirmation of persistent trophoblastic disease and for urinary hCG levels in excess of 1500 IU/L at time of second evacuation.[28] Several groups have discussed the optimal characteristics of candidates for repeat uterine evacuation.[28-32] Repeat surgical treatment or single-agent systemic therapy should be followed by hCG monitoring every 2 weeks until the patient has 3 consecutive normal assays, followed by monthly hCG monitoring for an additional 6 months. For persistent hCG elevation (ie, plateau or rise), follow GTN chemotherapy recommendations, which are stratified by patient response to initial therapy and the magnitude of hCG elevation.

For presence of metastatic disease, histopathologic diagnosis of choriocarcinoma, or extrauterine disease, follow recommendations for staging and treatment in the algorithms for GTN, which are stratified by risk group/prognostic score.

Gestational Trophoblastic Neoplasia

Presentation and Workup

The presentation of GTN can vary depending upon the antecedent pregnancy event and disease type and extent. Post-molar GTN, including invasive mole or choriocarcinoma, can be associated with irregular bleeding after initial treatment for molar pregnancy, an enlarged and irregular uterus, and bilateral ovarian enlargement. However, these signs may be absent in patients with choriocarcinoma associated with normal, non-molar pregnancies. Trophoblastic tumors have fragile vessels and as a result, metastatic lesions are often hemorrhagic. In addition to bleeding, metastatic lesions may be associated with neurologic or pulmonary symptoms. ETT and PSTT typically present with irregular uterine bleeding arising after some time has passed from a previous pregnancy.[2,3,33]

Workup for GTN includes history and physical examination and metastatic imaging workup, to include chest/abdominal/pelvic CT scan with contrast (or MRI if contrast is contraindicated) as well as brain MRI (preferred) or CT with contrast if pulmonary metastasis. Pelvic ultrasound or MRI should also be performed. Visible lesions in the lower genital tract should not be biopsied due to hemorrhage risk. Additionally, the NCCN Panel recommends repeat CBC differential with platelets; liver, renal, and thyroid

function testing; and hCG assay. If hCG is elevated with no evidence of disease on imaging, consider the possibility of LH crossover or phantom hCG.[34] Elevated hCG with normal hyperglycosylated hCG may indicate quiescent GTN not requiring immediate/further treatment.[35]Based on these findings, GTN should be staged and scored according to the current FIGO staging and prognostic scoring system.[25,36] GTN staging is based on tumor location and extent: stage I disease is uterine-confined, stage II involves direct extension or metastasis to other genital structures, stage III disease is determined by lung metastasis, and stage IV disease includes non-pulmonary distant metastasis. The current FIGO prognostic scoring system was adapted from the WHO classification, which incorporated prognostic factors from Bagshawe's scoring system.[37,38] FIGO prognostic scoring is based on individual risk factors that have been shown to be predictive of GTN that is resistant to single-agent chemotherapy, such as age, antecedent pregnancy, interval from index pregnancy, pretreatment hCG, largest tumor size (including the uterus), site and number of metastases, and previous chemotherapy regimens that were unsuccessful. The sum of individual scores denotes the FIGO prognostic score of low-risk GTN (<7) or high-risk GTN (≥7).[25,36,39] This prognostic scoring system is not valid for the ITTs ETT and PSTT.[10]

Histopathologic assessment is also recommended by the Panel as part of initial workup. The immunohistochemical (IHC) markers melanoma cell adhesion molecule (Mel-CAM/CD146), human placental lactogen (hPL), beta-human chorionic gonadotropin (β-hCG), p63, cyclin E, and Ki-67 are all differentially expressed between PSTT, ETT, and choriocarcinoma.[15,40,41] Given that recommended treatment regimens for each of these GTN subtypes differ significantly, accurate diagnosis is essential for avoiding unnecessary treatment and optimizing patient outcomes.

