Multimodality Imaging in the Diagnosis and Staging of Gestational Choriocarcinoma

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Indian J Radiol Imaging

Abstract

Choriocarcinoma is an uncommon, highly invasive malignancy arising from the placental trophoblastic tissue. Though staging is clinical, imaging has significant role in the diagnosis, staging, prognostic risk scoring, and management of choriocarcinomas. The purpose of this article is to review the role of multimodality imaging in the diagnosis, staging, and management of choriocarcinomas in correlation with clinicopathologic findings.

Keywords

► choriocarcinoma
► ultrasound
► color Doppler
► computed tomography
► positron emission tomography
► magnetic resonance imaging

Introduction

Choriocarcinoma is an uncommon, rapidly proliferating, highly vascular and invasive malignancy arising from the placental trophoblastic tissue. Tumors arising from the placental tissue include benign hydatidiform moles and the malignant gestational trophoblastic neoplasms (GTNs). The two benign tumors, complete and partial hydatidiform moles, are not included in the tumor registries as they usually follow a benign course. The World Health Organization (WHO) classifies malignant GTNs into the following four categories: invasive hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (EPT).

GTNs arise from uterine placental tissue following any pregnancy event that include hydatidiform mole, incomplete or complete abortion, and a normal full-term gestation. About 10% of complete hydatidiform moles and 0.5% of partial hydatidiform moles undergo malignant transformation by either persisting locally in the uterus or by metastasizing, and are referred to as persistent trophoblastic neoplasms.

Even though choriocarcinoma is the most common GTN with a propensity for rapid progression and widespread...
metastases compared with the other three GTNs, the majority of studies available in the literature are focused on either the entire spectrum of the gestational trophoblastic diseases or the more common form, the hydatidiform mole. Diagnosing and differentiating choriocarcinoma from other GTNs is important, as it has distinctive biological, clinical, and pathological features, requiring aggressive therapeutic approach.

Choriocarcinomas significantly differ from other gynecologic malignancies in staging and management. In most gynecologic malignancies, staging is surgical and pathological, whereas in choriocarcinomas the staging is clinical. Another major difference is that choriocarcinomas are restaged by including new findings and risk score, whenever a change in therapy is contemplated (indicated by an rTNM staging), while in other gynecologic malignancies, the initial staging remains unchanged, irrespective of the new findings during the course of disease.

The Fédération Internationale de Gynécologie et d’Obstétrique (FIGO) classifies choriocarcinoma into four stages depending upon the anatomic location of the tumor (Fig. 1). In 2000, the FIGO anatomic staging was combined with the WHO prognostic scoring system by assigning points for each of the following factors: patient age, antecedent pregnancy type, interval in months from gestational event, β-human chorionic gonadotropin (βhCG) levels, site and number of metastases, tumor size, and previous chemotherapy status (Table 1). Currently, the classification includes anatomic staging indicated by Roman numerals (stage I–IV), followed by risk factor score in Arabic numerals (low-risk disease for score <7 and high-risk disease for score >7).

This article is based on the literature review on choriocarcinoma from both PubMed and non-PubMed indexed journals, WHO and FIGO classification and risk scoring, American Joint Committee on Cancer (AJCC) eighth edition on staging of choriocarcinoma, American College of Radiology (ACR) appropriateness criteria for imaging in choriocarcinoma, clinical practice guidelines from European Society for Medical Oncology (ESMO), the consensus review and the joint report from the International Society for the Study of Trophoblastic Disease (ISSTD), European Organisation for Treatment of Trophoblastic Diseases (EOTTD), and the Gynecologic Cancer Intergroup.

In this review, we present the role of multimodality imaging in staging of choriocarcinoma with a brief review of the histopathology, clinical features, complications, and management.

Historically, Felix Marchand, the German pathologist, was the first person to discover the association between GTN and pregnancy, and accurately describe the clinical and histological features of choriocarcinoma. The incidence of gestational choriocarcinoma (generally expressed in relation to the total number of pregnancies in a community rather than the total population) is much varied across the globe, occurring approximately 1 in 20,000 to 40,000 pregnancies, with higher incidence reported from Asia and Africa compared with Europe and America.

