American College of Radiology
ACR Appropriateness Criteria®
Gestational Trophoblastic Disease

<u>**Variant 1:**</u>   **Suspected or initial diagnosis of gestational trophoblastic disease (GTD).**

Procedure	Appropriateness Category	Relative Radiation Level
US pelvis transvaginal	Usually Appropriate	O
US duplex Doppler pelvis	Usually Appropriate	O
US pelvis transabdominal	Usually Appropriate	O
Radiography chest	May Be Appropriate	☢
CT abdomen and pelvis with IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	☢☢☢☢
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	☢☢☢
CT chest with IV contrast	Usually Not Appropriate	☢☢☢
CT chest without and with IV contrast	Usually Not Appropriate	☢☢☢
CT chest without IV contrast	Usually Not Appropriate	☢☢☢
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢
MRI head without and with IV contrast	Usually Not Appropriate	O
MRI head without IV contrast	Usually Not Appropriate	O
MRI pelvis without and with IV contrast	Usually Not Appropriate	O
MRI pelvis without IV contrast	Usually Not Appropriate	O

Variant 2: **Staging and risk assessment: suspected or established diagnosis of gestational trophoblastic neoplasia (GTN).**

Procedure	Appropriateness Category	Relative Radiation Level
US pelvis transvaginal	Usually Appropriate	O
Radiography chest	Usually Appropriate	☢
US duplex Doppler pelvis	Usually Appropriate	O
US pelvis transabdominal	Usually Appropriate	O
CT abdomen and pelvis with IV contrast	Usually Appropriate	☢☢☢
CT chest with IV contrast	Usually Appropriate	☢☢☢
MRI pelvis without and with IV contrast	Usually Appropriate	O
MRI head without and with IV contrast	May Be Appropriate	O
CT chest without IV contrast	May Be Appropriate	☢☢☢
CT head with IV contrast	May Be Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	☢☢☢☢
MRI pelvis without IV contrast	May Be Appropriate (Disagreement)	O
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	☢☢☢☢
MRI head without IV contrast	Usually Not Appropriate	O
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	☢☢☢
CT chest without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢

Variant 3:   **Surveillance of GTN, including refractory, relapsed, or quiescent GTN.**

Procedure	Appropriateness Category	Relative Radiation Level
CT abdomen and pelvis with IV contrast	Usually Appropriate	☢☢☢
US duplex Doppler pelvis	Usually Appropriate	O
US pelvis transvaginal	Usually Appropriate	O
CT chest with IV contrast	Usually Appropriate	☢☢☢
MRI head without and with IV contrast	Usually Appropriate	O
US pelvis transabdominal	Usually Appropriate	O
MRI pelvis without and with IV contrast	May Be Appropriate	O
CT abdomen and pelvis without and with IV contrast	May Be Appropriate (Disagreement)	☢☢☢☢
CT chest without IV contrast	May Be Appropriate	☢☢☢
CT head with IV contrast	May Be Appropriate	☢☢☢
CT head without and with IV contrast	May Be Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	☢☢☢☢
MRI head without IV contrast	May Be Appropriate (Disagreement)	O
MRI pelvis without IV contrast	May Be Appropriate (Disagreement)	O
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
Radiography chest	Usually Not Appropriate	☢
CT chest without and with IV contrast	Usually Not Appropriate	☢☢☢

Variant 4:   Assessment of complications: GTD and GTN.

Procedure	Appropriateness Category	Relative Radiation Level
CT abdomen and pelvis with IV contrast	Usually Appropriate	☢☢☢
CT chest with IV contrast	Usually Appropriate	☢☢☢
US pelvis transvaginal	Usually Appropriate	O
CT head without IV contrast	May Be Appropriate	☢☢☢
MRI head without and with IV contrast	May Be Appropriate	O
US duplex Doppler pelvis	May Be Appropriate	O
CT abdomen and pelvis without and with IV contrast	May Be Appropriate (Disagreement)	☢☢☢☢
CT abdomen and pelvis without IV contrast	May Be Appropriate	☢☢☢
CT chest without and with IV contrast	May Be Appropriate (Disagreement)	☢☢☢
CT chest without IV contrast	May Be Appropriate	☢☢☢
CT head with IV contrast	May Be Appropriate	☢☢☢
CT head without and with IV contrast	May Be Appropriate	☢☢☢
MRI head without IV contrast	May Be Appropriate	O
MRI pelvis without and with IV contrast	May Be Appropriate	O
MRI pelvis without IV contrast	May Be Appropriate	O
Radiography chest	May Be Appropriate	☢
US pelvis transabdominal	May Be Appropriate	O
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☢☢☢☢

GESTATIONAL TROPHOBLASTIC DISEASE

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Summary of Literature Review

Introduction/Background

Gestational trophoblastic disease (GTD), or abnormal proliferation of placental trophoblastic tissue, is a rare complication of pregnancy. There is considerable variation in the worldwide distribution of GTD, with the highest frequencies reported in Asia and the Middle East and lower rates on the order of 1 per 1,000 pregnancies in Europe and North America [1,2]. Extremes of maternal age and personal history of GTD are known risk factors [1-3].