Low-Risk GTN

First-Line Therapy

As noted above, low-risk GTN is defined as a FIGO prognostic score of less than 7. Standard first-line treatment for low-risk GTN is single-agent chemotherapy using methotrexate or dactinomycin. Numerous studies have evaluated these agents, but differences in inclusion criteria and dosage regimens have made it challenging to determine a superior regimen. While some consider methotrexate to have a more favorable adverse effect profile, dactinomycin may achieve similar or better efficacy with a less-frequent infusion schedule.[4,20,39,42,43] A 2016 Cochrane Database review of RCTs in low-risk GTN showed with moderate-certainty evidence that first-line methotrexate may be more likely to fail than dactinomycin (risk ratio [RR], 3.55; 95% confidence interval [CI], 1.81–6.95; 6 trials, 577 participants; I(2) = 61%).[43] Similarly, the authors concluded that dactinomycin is more likely to lead to a primary cure than methotrexate (RR, 0.65; 95% CI, 0.57–0.75; six trials, 577 participants; I(2) = 26%).[43] However, 55% of the data came from trials of weekly IM methotrexate, which seems to be less effective than the 5- or 8-day methotrexate regimens. A closed phase III RCT (NCT01535053) comparing pulse dactinomycin to multiday methotrexate regimens noted primary remission rates of 75% for pulse dactinomycin versus 88.5% for the multiday methotrexate regimens (5-day > 8-day). Overall quality-of-life scores were similar. Alopecia was more common with dactinomycin, mucositis was more common with the methotrexate regimens, and no patient required multiagent chemotherapy or salvage surgery to reach remission.[44]

Currently supported regimens of dactinomycin include a 5-day regimen (10–12 mcg/kg or flat 0.5 mg dose IV, repeated every 2 weeks) or a dactinomycin pulse regimen (1.25 mg/m^2, IV, repeated every 2 weeks).[20] Primary remission rates for initial treatment with 5-day dactinomycin range from 77% to 94%, and for pulse dactinomycin, from 69% to 90%.[39] For

methotrexate, currently supported regimens include 5-day methotrexate (0.4 mg/kg IV or IM daily x 5 days, repeated every 2 weeks) or an 8-day regimen of methotrexate alternating with leucovorin rescue (1.0–1.5 mg/kg IM, every other day x 4 days, alternating with leucovorin, 15 mg PO, repeated every 2 weeks).[20] Primary remission rates for multiday methotrexate regimens range from 87% to 93% for the 5-day protocol, and from 74% to 93% for 8-day methotrexate with leucovorin rescue.[39]

Methotrexate regimens that are no longer recommended due to lesser efficacy include weekly IM methotrexate (30–50 mg/m^2) and pulse-dose IV infusion methotrexate.[39,45,46] Although weekly IM methotrexate was successful in 70% of patients with a prognostic score of 0–1, the success rate fell to 40% and 12% with a prognostic score of 2–4 and 5–6, respectively.[4,45] In a large case series (n = 618), 8-day methotrexate was comparatively more successful when analyzed by prognostic score subgrouping.[16]

The Guidelines note that a multiday methotrexate regimen is typically used as first-line therapy in low-risk GTN due to its generally favorable toxicity profile. Dactinomycin is often used as a secondary therapy for patients with methotrexate toxicity or effusions contradicting the use of methotrexate. Alternative single-agent options for treatment of low-risk GTN that are primarily used in Asia include etoposide and fluorouracil.[39,47,48]

Monitoring/Response Assessment During First-Line Therapy

The NCCN Panel recommends monitoring chemotherapy response by hCG assay every 2 weeks, at the start of each treatment cycle.[42] Upon hCG normalization, continuation of therapy is recommended for two to three additional treatment cycles past normalization to minimize the risk of recurrence.[3,5,20] Surveillance should include monthly hCG for 1 year, along with contraception (oral contraception preferred). Chemotherapy resistance is indicated by a plateau in hCG (<10% change) over three consecutive cycles or a rise in hCG (>10% change) over two consecutive cycles.[4,42] Second-line chemotherapy is then indicated.