Choriocarcinomas are usually underdiagnosed as most women after pregnancy event are initially asymptomatic and
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choriocarcinomas. Choriocarcinomas lack in
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the GTDs has varying amounts of these three abnormally
appear as bluish or purplish nodules.

are commonly diagnosed on pelvic examination and they
relating to low socioeconomic status.
pregnancy, extremes of maternal age, diet, and nutrition
tochemistry (IHC), and imaging
based on the levels of
patients, the diagnosis of choriocarcinoma is retrospective
histopathological examination. In the majority of the
moles, invasive moles, and choriocarcinomas, and elevated
hPL is a feature of PSTT.

Apart from confirming the histologic diagnosis, estimation
and serial monitoring of the tumor markers secreted by
these trophoblastic cells form the clinical basis of diagnosis
and follow up protocols in the treatment of GTN.

Macroscopically, primary choriocarcinomas appear as
markedly hemorrhagic or necrotic masses of varying sizes.

Microscopically, choriocarcinomas exhibit large multinucle-
ated syncytiotrophoblasts interspersed with polygonal
mononuclear cytotrophoblasts in the background of exten-
sive necrosis and hemorrhage. Choriocarcinomas produce
placental and epidermal growth factors causing exuberant
and aberrant neo-angiogenesis, resulting in hypervascular
and hemorrhagic lesions: the hallmark of choriocarcinoma
and its metastases.11 Histopathology remains the gold stan-
standard for the diagnosis of GTNs, and choriocarcinomas exhibit
100% positivity to βhCG on IHC.12

Clinical and Laboratory Features
Patients usually present with abnormal vaginal bleeding,
uterine enlargement, pelvic pain, and anemia, following any
pregnancy event. However, a few asymptomatic patients can
directly present with signs and symptoms of metastatic
lesions in the lung (cough, chest pain, dyspnea, hemoptysis,
pulmonary arterial hypertension), brain (intracranial bleed-
ing or raised intracranial tension causing headache, vomit-
ing, convulsions, and motor or sensory deficit), and abdomen
(peritoneal/gastrointestinal bleeding).5–9 Vaginal metastases
are commonly diagnosed on pelvic examination and they
appear as bluish or purplish nodules.8,10

Histopathology
Placental tissue contains both chorionic villi and tropho-
blasts. The presence of molar villi along with the tropho-
blastic tissue is a histological feature of benign hydatidiform
moles and malignant invasive mole, unlike the rest of the
GTNs (choriocarcinoma, PSTT, and EPT), which lack villous
structures. The trophoblast is a gestational tissue comprising
three types of cells: cytotrophoblasts, syncytiotrophoblasts,
and intermediate trophoblasts. The syncytiotrophoblasts
synthesize βhCG and intermediate trophoblasts synthesize
serum human placental lactogen (hPL), whereas cytotropho-
blasts do not have any role in hormonal synthesis.7 Each of
the GTDs has varying amounts of these three abnormally
proliferating trophoblastic cells. Choriocarcinomas lack in-
termEDIATE trophoblasts, but they are significantly present in
PSTT. Therefore, elevated βhCG is a feature of hydatidiform
moles, invasive moles, and choriocarcinomas, and elevated
hPL is a feature of PSTT.

not routinely subjected to βHCG monitoring or placental
histopathological examination. In the majority of the
patients, the diagnosis of choriocarcinoma is retrospective
based on the levels of βHCG, histopathology, immunohis-
tochemistry (IHC), and imaging findings.