The term GTD encompasses a range of disorders: from benign hydatidiform mole to malignant forms collectively referred to as gestational trophoblastic neoplasia (GTN). Distinct morphologic and cytogenetic features distinguish 2 types of hydatidiform mole: complete and partial. Both can evolve into GTN, with reported frequency up to 20% after a complete molar pregnancy and less often after partial hydatidiform mole [4,5]. GTN may also follow genetically normal pregnancies or miscarriage. GTN includes invasive mole, choriocarcinoma, and 2 very rare tumor types: placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT) [6-8]. Although only the latter 3 diseases are truly neoplastic, invasive mole is included in GTN given its tendency to exhibit clinically malignant behavior with local uterine invasion and occasional metastases, predominantly to the lung, despite having a benign histology [8]. Among the 3 malignant subtypes of gestational trophoblastic neoplasms, choriocarcinoma is the most common. Moreover, as most invasive moles are largely nonmetastatic, and both PSTT and ETT are extremely rare, the term "metastatic GTN" is often used interchangeably with choriocarcinoma.

Because beta-human chorionic gonadotropin (β-hCG) is elevated to some extent by all forms of GTD, this biochemical marker is useful in facilitating early disease detection and diagnosis, monitoring treatment response, and in follow-up [4]. The availability of sensitive assays to detect serum β-hCG, coupled with early ultrasound (US) evaluation, has shifted the presentation and diagnosis of suspected GTD into the first trimester, often before symptoms have developed [9,10]. Vaginal bleeding is common among women with complete hydatidiform mole and often prompts an early US examination, whereas women with partial mole tend to come to clinical attention slightly later, frequently after miscarriage [9,10]. Thus, the diagnosis of partial mole is typically made in hindsight through histologic evaluation of curettage specimens rather than prospectively based on symptoms and US findings [11].

The clinical presentation of GTN varies with the antecedent gestational event, presence of metastases, and histology of the tumor [2,3]. Rising or plateaued serum β-hCG during follow-up after molar evacuation can be the sole indication of invasive mole or choriocarcinoma [4]. Because the majority of postmolar GTN is either invasive mole or, less often, choriocarcinoma, both of which are highly responsive to chemotherapy, treatment is frequently initiated without a histopathologic diagnosis other than antecedent pregnancy. Choriocarcinoma is the presumptive histology in women with metastatic GTN because of both its relative frequency and common occurrence of metastases compared with the other malignant forms of GTN, PSTT, or ETT [12]. Clinically, the

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majority of these women have had prior nonmolar pregnancies and come to clinical attention with signs and symptoms related to the location of their metastases, often to lung or vagina [2,13]. By contrast, women with PSTT and ETT may have a large local disease burden in the absence of distant metastases, and diagnosis may be delayed because of serum β-hCG levels that are disproportionately low for tumor volume [14,15]. As such, the diagnosis of PSTT or ETT is often retrospective and based on review of pathology, immunohistochemistry, and imaging findings [14,15].

On the whole, women with GTD have a favorable prognosis for cure with early adequate treatment, despite the presence of metastatic disease in some patients. Patients with benign but premalignant lesions are managed with uterine evacuation and enrolled in postoperative hCG surveillance [16]. Hysterectomy in patients not opting to preserve fertility does not eradicate risk of postmolar GTN [16-19]. If malignant GTN other than ETT or PSTT is suspected or has been established, further evaluation for potential metastatic lesions is initiated, clinical risk factors determined, and patients stratified into low- or high-risk groups based on the modified World Health Organization (WHO) prognostic scoring system as adapted by and combined with the international Federation of Gynecology and Obstetrics (FIGO) anatomic staging system [2,20]. This combines anatomic staging with assessment of prognostic factors: patient age, type of antecedent pregnancy, interval from gestational event to chemotherapy, hCG concentration, number and site of metastases, largest tumor mass, and previous chemotherapy. Points are assigned for each variable to determine risk of resistance to single-agent chemotherapy. Scores exceeding 6 predict high-risk disease refractory to monochemotherapy, with patients maintaining good prognosis if managed with intensive combination chemotherapy [10]. Patients with brain metastases are automatically assigned a high-risk disease status, regardless of score [12]. Adjuvant surgical and/or radiation therapy can be added selectively to decrease disease burden and remove resistant lesions [21-23]. ETT and PSTT, biologically distinct tumors that are relatively refractory to chemotherapy and grow more slowly with local lymphatic rather than hematogenous metastases, are staged anatomically and primarily treated surgically [24].

Special Imaging Considerations

A healthy twin live fetus may coexist alongside a partial or complete molar pregnancy. A rare phenomenon, this has been estimated to occur in 1 in 20,000 to 100,000 pregnancies [10]. The management of this entity is controversial as there is some concern that these patients may be more prone to developing GTN among other potential serious complications, such as pre-eclampsia, thyrotoxicosis, hemorrhage, trophoblastic embolism, and fetal demise [25,26]. Evidence from a series of 77 cases, however, suggests that approximately 40% of these patients may successfully deliver a healthy baby without increased incidence of malignant transformation [10,27]. Because this scenario is exceedingly rare, there is little high-quality evidence to support imaging guidelines.

Discussion of Procedures by Variant

Variant 1: Suspected or initial diagnosis of gestational trophoblastic disease (GTD).