Second-Line Single-Agent Therapy

Currently, there are no RCT data on second-line therapy for low-risk GTN, but general evidence and consensus supports a change to the alternative single-agent chemotherapy for patients who have had a good initial response to chemotherapy but experience hCG plateau, or for patients who experience toxicity that limits the dose or frequency of treatment.[4,20,49] Adjuvant hysterectomy with salpingectomy can be considered for patients with localized disease in the uterus for whom fertility preservation is not desired. The ovaries are left in situ, even in the presence of theca lutein cysts.

Second-line dactinomycin is considered to have an acceptable response rate in patients with low levels of hCG, but multiagent chemotherapy may be favored in the second-line setting for patients whose hCG exceeds a given threshold.[16,50,51] The hCG threshold for considering dactinomycin versus multiagent regimens has been debated and revised over time.[3,16,20,51,52]

Dactinomycin has been associated with a complete response rate of approximately 75% in large case series of patients with methotrexate-resistant GTN.[53,54] A retrospective review of 358 patients with low-risk GTN identified 68 patients who were determined to have resistant disease after a 5-day methotrexate regimen (n = 68). The complete response rate to secondary dactinomycin was 75%, and all patients who required third-line multiagent chemotherapy with or without surgery achieved permanent remission. Clinicopathologic diagnosis of choriocarcinoma (vs. post-molar GTN) was significantly associated with resistance to secondary dactinomycin.[53] In a recent retrospective review of 877 patients with GTN initially treated with 8-day methotrexate, 103 patients required second-line therapy and were placed on a 5-day dactinomycin protocol.[54] Complete

response to second-line dactinomycin was observed among 75.7% (n = 78). Among the 25 patients who required third-line treatment for resistant disease or relapse, overall survival was 100%.[54]

Second-Line Multiagent Therapy

For patients with poor response to single-agent chemotherapy or those who initially responded to initial therapy but experienced a subsequent rapid rise in hCG levels, repeat disease workup for metastasis and transition to combination chemotherapy.[3,5] The most commonly used regimen in this setting is EMA/CO (etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine).[16,49,55] The use of EMA/CO in this setting is based upon its efficacy in managing high-risk GTN.[56] Cure rates with EMA/CO approach 100% even in the presence of relapsed/resistant low-risk GTN.[3,5,55] As with single-agent second-line therapy, hysterectomy with salpingectomy may also be considered.

Monitoring/Response Assessment During Second-Line Therapy

For both single-agent and multiagent second-line therapy, hCG levels should be monitored every 2 weeks, but a more rapid response assessment is warranted if hCG levels plateau or rise. The Panel recommends additional treatment if patients experience an hCG plateau over two consecutive treatment cycles or an hCG rise over 1 cycle. For persistent disease after single-agent therapy with or without hysterectomy/salpingectomy, repeat workup to assess for metastasis and transition to EMA/CO combination therapy. For persistent or recurrent disease after EMA/CO combination therapy with or without hysterectomy/salpingectomy, treat per the high-risk GTN algorithm with etoposide/platinum-based regimens and surgical resection as feasible.

High-Risk GTN

High-risk GTN is defined as a prognostic score greater than or equal to 7 or FIGO stage IV disease.[25,36] High-risk disease is relatively rare among patients with post-molar GTN, estimated at only 6% (39/618) in a large case series.[16] High-risk GTN should be treated with multiagent chemotherapy. Adjuvant surgery or radiation therapy may be included. With a multimodal approach, cure rates have reached approximately 90%, including almost all patients with only lung/vaginal metastases and 70% for patients with stage IV disease.[5] Factors associated with poorer outcomes include liver and brain metastases, particularly if co-occurring. However, the prognosis for these patients has improved over time.[57-59]

Primary Chemotherapy

EMA/CO, in which EMA and CO are given on alternate weeks, is the most commonly used initial regimen for high-risk disease. Based on existing evidence, this regimen is thought to provide the best combination of efficacy with acceptable toxicity for treating patients with high-risk GTN. Multiple groups have confirmed the efficacy of EMA/CO, reporting complete response rates of 62% to 78% and long-term survival rates of 85% to 94%.[55,56,60-67]