Risk factors are prior spontaneous abortion or molar
pregnancy, extremes of maternal age, diet, and nutrition
relating to low socioeconomic status.6,7

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Risk score</th>
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<tr>
<td>Age (y)</td>
<td>&lt;40</td>
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<tr>
<td>Antecedent pregnancy</td>
<td>Hydatidiform mole</td>
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<tr>
<td>Interval months from index pregnancy</td>
<td>&lt;4</td>
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<tr>
<td>Pretreatment hCG (IU/mL)</td>
<td>&lt;10⁵</td>
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<tr>
<td>Largest tumor size, including uterus (cm)</td>
<td>&lt;3</td>
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<tr>
<td>Site of metastases</td>
<td>Lung</td>
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<tr>
<td>Number of metastases identified</td>
<td>1–4</td>
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<td>Previous failed chemotherapy</td>
<td>Single drug</td>
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<td>Total score</td>
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Abbreviations: hCG, human chorionic gonadotropin.

Microscopically, primary choriocarcinomas exhibit large multinucle-
ated syncytiotrophoblasts interspersed with polygonal
mononuclear cytotrophoblasts in the background of exten-
sive necrosis and hemorrhage. Choriocarcinomas produce
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and its metastases.11 Histopathology remains the gold stan-
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Imaging
Ultrasound
Ultrasound (US) is the first line of imaging in the evaluation
of the pelvis, and one of its primary roles is to exclude a
normal or ectopic gestation in patients with elevated βhCG.
On US, the uterus is often asymmetrically enlarged and
choriocarcinomas appear as heterogeneously hypoechoic
or hyperechoic mass lesions infiltrating the myometrium
with intraskeletal anechoic cystic foci reflecting the vascular,
hemorrhagic, and necrotic components (Fig. 2).

On color Doppler US, choriocarcinomas appear as
extremely vascular masses, typically exhibiting the chaotic
internal vessels and arteriovenous shunts with color alias-
ing.7,9 Color Doppler excellently depicts the abnormally
proliferating hypervascular trophoblastic tissue with char-
acteristic myometrial invasion and neoangiogenesis.7,9 Color
Doppler is also useful in differentiating choriocarcinomas
from other hypovascular or avascular conditions like
retained products of conception, focal adenomyomas, fibroids, and clots or blood products simulating solid masses.3,7,13 The sensitivity of US in the detection of choriocarcinoma in literature varies widely, ranging from 41 to 86%.14 Spectral Doppler of the hypervascular lesions in choriocarcinoma exhibit lower resistive index (RI) and pulsatility index (PI) compared with benign hydatidiform moles. Lin et al reviewed 28 studies on GTN and concluded that abnormal myometrial vascularization and lower uterine artery Doppler indices have correlated with the persistence of local disease, progression to invasive disease, and decreased response to chemotherapy.14 Several other studies have also found that uterine artery PI of ≤ 1 is an independent predictor of methotrexate resistance during the treatment.13–17 Low uterine artery PI and hypervascular nodules in uterine endo-myometrium can be early predictors of subsequent development of malignancy in postmolar pregnancies; therefore, patients with these findings are advised to undergo regular monitoring with serum βhCG levels and pelvic USG. Predictive models are under development for the assessment of uterine vascularity using uterine artery PI to establish cutoff points to decide single drug methotrexate versus multidrug therapy in the early phase of disease.15–17 Contrast-enhanced US (CEUS) using microbubbles is a recent technique to evaluate the blood perfusion patterns and microvasculature of target organs. Su et al have shown that diffuse enhancement of lesions with better delineation of the boundaries is seen in GTN with CEUS compared with benign uterine lesions.18

**Computed Tomography**

On noncontract enhanced computed tomography (CT), the uterus is often enlarged and choriocarcinomas appear as ill-defined hypodense focal lesions. Myometrial invasion by the lesion and endo-myometrial differentiation are relatively indistinctive on plain CT. However, on contract enhanced CT (CECT), these lesions exhibit intense heterogeneous enhancement due to their high vascularity. Vascular abnormalities including arteriovenous malformations (AVMs), arteriovenous shunts and pseudoaneurysms are seen as markedly enhancing foci during the early arterial phase. MDCT with multiplanar reconstruction helps in identifying extrauterine disease, adjacent organ involvement, and locoregional metastases (►Fig. 3).