GTD may present with vaginal bleeding or elevated serum β-hCG as the initial gestational event, in the postpartum state, as a histologic diagnosis after pregnancy loss, or, rarely, as a twin alongside a genetically normal pregnancy. The following recommendations pertain to any of these scenarios. Clinical or imaging evidence of metastatic disease implies that GTD has progressed to GTN, as discussed in Variants 2 through 4.

US Pelvis Transvaginal

Transvaginal US is the accepted standard in the evaluation of early pregnancy and suspected complications. Although <50% of hydatidiform moles were prospectively identified on US in studies published >10 years ago [21,22], a more recent study reported improved sensitivity using contemporary US equipment with 86% of complete moles and 41% of partial moles diagnosed prospectively [23]. Reported sensitivity of US detection is higher for complete mole, with its more pronounced hydropic changes of chorionic villi and absence of a gestational sac, than for partial mole [9,28]. Features suspicious for partial mole include an enlarged placenta or cystic changes within the decidual reaction in association with either an empty sac (>20 mm in diameter) or a delayed miscarriage (fetal pole with crown-rump length >6 mm but no cardiac activity) [22]. Differential diagnosis in partial molar pregnancy may include missed abortion [29] and retained products of conception. There is no substantial evidence to support a role for grayscale US features in risk stratification for future development of GTN [30,31]. Enlarged ovaries with multiple theca lutein cysts may be a helpful secondary finding in suspected GTD but are noted in <50% of patients [29,30].

US Pelvis Transabdominal

Transvaginal US has superior sensitivity and specificity in the diagnosis of uterine masses when compared with transabdominal US, although given the rarity of GTD, literature comparing both modalities is lacking [32].

US Duplex Doppler Pelvis

There is some support for a role for Doppler US in the initial diagnosis and postevacuation follow-up of patients with GTD. A lower uterine artery resistive index before molar evacuation is associated with the development of trophoblastic tumors, a potentially useful means to prospectively recognize patients who are at high risk for progression and warrant closer follow-up [33,34]. In a prospective analysis of 246 women with complete mole, Doppler pulsatility index showed potential as a predictor of subsequent development of GTN [35]. In a retrospective analysis of 189 patients with hydatidiform mole, US evidence of nodules and hypervascularization within the myometrium or endometrium 3 weeks following initial molar evacuation had a high specificity (95.5%) but low sensitivity (53.9%) for later development of GTN [33,34]. Doppler US can also confirm the absence of vascular flow within a mass, a useful technique in patients with GTD where clot or blood products may simulate solid tissue.

Radiography Chest

By definition, GTD is nonmetastatic at initial presentation when it arises in its benign form (hydatidiform mole). However, when GTD becomes or presents as GTN, the lungs are the initial and most common metastatic site [36]. Thoracic imaging is useful to evaluate the presence, number, and size of pulmonary metastases if other clinical features support a diagnosis of GTN (persistent or rising serum β-hCG, histologic diagnosis of choriocarcinoma, or clinical evidence of metastases), a task historically performed with chest radiographs per FIGO criteria [20]. The primary evidence for investigations to diagnose lung metastases with chest radiography in patients with benign disease (hydatidiform mole) at initial presentation is not strong, with disagreement between professional societies regarding its use. Recommendations of the American College of Obstetricians and Gynecologists include a pre-evacuation chest radiograph but not chest CT in this group of patients [19]. Published management guidelines for trophoblastic diseases by the European Society for Medical Oncology do not include any form of thoracic imaging in the initial evaluation of this same group of patients [37].

CT Chest

GTD is nonmetastatic by definition when in its benign form, but the lungs are the most common site of metastasis in GTN [36]. The primary evidence for investigations to diagnose lung metastases with chest CT in patients with benign disease (hydatidiform mole) at initial presentation is not strong with disagreement between professional societies regarding its use. Approximately 30% to 40% of patients assumed to have nonmetastatic disease by radiographs may have evidence of micrometastases on CT [20,38-40]. However, the clinical importance of these tiny lesions remains controversial with no definitive impact on long-term survival, leading some authors to conclude that chest CT does not have a role in initial assessment of GTN [38,41]. Recommendations of the American College of Obstetricians and Gynecologists include a pre-evacuation chest radiograph but not chest CT in this group of patients [19]. Published management guidelines for trophoblastic diseases by the European Society for Medical Oncology do not include any form of thoracic imaging in the initial evaluation of this same group of patients [37]. Thoracic imaging is useful to evaluate the presence, number, and size of pulmonary metastases if other clinical features support a diagnosis of the malignant form of GTD, GTN (persistent or rising serum β-hCG, histologic diagnosis of choriocarcinoma, or clinical evidence of metastases) [20]. The use of low-dose CT as a means to assess pulmonary metastases in patients with GTD was evaluated in a small study comparing standard- and low-dose CT examinations [42]. Although the number of nodules detected on the low-dose CT protocols was significantly less than the number identified on standard-dose CT examinations, the disease staging and risk scores of the patients were not impacted. Because the lungs are the most common site of GTN metastases, the use of intravenous (IV) contrast is not necessary to improve lesion detection.

CT Head

If physical examination and chest radiographs are normal in a patient with GTD, metastases to other sites are unlikely, and further imaging investigation is not indicated [37,43].

CT Abdomen and Pelvis

If physical examination and chest radiographs are normal in a patient with GTD, metastases to other sites are unlikely, and further imaging investigation is not indicated [37,43].