Reports of other regimens that have been used in first-line treatment of high-risk GTN include EMA/EP (etoposide, methotrexate, dactinomycin alternating with etoposide and cisplatin)[68,69] and EP/EMA (etoposide and cisplatin alternating with etoposide, methotrexate, and dactinomycin).[70]

Due to the lack of RCTs in this setting, systematic reviews have been unable to draw conclusions regarding a superior combination regimen for primary treatment of high-risk GTN.[49,71] EMA/EP (or EP/EMA) is highly active and considered by some to be superior to EMA/CO for ultra-high-risk disease; however, its use as standard initial therapy is limited by

increased toxicity and inability to provide adequate salvage chemotherapy if required for persistent/recurrent disease.[4,70]

Induction Chemotherapy for Extensive Metastatic Disease

Patients with widespread metastatic GTN, as evidenced by prognostic score greater than 12, have a poorer prognosis.[72,73] Initiation of standard combination chemotherapy in these patients can lead to tumor collapse with hemorrhage, metabolic acidosis, septicemia, and/or multiple organ failure, resulting in the potential for early death (ie, within 4 weeks).[20,55,73] Efforts to improve outcomes for this ultra-high-risk population have included induction chemotherapy with etoposide and cisplatin prior to initiating EMA/CO.[55,73] In a case series of 140 patients with high-risk GTN, 33 patients who were determined to have large disease burden (ie, ultra-high-risk GTN) received low-dose induction chemotherapy with etoposide/cisplatin prior to EMA/CO therapy (etoposide 100 mg/m² IV and cisplatin 20 mg/m² IV on days 1 and 2, every 7 days for 1–3 courses). Overall survival and early death rate were 94.3% and 0.7%, respectively, for the high-risk GTN cohort, representing a considerable improvement over outcomes reported for an earlier cohort who did not receive induction chemotherapy.[55] Thus, the Panel recommends considering induction low-dose EP (etoposide 100 mg/m^2/day IV and cisplatin 20 mg/m^2/day IV) for 1–3 cycles prior to EMA/CO treatment.

Management of CNS Metastases

Additional treatment considerations are recommended for patients with central nervous system (CNS) metastases, who may require emergency intervention to manage intracranial bleeding or elevated intracranial pressure.[4,74] Rates of CNS metastases are low with post-molar GTN, but approximately 20% of patients with choriocarcinoma have CNS involvement.[74] [4,58,75-78] EMA/CO should be modified to include high-dose methotrexate (1000 mg/m^2) and additional 15-mg oral doses of leucovorin every 6 hours for 12 doses, starting 32 hours after the start of the methotrexate infusion.[74]

The Panel recommends that whole-brain radiation or stereotactic brain radiotherapy (SBRT) with or without intrathecal methotrexate also be considered for patients with brain metastases.[4,20,58,75-78] Reported cure rates with brain metastases range from 50% to 80%, depending on the patient's symptoms as well as number, size, and location of brain lesions.[58,74,75,77,79-82]

Monitoring/Response Assessment During First-Line Therapy

Monitoring and response assessment during first-line treatment of high-risk GTN is the same as for low-risk GTN. Patients who respond to primary chemotherapy but subsequently experience a low-level hCG plateau, those who have an incomplete response to primary treatment, and those who experience relapse from remission require further treatment (ie, salvage chemotherapy and/or adjuvant surgery).