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI), due to its exquisite soft-tissue resolution, is the modality of choice for local staging of...
the majority of pelvic malignancies including choriocarcinoma. On MRI, choriocarcinomas are seen as focal lesions that are iso- to hyperintense on T1-weighted (T1W) images and heterogeneously hyperintense on T2W images. Hemorrhagic foci appear as hyperintense areas on T1W sequences, and necrotic foci are seen as ill-defined hypo- and hyperintense areas within the lesion. Tumor vasculature appears as multiple tortuous flow voids on both T1W and T2W sequences. The lesions exhibit diffusion restriction and have low apparent diffusion coefficient (ADC) values, hence appear bright on diffusion-weighted sequences (DWI) and dark on ADC maps (►Fig. 4). Contrast-enhanced MRI shows marked enhancement of the tumor due to its inherent hypervascular nature and neo-angiogenesis. Larger lesions are seen diffusely involving the entire myometrium with loss of normal zonal anatomy (►Fig. 5). Vascular malformations associated with choriocarcinoma can be seen as multiple tortuous hyperintense vessels in uterine myometrium and parametrium. Preoperative assessment by MRI is advantageous than US in identifying the depth of myometrial invasion, extrametrial extension, adjacent organ invasion, and accurate differentiation of T1 and T2 stages.3

Positron Emission Tomography/Computed Tomography

Although currently not indicated in the management, studies have found that fluorine-18 fluorodeoxyglucose (18F-FDG) PET/CT is useful in identifying occult lesions, metastases at unusual sites, recognizing residual/persistent metabolically active disease, detecting recurrences, and monitoring the therapeutic response.19,20 PET/CT is also being used to exclude lesions elsewhere in the body before planning pulmonary wedge resection in patients with oligometastatic disease to the lung.3

Angiography

Angiography may be needed for the evaluation of vascular complications of choriocarcinoma. It is not routinely performed unless an intervention is planned, as CT angiography can demonstrate the vascular malformations in equal detail. In patients presenting with intractable uterine bleeding or bleeding from vaginal metastases and patients with AVMs, angiography provides a vascular road map prior to selective embolization of uterine arteries and its branches. Therapeutic angiography is also performed during chemoembolization of vascular hepatic metastases.7

Metastatic Spread and Staging

Angioinvasion is one of the characteristic features of choriocarcinoma; hence, extensive metastases due to early vascular invasion occur even when the primary malignant lesion is quite small. Rarely patients can directly manifest with features of distant metastases with normal pelvic US.21 Metastases can occur from immediate postabortion or postpartum period to several years later in life.9,10 Metastatic spread occurs predominantly through hematogenous dissemination, and the common sites are the lung (80%), vagina (30%), pelvis (20%), brain (15%), and liver (10%).3 Rare sites include the kidney, gastrointestinal tract, skin, and spleen, but isolated metastasis to these sites is unusual in the absence of lung or vaginal lesions.5–9 Vaginal metastases due to contiguous spread are the most common extrametrial lesions of choriocarcinoma, and other pelvic sites include the ovaries, fallopian tubes, and broad ligaments. US, compared with CT and MRI, has poor sensitivity in detecting vaginal metastases, though the positive predictive value is high.3 Transvaginal US may better depict the lesion and internal cystic spaces invading the
Fig. 4  Stage I choriocarcinoma confined to the uterus in a 24-year-old woman. (A, B) Sagittal T2-weighted (T2W) and axial short tau inversion recovery (STIR) T2W images show a heterogeneously hyperintense lesion (★) in the uterus. (C, D) Axial diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) images show the lesion appearing bright on DWI and dark on ADC (★).