MRI Head

If physical examination and chest radiographs are normal in a patient with GTD, metastases to other sites are unlikely, and further imaging investigation is not indicated [37,43].

MRI Pelvis

To our knowledge, there is no evidence to support the routine use of MRI for initial evaluation of known or suspected GTD. Evaluation of MRI in patients with hydatidiform mole is limited to small series and cases reports [44-46]. Diffusion-weighted imaging has been evaluated as a potential predictor of subsequent GTN development in a small retrospective study and was not found to be useful [46].

FDG-PET/CT Skull Base to Mid-Thigh

To our knowledge, there is no evidence to support the routine use of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT for initial evaluation of known or suspected GTD. Preliminary limited data suggest a potential role for FDG-PET/CT in the identification of patients who are likely to develop GTN following initial treatment for molar pregnancy [47]. A significant difference in the standardized uptake value-max (SUV_{max}) of pre-evacuation intrauterine molar tissue in patients who achieved normalization of hCG versus those who progressed to GTN following dilatation and curettage was observed in this single retrospective study of 11 patients [47].

Variant 2: Staging and risk assessment: suspected or established diagnosis of gestational trophoblastic neoplasia (GTN).

GTD not cured by initial evacuation is referred to as GTN. It can remain confined to the uterus or may be metastatic in up to 30% of cases but is most commonly heralded by plateaued or rising serum β-hCG, evidence of persistent trophoblastic activity [4,48,49]. Invasive mole is the most common form of GTN after molar pregnancy [50]. Choriocarcinoma, though less common, can also occur in this population. Although suspected or confirmed GTN warrants workup for metastatic disease and subsequent evaluation of risk factors, extensive a priori imaging investigation is generally not needed in the subset of women with invasive mole [10,13]. Rather, investigation for metastatic disease can be guided by the results of thoracic imaging. Because lung metastases typically precede metastases to other sites, imaging of other organs may not be necessary in the absence of pulmonary lesions and a normal physical examination [2,43]. Conversely, a positive chest radiograph mandates further imaging to search for additional sites of metastatic disease [10,37]. Although it may be common practice at some institutions to evaluate patients with a CT of the head, chest, abdomen, and pelvis at initial presentation to expedite chemotherapy selection, there is no evidence in the literature or expert consensus to support this procedure.

After nonmolar pregnancy, the principal trophoblastic lesion is choriocarcinoma and the percentage of patients with metastatic disease is higher given its propensity for vascular invasion and later diagnosis that is due to the absence of routine β-hCG monitoring [50]. Accordingly, the European Society for Medical Oncology clinical practice guidelines and consensus review from the joint report of the International Society for the Study of Trophoblastic Disease, European Organisation for Treatment of Trophoblastic Diseases (EOTTD), and the Gynecologic Cancer InterGroup recommend more extensive imaging investigations, including contrast-enhanced CT chest and abdomen, MRI of the brain and pelvis, and Doppler US of the pelvis [7,37]. Though rare, PSTT and ETT are also more common after nonmolar gestations [14,50].

US Pelvis Transvaginal

In women with persistently elevated serum β-hCG, US is generally recommended to evaluate for normal intrauterine pregnancy and may be useful to measure uterine volume and assess local tumor extension. Although the depth of uterine involvement does not directly impact the patient's prognostic score, it may influence treatment decisions, particularly if there is imaging evidence of extensive uterine disease and if hysterectomy is considered [45,51,52]. Because treatment of invasive mole/choriocarcinoma differs from that of PSTT or ETT, distinction of these tumors has clinical importance. However, the US features of the subtypes of GTN are indistinguishable from one another [53-55] and may overlap with other processes, such as fibroids, adenomyosis, and occasionally ectopic pregnancy [15,44]. Some centers avoid transvaginal US in women with GTN because of the risk of major bleeding as a consequence of a nondetected vaginal metastasis [37].

US Pelvis Transabdominal

Transvaginal US has superior sensitivity and specificity in the diagnosis of uterine masses when compared with transabdominal US, although, given the rarity of GTN, literature comparing both modalities is lacking [32].

US Duplex Doppler Pelvis
There is some evidence to support a role for Doppler US in GTN. A recent systematic literature review summarizing data from 28 studies up to 2014 demonstrated a lower uterine artery resistance pattern in women with GTN compared with women with hydatidiform mole, recent termination, no current pregnancy, or first trimester pregnancy [34]. Doppler measurement of the uterine artery pulsatility index serves as a noninvasive marker of tumor vascularity and neoangiogenesis and may prove useful in patient selection for first-line therapy [56-58]. In patients with low-risk disease, a uterine artery pulsatility index of ≤1 may be useful to predict resistance to first-line chemotherapeutic agents [56,58]. Three-dimensional power Doppler has also been investigated as a potential quantitative method to identify patients with GTD and to assess tumor treatment response in a small study [59]. Doppler US can also confirm the absence of vascular flow within a mass, a useful technique in patients with GTD where clot or blood products may simulate solid tissue.