Salvage Chemotherapy

Approximately 30% to 40% of high-risk patients will have an incomplete response to first-line therapy or experience relapse from remission.[83,84] Most of these patients have multiple metastases to sites other than the lung and vagina and many will have received inadequate initial therapy.[85,86] Salvage chemotherapy with drug regimens employing etoposide and a platinum agent, often combined with surgical resection of persistent tumor, will result in cure of about 80% to 90% of patients with high-risk disease.[87]

EMA/EP or EP/EMA regimens are considered the most appropriate therapy for patients who have responded to EMA/CO but have plateauing low hCG levels or have developed re-elevation of hCG after a complete response to EMA/CO.[88,89] The rate of complete response/remission with

EMA/EP for disease resistant to EMA/CO has been reported between 75% and 85%.[66,88-91]

Additional drug combinations containing etoposide and a platinum agent have been effective in patients who have developed disease resistant to methotrexate-containing regimens. The Panel prefers the use of the following four regimens for methotrexate-resistant GTN: TP/TE (paclitaxel and cisplatin alternating weekly with paclitaxel and etoposide), BEP (bleomycin, etoposide, and cisplatin), VIP (etoposide, ifosfamide, and cisplatin), and ICE (ifosfamide, carboplatin, and etoposide).[49,87,90,92,93] Additionally, TIP (paclitaxel, ifosfamide, and cisplatin) has been used as a salvage chemotherapy regimen in germ cell tumors, including those with choriocarcinoma components.[94-97]

Etoposide-platinum–containing regimens require the use of granulocyte colony-stimulating factor (G-CSF) support to prevent neutropenic complications and treatment delays.[87,92,98] The overall success of salvage therapy in this group of patients is about 80%. Factors associated with worse survival outcomes include high hCG at the start of salvage therapy, greater number of metastatic sites, metastases to sites other than the lung and vagina (stage IV), and FIGO score greater than 12.

Additional Agents/Regimens with Potential Activity in Treatment-Resistant GTN

Several additional treatment regimens have been shown to have some activity when treating resistant GTN, including high-dose chemotherapy (HDC) with peripheral stem cell transplant, immunotherapy, and other chemotherapy regimens. For a subset of patients with resistant disease despite multidrug chemotherapy, HDC with autologous stem cell support has been reported to produce sustained complete responses.[99-103] A retrospective study of 32 patients with refractory choriocarcinoma or poor-prognosis PSTT/ETT who underwent HDC with peripheral blood stem cell support reported a sustained complete response in 7 patients, with 13 of 32 patients remaining disease free at the time of analysis following HDC with or without additional therapy.[101]

Pembrolizumab is a monoclonal antibody that inhibits programmed cell death protein 1 (PD-1), which functions as a checkpoint protein for regulation of various immune cells, including T cells with potential antitumor activity.[104-106] Programmed death ligand 1 (PD-L1) is strongly expressed by GTN.[107,108] Outcomes were recently reported for four patients with drug-resistant GTN who received pembrolizumab, including two cases of metastatic choriocarcinoma and two cases of metastatic PSTT or mixed PSTT/ETT.[109] All patients had tumors with high levels of PD-L1 expression. Durable response to pembrolizumab was observed in three of the four cases. The patient whose disease did not respond to pembrolizumab had strong PD-L1 tumor expression but an absence of tumor-infiltrating lymphocytes.[109] Based on these data, the NCCN Panel also added nivolumab, another PD-1 inhibitor, to the list of regimens that may potentially be effective against treatment-resistant GTN.

Avelumab, a PD-L1 inhibitor, may also be effective against treatment-resistant GTN. Results from a phase II study enrolling 15 patients with GTN who experienced disease progression after single-agent chemotherapy suggested that avelumab was effective in normalizing hCG levels in approximately half of the patients.[110]

Gemcitabine, capecitabine, and fluorouracil may also have potential for treating GTN in this setting. Limited data have suggested activity of gemcitabine, administered with or without a platinum agent.[111] Additional support for the potential activity of these regimens in GTN can be found in the data for treating germ cell tumors. Successful use of capecitabine as single-agent salvage chemotherapy has been reported.[112,113] Groups in Asia have also reported on fluorouracil, primarily in combination with dactinomycin.[114]