Radiography Chest
The lungs are the most common site of metastasis in GTN [7,36,60]. Chest radiographs are the primary imaging method recommended by FIGO to detect and count lung metastases for purposes of risk assessment in patients with GTN. However, approximately 30% to 40% of patients assumed to have nonmetastatic disease by radiographs may have CT evidence of micrometastases [20,38,39]. The emphasis on radiographs may in part reflect the global scope of FIGO, which provides recommendations that must apply to both industrialized countries and underresourced medical care environments. CT chest may be preferred where available because of its greater sensitivity, although controversy persists regarding the prognostic significance of tiny nodules detected by CT, as discussed below. However, the statement that chest radiographs are used for counting the number of metastases, not CT chest, was also rated as highly appropriate by a panel of 45 experts from 16 countries in association with the EOTTD [6].

CT Chest
The lungs are the most common site of metastasis in GTN [7,36,60]. Approximately 30% to 40% of patients assumed to have nonmetastatic disease by radiographs may have CT evidence of micrometastases [20,38-40]. However, the clinical importance of these tiny lesions remains controversial as there is no definitive evidence of impact on long-term survival [38,41]. Assessment of the literature is complicated by the fact that suspected pulmonary micrometastases from GTN are often not confirmed histologically because they typically regress completely with treatment and biopsy is not recommended [40]. Despite some disagreement in the literature regarding modality choice to diagnose lung metastases, patients with suspected or confirmed GTN are often initially evaluated with chest CT at many institutions. Although micrometastases are not thought to impact survival, their presence increases the likelihood of other areas of metastatic involvement and should trigger other anatomic imaging [19]. Otherwise stated, the negative predictive value of chest CT in patients with GTN is high and of substantial clinical value because hepatic or brain metastases are very unlikely in the absence of pulmonary metastases [37]. Because the lungs are the most common site of GTN metastases, the use of IV contrast is not necessary to improve lesion detection.

The use of low-dose CT as a means to assess pulmonary metastases in patients with GTN was evaluated in a small study comparing standard- and low-dose CT examinations [42]. Although the number of nodules detected on the low-dose CT protocols was significantly less than the number identified on standard-dose CT examinations, the disease staging and risk score of the patients were not impacted.

CT Head
Imaging of the brain is indicated when clinical signs suggest central nervous system disease and also in women with high-risk disease or significant pulmonary involvement [61,62]. Because GTN metastases are typically vascular, IV contrast enhancement is necessary to improve lesion detection. If physical examination and chest radiographs are normal in a patient with GTN, metastases to other sites are unlikely, and further imaging investigation is not indicated [37,43]. Brain metastasis almost always occurs in the context of pulmonary metastasis, underscoring the "lungs first" paradigm [12]. Brain metastases portend a worse prognosis than vaginal or pulmonary metastases and develop in 8% to 15% of patients with metastatic GTN [12,16]. GTN metastases to the brain are often solitary, may be hemorrhagic, and the interval between the initial diagnosis of metastatic GTN and the subsequent diagnosis of brain metastases can be long [12].

The EOTTD expressed a strong preference for MRI over CT for neurologic staging in a study that assessed the level of agreement among an expert panel regarding the management of patients with GTD [6]. However, in the setting of urgent neurologic findings that are due to space-occupying or hemorrhagic metastases, the ACR

Appropriateness Criteria® topic on "Headache" [63] or the ACR Appropriateness Criteria® topic on "Acute Mental Status Change, Delirium, and New Onset Psychosis" [64] may be consulted.

CT Abdomen and Pelvis
The formalized consensus of the EOTTD strongly supports the statement, "in case of lung metastases, investigation for abdominal and brain metastases is recommended" [6]. Among women with metastatic GTN, approximately 30% will have vaginal involvement and 10% will have liver involvement [36], supporting a role for contrast-enhanced CT abdomen and pelvis, particularly in GTN following nonmolar pregnancy or confirmed choriocarcinoma, ETT, or PSTT. Because GTN metastases are typically vascular, IV contrast enhancement is necessary to improve lesion detection.

MRI Head
Imaging of the brain is indicated when clinical signs suggest central nervous system disease, and also in women with high-risk histology or significant pulmonary involvement [61,62]. Because GTN metastases are typically vascular, IV contrast enhancement is useful to improve detection. Brain metastases portend a worse prognosis than vaginal or pulmonary metastases and develop in 8% to 15% of patients with metastatic GTN [12,16]. As above, brain metastasis almost always occurs in context of pulmonary metastasis, underscoring the "lungs first" strategy [12]. GTN metastases to the brain are often solitary and may be hemorrhagic, and the interval between the initial diagnosis of metastatic GTN and the subsequent diagnosis of brain metastases can be long [12].

The formalized consensus of the EOTTD also strongly supports the statement, "in case of lung metastases, investigation for abdominal and brain metastases is recommended" and strongly favors MRI over CT because of its higher sensitivity [6].

MRI Pelvis
In women with GTN, pelvic MRI can delineate uterine and vaginal masses, and may provide useful detail regarding the depth of local invasion [44,46,61]. Local staging information is particularly relevant in patients with ETT or PSTT because these tumors may have extensive uterine involvement [14,15,52]. ETT and PSTT are both relatively chemoresistant, and surgical resection may have a primary role in therapy if the tumor is confined to the uterus. As such, MRI has the potential to provide important information for treatment planning. Local parametrial invasion, vaginal involvement, and pelvic extension are all better assessed with MRI than US [44]. Because the primary tumor and GTN metastases are typically vascular, IV contrast enhancement is useful to improve lesion detection. Vaginal gel may be useful to distend the vagina, optimizing the delineation of any masses or extension, if present. The majority of patients with postmolar GTN not treated with hysterectomy will have locally invasive disease [17].

Given the rare nature of ETT and PSTT, there are few consistent descriptions of imaging features, limited to small series and case reports [15,52,65]. MRI assessment of lymph node status is important to treatment planning in patients with PSTT and ETT, but other forms of GTN predominantly spread via hematogenous routes.

FDG-PET/CT Skull Base to Mid-Thigh
The role of FDG-PET/CT in the evaluation of patients with GTN is inconclusive and evolving given the uncommon nature of the disease. There is some evidence that FDG-PET/CT may be useful to precisely map tumor extent prior to chemotherapy, as well as to monitor tumor response and identify sites of persistent disease following therapy [66-69]. One systematic review included 19 papers totaling 81 cases of GTN, with FDG-PET/CT used in the initial staging in 59 of 81 patients and in the follow-up after initial chemotherapy in 22 of 81 patients [47]. The largest study included in this review (41 patients) showed concordance between FDG-PET or PET/CT and conventional studies that ranged from 81% to 91% with the highest discordance in chest CT, all false-negative [68]. Among all summarized data, FDG-PET or PET/CT studies facilitated localization of persistent or unusual sites of metabolically active disease, enabled distinction of false-positive lesions on conventional studies related to areas of necrotic or hemorrhagic tissue, and identified additional or occult lesions in a small number of patients. Small lesion size, paucity of FDG-avid cells, and poorly differentiated tumors may contribute to false-negative studies.

Variant 3: Surveillance of GTN, including refractory, relapsed, or quiescent GTN.

GTN is highly chemosensitive and associated with excellent outcomes, but drug resistance and relapse can occur. This is more common in patients with high-volume disease at diagnosis or in those with inadequate initial therapy. Up to 12.5% of patients with high-risk disease will develop recurrence after initial remission [19].

Because of serial post-treatment β-hCG surveillance, detection is early, ensuring that the volume of recurrent or resistant disease is small [10]. Clinically silent residual lesions detected by imaging after chemotherapy for low-risk GTN are not predictive of recurrence risk and require no additional treatment because radiographic evidence of tumor regression can lag behind a favorable biochemical response to treatment [7,16]. Recurrence risk drops to 1% only 1 year after remission [19].

Quiescent GTD is a form of low-volume persistent disease that is resistant to treatment because insufficient syncytiotrophoblastic and cytotrophoblastic cells remain to sustain an adequate response to chemotherapy. Given the small number of patients who develop quiescent GTD, treatment can be challenging and management remains anecdotal. This disorder usually follows a molar pregnancy but can follow any gestational event. Typically, laboratory evaluation shows very low but persistent levels of β-hCG (for at least 3 months) despite chemotherapy and, occasionally, even surgery, with no imaging or clinical evidence of GTN [2,70]. Quiescent GTD is biochemically monitored, and imaging is not indicated without evidence of a rising β-hCG or localizing signs of clinical disease [70].

US Pelvis Transvaginal
Pelvic US may be used to evaluate the uterus for recurrent GTN in the setting of rising β-hCG [61]. Because patients with previous GTN are at slightly higher risk of developing GTD with subsequent pregnancies (1%–2% risk), a pelvic US scan is also recommended at 10 weeks gestation to document normal fetal development in any new pregnancy [2,13].

US Pelvis Transabdominal
Transvaginal US has improved sensitivity and specificity in the diagnosis of uterine masses when compared with transabdominal US, although given the rarity of this disorder, series that compare both modalities in patients with GTN are lacking [32].

US Duplex Doppler Pelvis
Pelvic US may be used to evaluate the uterus for recurrent GTN in the setting of rising β-hCG [61]. Grayscale US features combined with power Doppler may help to distinguish delayed response from true chemoresistance according to a study of 24 patients [57]. In this study, uterine GTN was identified by US in 83% of patients. All patients with biochemically determined treatment response had US evidence of lesion regression. Three of the remaining 7 patients deemed methotrexate-resistant by biochemical criteria also developed US evidence of treatment response, ultimately with delayed but complete clinical response to methotrexate confirmed by resolution of hCG.

Radiography Chest
Evaluation of lung metastases in patients with relapsed or refractory disease is better accomplished with chest CT because primary prognostic scoring is no longer an issue in this patient population.

CT Chest
Because GTN metastases involve the lungs rather than the mediastinum, IV contrast enhancement is not necessary to improve lesion detection. Although radiographic evidence of tumor regression can lag behind a favorable biochemical response to treatment, thoracotomy with wedge resection of pulmonary lesions is sometimes performed in patients with persistent nodules. This is generally only indicated with isolated chemoresistant lesions in the absence of disease elsewhere [16,71]. Regardless, it remains the most common surgical procedure for extrauterine metastases [16,18,71].

CT Head
Although a head CT is acceptable as a means to document brain metastases (FIGO), the formalized consensus of the EOTTD favors MRI over CT in the detection of brain metastases [6]. Because GTN metastases are typically vascular, IV contrast enhancement is necessary to improve lesion detection.

CT Abdomen and Pelvis
CT abdomen and pelvis is useful to exclude disseminated disease in patients with high-risk or recurrent GTN who are being considered for salvage hysterectomy [16] or to evaluate for recurrence of tumors after surgical resection. In the specific context of oligometastatic disease to lung with potential for pulmonary wedge resection, CT abdomen and pelvis has particular utility for exclusion of additional disease sites [16,18]. Because GTN metastases are typically vascular, IV contrast enhancement is necessary to improve lesion detection.