Adjuvant Surgery

Adjuvant surgical procedures, especially hysterectomy with salpingectomy and pulmonary resection, may be required to manage high-risk, chemotherapy-resistant disease. Select patients with isolated disease, especially in the uterus and lungs, may be candidates for surgical resection.[115-117] PET/CT imaging may be useful for detecting isolated metastatic sites that are amenable to targeted surgery.[118] Additionally, interventional procedures to prevent or control hemorrhage are important components in the management of high-risk GTN.[4] Selective arterial embolization can be used to manage bleeding from the uterus/vagina or other tumor sites.[119-121] In one case series, nearly 50% of patients with high-risk disease underwent some form of surgical procedure during the course of treatment in order to effect cure.[122]

Intermediate Trophoblastic Tumors

Whereas molar pregnancies and choriocarcinoma are derived from villous trophoblast (ie, cytotrophoblast and syncytiotrophoblast), ITTs (including PSTT and ETT) develop from extravillous trophoblast (ie, intermediate trophoblast). ITTs comprise approximately 1% of GTN cases, and as such, their biologic behavior and treatment are less well established. These tumors typically develop months to years following normal pregnancies, but can occur after any pregnancy event. A recent series of 62 cases of ITT suggested that interval between antecedent pregnancy and disease onset may be longer for ETT than PSTT.[123]

PSTT and ETT are generally slow-growing tumors that can metastasize months or years after initial primary tumor development and often present with abnormal uterine bleeding or amenorrhea. The vast majority of ITTs secrete hCG, but at significantly lower levels compared with other types of GTN. As such, hCG is a less reliable tumor marker for these subtypes of GTN. At diagnosis, metastases are noted in 30% to 50% of cases, most commonly to the lungs. Unlike other GTNs, these have a greater propensity for lymphatic spread. Data are currently being collected in a global database of PSTTs and ETTs through the efforts of the International Society for the Study of Trophoblastic Disease (ISSTD).[10,124-129]

ITTs can be differentiated from other types of GTN via their histopathologic characteristics.[10] In PSTT, IHC staining reveals the diffuse presence of Mel-CAM (CD146) and human placental lactogen (hPL), whereas hCG staining is only focal. Cytogenetic studies have revealed that PSTTs are more often diploid than aneuploid.[130] Serum hPL measurements are not clinically useful in monitoring disease course or guiding clinical management.[127,128,131,132] ETT is distinguished from PSTT by its smaller, fairly monomorphic cells and a nested, nodular, well-circumscribed growth pattern. IHC reveals strong expression of p63, but weak expression of Mel-CAM and hPL.[133] Greater than 50% of cells in ETT also express cyclin E. It frequently involves the lower uterine segment and endocervix, and because of its epithelioid histologic appearance and expression of p63, ETT can be confused with squamous cell carcinoma.[10,133,134]

Due to the rarity of these tumors, generally small cohort sizes preclude rigorous statistical analysis of risk factors in ITT. The FIGO prognostic scoring system for GTN does not correlate well with outcomes in PSTT and ETT.[10] Based on findings from the largest existing database, PSTT and ETT accounted for 125 of 54,743 cases of GTD (0.23%), with post-treatment 5- and 10-year survival estimates of 80% and 75%, respectively. The most important prognostic factors include advanced disease stage and interval from last known pregnancy event of greater than or equal to 48 months.[125,128,129,135] Additional risk factors associated with less favorable outcomes are advancing age, deep myometrial invasion, tumor necrosis, large tumor size, and mitotic index.[10,129,136]

Treatment Approach

ITTs are relatively chemoresistant and thus follow a somewhat different treatment paradigm than invasive mole and choriocarcinoma, with surgical intervention playing a more critical role. Treatment of PSTT and ETT is mainly determined by presence or absence of metastatic disease, with some consideration given to high-risk factors. The survival rate is approximately 100% for nonmetastatic disease and 50% to 60% for metastatic disease. Increased use of platinum-based CT over time has led to improved overall survival for the subset of patients with ITT who have an overall poor prognosis (ie, interval ≥48 months from last known pregnancy event).[125,127-129]