MRI Head

Rising serum β-hCG may be an indication for cranial imaging, particularly for high-risk histologies. GTN metastases are often solitary and may be hemorrhagic, and the interval between the initial diagnosis of metastatic GTN and the subsequent diagnosis of brain metastases ranges from 0 to 60 months [12]. MRI of the brain is preferred over CT for the detection of metastatic lesions and can further allow assessment of associated hemorrhage [61]. Because GTN metastases are typically vascular, IV contrast enhancement is useful to improve lesion detection.

MRI Pelvis

Uterine volume, myometrial heterogeneity, and tumor hypervascularity decrease following successful chemotherapy for GTN, with restoration of normal zonal anatomy 6 to 9 months following completion of therapy [44,45,61]. To our knowledge, there are no formal studies evaluating the role of MRI in recurrent or relapsed GTN, but given the tissue contrast of MRI and the high incidence of local invasion in some forms of GTN [17], it is conceivable that MRI could play a useful role in identifying patients who may benefit from salvage hysterectomy because of isolated disease persistence in the uterus [16]. Because GTN metastases are typically vascular, IV contrast enhancement is useful to improve lesion detection. In a small group of patients with recurrent PSTT with initial normalization of β-hCG (12 of 56 patients), the majority recurred in the pelvis, with a smaller number of patients having recurrent disease in the lung and liver [24].

FDG-PET/CT Skull Base to Mid-Thigh

The role of FDG-PET/CT in the evaluation of patients with refractory or recurrent GTN is incompletely defined and evolving, given the uncommon nature of the disease. FDG-PET/CT may help to identify the site of active or occult disease and facilitate planning for surgical resection and potential cure [10,66,67,69,72]. However, the evidence basis is small and retrospective.

Variant 4: Assessment of complications: GTD and GTN.

Patients with GTD can present with complications related to invasive mole or metastatic lesions, in large part because of the highly vascular nature of this disease process. Some of these complications can be severe and life-threatening. Hemorrhage is the most common complication and can result from tumor invading the uterus or from other sites of metastatic tumor involvement, including lungs, brain, vagina, and liver [2,16,50,73]. Selective angiographic localization and embolization can be used to identify and treat lesions with active hemorrhage as well as post-treatment sequelae, such as arteriovenous malformation [18]. Hysterectomy may be indicated for severe uterine hemorrhage or rupture [2,18]. Although rare in the United States, patients with invasive mole may present with hemoperitoneum that is due to molar tissue penetrating the full thickness of the myometrium [20]. Finally, adnexal torsion or rupture may occasionally complicate theca lutein cysts, necessitating surgical removal [16]. Imaging evaluation in the setting of suspected GTN complications should be guided by location of clinical signs and symptoms.

US Pelvis Transvaginal

GTN can be complicated by uterine vascular malformations, such as arteriovenous shunts and pseudoaneurysms, which are described in up to 15% of cases following complete response to chemotherapy. These can be detected by transvaginal US but are best delineated with Doppler US [44]. Although these findings are insignificant if asymptomatic and associated with a normal β-hCG, such malformations occasionally result in life-threatening vaginal or intraperitoneal hemorrhage [44]. Theca lutein cysts develop in up to 37% of patients with GTN [61]. Pelvic pain related to torsion or rupture of these cysts can be effectively evaluated with pelvic US.

US Pelvis Transabdominal

Transvaginal US has improved sensitivity and specificity in the diagnosis of uterine masses and abnormalities when compared to transabdominal US, although given the rarity of this disorder, series comparing both modalities in patients with GTD are lacking [32]. At some institutions, patients with GTN are not evaluated with transvaginal US due to the risk of major bleeding as a consequence of a nondetected vaginal metastasis [37].

US Duplex Doppler Pelvis

GTN can be complicated by uterine vascular malformations such as arteriovenous shunts and pseudoaneurysms, described in up to 15% of cases following complete response to chemotherapy, and best delineated with Doppler US [44]. Although these findings are insignificant if asymptomatic and associated with a normal hCG, such malformations occasionally result in life-threatening vaginal or intraperitoneal hemorrhage [44].

Radiography Chest

We are unaware of any recent formal assessment regarding the use of chest radiography to assess pulmonary complications in GTN. Lung infarct and secondary pulmonary arterial hypertension associated with trophoblastic tumor thrombus may be appreciated on chest radiography. Likewise, sequelae of endobronchial metastasis such as volume loss or airspace disease and pleural effusions that follow hemorrhage into parenchymal and intravascular metastases could potentially be visible [44,45].

CT Chest

A variety of pulmonary complications may be evaluated using chest CT [44,45], including trophoblastic tumor thrombus, associated lung infarct, and secondary pulmonary arterial hypertension. Unusual manifestations of lung metastases may be perceptible such as an endobronchial lesion with secondary obstruction and volume loss. Airspace disease and pleural effusion may follow hemorrhage into parenchymal and intravascular metastases [44,45]. Because detection of these complications may require opacification of the vessels, IV contrast enhancement is necessary to improve lesion conspicuity, although hemorrhagic complications would be visible on an unenhanced study.