Hysterectomy with salpingectomy, with or without pelvic lymph node biopsy, is the recommended treatment for nonmetastatic (stage I) disease. Hysterectomy with salpingectomy and chemotherapy are recommended for metastatic disease. Metastasectomy (if feasible) should also be performed for isolated distant disease, especially in the lungs. EMA/EP and EP/EMA are preferred chemotherapy regimens for patients with metastatic disease; other regimens that are effective against treatment-resistant GTN may also have some efficacy in metastatic ITTs. All of these regimens may also be considered for patients with nonmetastatic disease who have one or more adverse prognostic factors (ie, interval from index pregnancy ≥2 years, deep invasion, necrosis, mitotic count >5/10 HPFs).[137]

Monitoring and Surveillance

Post-treatment hCG levels should be monitored as indicated for GTN, although hCG is a less reliable tumor marker for ITTs versus post-molar GTN. The Panel recommends surveillance with PET/CT at the completion of chemotherapy and then every 6 to 12 months for 2 to 3 years.

Post-Treatment Recurrence or Progression of ITTs

Systemic therapy regimens recommended for primary treatment of metastatic disease may have some efficacy in patients experiencing recurrence or progression of nonmetastatic or metastatic ITTs. Alternatively, patients with metastatic ITTs may forego additional chemotherapy and instead receive best supportive care (see *NCCN Guidelines for Palliative Care*).

Gynecologic Survivorship

Treatment for gynecologic cancer typically involves surgery, chemotherapy, hormone therapy, radiation therapy, and/or immunotherapy, which may cause acute, short-term, and long-term toxicities. Surgical approaches may be extensive and cause adhesions to form, which in turn may cause pain and contribute to the development of small bowel obstruction, urinary or gastrointestinal complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a variety of urinary, bowel, and/or sexual effects), and lymphedema.[138,139] Chemotherapy agents vary, though commonly used regimens may pose a significant risk of neurotoxicity, cardiac toxicity, cognitive dysfunction, and the development of hematologic cancers.[140] Long-term estrogen deprivation may cause symptoms such as hot flashes, vaginal dryness, and bone loss. Radiation therapy may cause long-term complications (eg, fibrosis, stenosis, vulvovaginal atrophy)[141,142] and may predispose patients to subsequent cancers of the skin, subcutaneous tissue, and/or underlying organs that are proximal to the radiation field.[143] Use of immunotherapy agents in gynecologic cancers is emerging, and to date, long-term effects of these treatments are unknown.[144,145]

Following completion of treatment, all gynecologic cancer survivors should receive regular general medical care that focuses on managing chronic diseases (eg, depression, diabetes, hypertension), monitoring cardiovascular risk factors, receiving recommended vaccinations, and

encouraging adoption of a healthy lifestyle (eg, promoting exercise, smoking cessation).[146,147] In order to assess the late and long-term effects of gynecologic cancers, clinicians should comprehensively document the patient's history, including prior treatment history, and conduct a thorough physical examination followed by necessary imaging and/or laboratory testing.[147] As most treatments for gynecologic cancers will cause sexual dysfunction, early menopause, and infertility, special attention to the resultant medical and psychosocial implications is needed. All women, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness.[148] Post-radiation use of vaginal dilators and moisturizers is recommended.[141,149] Psychosocial effects may include psychological (eg, depression, anxiety, fear of recurrence, altered body image), financial (eg, return to work, insurance concerns), and interpersonal (eg, relationships, sexuality, intimacy).[147] Patients should be referred to appropriate specialty providers (eg, physical therapy, pelvic floor therapy, sexual therapy, psychotherapy) as needed, based on prior treatment history and assessed risk of developing late effects and/or existing concerns.

Communication and coordination with all clinicians involved in the care of survivors, including primary care clinicians, is critical.[147,150] Providing survivors with a summary of their treatment and recommendations for follow-up is also recommended. To this end, the Society of Gynecologic Oncology (SGO) has developed templates for gynecologic cancer-specific Survivorship Care Plans to aid survivors and their clinicians in summarizing cancer history, treatments received, possible side effects, and recommended follow-up.[151]

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