CT Head

Craniotomy with surgical decompression is generally indicated for acute symptomatic treatment of patients with intracranial hemorrhage [16]. CT can be used to identify and localize lesions or to detect signs of increased intracranial pressure and mass effect in patients with acute neurologic symptoms and signs of deterioration. Hemorrhagic complications and structural changes related to mass effect would be visible without IV contrast, although lesion detection would be improved with IV contrast.

CT Abdomen and Pelvis

CT is indicated to detect metastatic disease in the staging of patients with GTN, but can also be used to identify sites of active hemorrhage or other tumor-related complications [74]. Liver metastases can be associated with catastrophic intraperitoneal hemorrhage and may require selective angiographic embolization techniques [16]. Use of CT abdomen and pelvis should be prompted by abdominopelvic location of patient symptoms in context of known GTN. Hemorrhagic complications would be evident without the use of IV contrast. IV contrast may be required to detect individual nonhemorrhagic lesions.

MRI Head

Craniotomy with surgical decompression is generally indicated for acute symptomatic treatment of patients with intracranial hemorrhage [16]. MRI can be used to identify and localize lesions or to detect signs of increased intracranial pressure and mass effect in patients with acute neurologic symptoms and signs of deterioration. Structural changes related to mass effect or signal characteristics associated with hemorrhage would be visible without IV contrast. Detection of individual lesions would be improved with IV contrast.

MRI Pelvis

Although pelvic MRI is considered a problem-solving tool in patients with vaginal bleeding [75], no studies specifically evaluate the use of MRI for GTD-related complications. Tortuous coiled flow voids corresponding to vessels located within the myometrium generally reflect a post-treatment vascular malformation. Complications related to hemorrhage or vascular malformations would be visible without IV contrast, although the detection of individual lesions and structural changes related to complications may be improved with IV contrast.

FDG-PET/CT Skull Base to Mid-Thigh

We are unaware of any evidence that evaluates or supports the role of FDG-PET/CT in assessing complications in patients with GTN.

Summary of Recommendations

- **Variant 1**: US pelvis transvaginal, US duplex Doppler pelvis, and US pelvis transabdominal are usually appropriate for the suspected or initial diagnosis of GTD. These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care).

- **Variant 2**: US pelvis transvaginal, US duplex Doppler pelvis, and US pelvis transabdominal are usually appropriate for local staging and risk assessment of suspected or established diagnosis of GTN. These procedure are complementary (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care.) A radiograph of the

chest and CT chest with IV contrast are usually appropriate for the detection of lung metastases in the staging and risk assessment of suspected or established diagnosis of GTN. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). CT abdomen and pelvis with IV contrast and MRI pelvis without and with IV contrast are usually appropriate for the staging and risk assessment of suspected or established diagnosis of GTN. These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care). The panel did not agree on recommending MRI pelvis without IV contrast for the staging and risk assessment of suspected or established diagnosis of GTN. There is insufficient medical literature to conclude whether or not these patients would benefit from this procedure. Performing this procedure in this patient population is controversial but may be appropriate.

- **Variant 3**: US pelvis transabdominal, US duplex Doppler pelvis, US pelvis transvaginal, CT chest with IV contrast, CT abdomen and pelvis with IV contrast, and MRI head without and with IV contrast, are usually appropriate in the surveillance of GTN including refractory, relapsed, or quiescent GTN in the setting of biochemical and/or localized signs of clinical disease. These procedures are complementary (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care.) The panel did not agree on recommending CT abdomen and pelvis without and with IV contrast, MRI head without IV contrast, and MRI pelvis without IV contrast in the surveillance of GTN. There is insufficient medical literature to conclude whether or not these patients would benefit from these procedures. Performing these procedures in this patient population is controversial but may be appropriate.

- **Variant 4**: CT abdomen and pelvis with IV contrast, CT chest with IV contrast, and US pelvis transvaginal are usually appropriate in the assessment of complications for GTD and GTN. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care) that should be chosen depending on the location of clinical signs and symptoms of suspected complications. The panel did not agree on recommending CT abdomen and pelvis without and with IV contrast and CT chest without and with IV contrast in the assessment of complications for GTD and GTN. There is insufficient medical literature to conclude whether or not these patients would benefit from these procedures. Performing these procedures in this patient population is controversial but may be appropriate.

Supporting Documents

The evidence table, literature search, and appendix for this topic are available at https://acsearch.acr.org/list. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

Safety Considerations in Pregnant Patients

Imaging of the pregnant patient can be challenging, particularly with respect to minimizing radiation exposure and risk. For further information and guidance, see the following ACR documents:

- ACR–SPR Practice Parameter for the Safe and Optimal Performance of Fetal Magnetic Resonance Imaging (MRI) [76]
- ACR-SPR Practice Parameter for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation [74]
- ACR-ACOG-AIUM-SMFM-SRU Practice Parameter for the Performance of Standard Diagnostic Obstetrical Ultrasound [77]
- ACR Manual on Contrast Media [78]
- ACR Guidance Document on MR Safe Practices; 2013 [79]

Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document [80].

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢☢	0.1-1 mSv	0.03-0.3 mSv
☢☢☢	1-10 mSv	0.3-3 mSv
☢☢☢☢	10-30 mSv	3-10 mSv
☢☢☢☢☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."		

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.