Fig. 5  Stage IV choriocarcinoma in a 29-year-old woman with lung and brain metastases. (A) Sagittal T2-weighted (T2W) image shows heterogeneously hyperintense lesion (★) diffusely involving the entire myometrium with loss of normal zonal anatomy in a grossly enlarged uterus. (B, C) Coronal and axial T2W magnetic resonance (MR) images of the abdomen and chest show primary uterine lesion (★) and multiple lung metastases (arrows). (D, E) T1W sagittal and T2W axial MR images of the brain show hemorrhagic metastases that are hyperintense on T1 and hypointense on T2 sequences with perilesional edema (arrows).
myometrium and adjacent organs; however, it should be avoided or performed with caution in patients with suspected vaginal metastasis due to the risk of severe bleeding.\textsuperscript{22}

CT is more sensitive than radiographs in detecting lung metastases, as 30 to 40\% of micro-metastases can be missed on radiographs.\textsuperscript{23} Pulmonary lesions are usually seen as well-defined rounded nodules and multiple nodules may exhibit a “cannonball” appearance, which is typical of hematogenous dissemination. Hemorrhagic pulmonary lesions appear as ill-defined nodules with adjacent ground-glass opacities (\textsuperscript{Fig. 6}). Metastatic lymphangitic carcinomatosis is uncommon in choriocarcinomas as the spread is predominantly hematogenous rather than lymphatic, and may occur late in the course of disease due to obstruction of lymphatics (\textsuperscript{Fig. 7}).

Less common imaging features in the chest include pulmonary vascular thrombi, pulmonary infarction, pulmonary hemorrhage, pleural effusions, and segmental/lobar collapse secondary to obstructing endobronchial lesions.\textsuperscript{3,23} Though chest CT is superior in diagnosing and characterizing lung lesions, counting of metastases for FIGO risk scoring is performed only on chest radiographs, as studies indicate that it does not alter the final outcome.\textsuperscript{3} The consensus statement of the EOTTD strongly recommends additional imaging (CECT of the abdomen and CE MRI of the brain) in the presence of lung lesions to rule out hepatic and brain metastases.\textsuperscript{22,24}

Metastases to liver appear as well-defined hyperechoic nodules on US, hyperdense nodules on CT, and T2 hyperintense nodules on MRI (\textsuperscript{Fig. 8}). They exhibit intense post-contrast enhancement due to their hypervascular nature and can occasionally undergo hemorrhagic transformation.

Brain metastases are seen in 8 to 15\% of patients with metastatic choriocarcinoma. They can be seen as solitary or multiple nodular lesions with adjacent edema at the gray–white matter junction, are often hemorrhagic, and exhibit avid contrast enhancement.\textsuperscript{14,24} MRI is more sensitive than CT for the evaluation of brain metastases, and patients with brain metastases are automatically assigned a high-risk disease status, regardless of score, as they augur worse prognosis.\textsuperscript{3,25}

Metastases to regional lymph nodes are relatively uncommon in choriocarcinomas and are seen only in approximately 0.5\% of patients. Evidence of any lymph nodal metastasis automatically upstages the disease to metastatic “M1b” stage.\textsuperscript{3}

\textbf{Fig. 6} Stage III choriocarcinoma with lung metastases. (A) Coronal reformatted contrast-enhanced computed tomography (CECT) image of the abdomen and pelvis reveals large heterogeneous hypodense lesion in an enlarged uterus (\textsuperscript{*}) with a metastatic lung nodule (arrow). (B) Axial CT of the chest in the lung window shows multiple nodules (“cannon ball” metastases). (C) Two weeks later, the patient developed acute breathlessness due to pulmonary hemorrhage and radiograph of the chest shows multiple nodules of varying sizes (arrows) with adjacent opacities.
Differential Diagnosis

Uterine lesions in patients of childbearing age can mimic choriocarcinomas, but normal hCG levels are useful in excluding GTD. Choriocarcinomas have to be differentiated from an invasive hydatidiform mole and PSTT, as both of them show elevated hCG (Fig. 9). Though extremely rare, nongestational choriocarcinomas of ovarian germ cell origin may be mistaken for gestational choriocarcinomas in patients with elevated βhCG. Gestational choriocarcinomas arise from placental tissue, may exhibit paternal chromosomes, and show good response to first-line chemotherapeutic drug methotrexate. However, nongestational choriocarcinomas arise from gonads or pluripotent germ cells, have maternal deoxyribonucleic acid (DNA), and are mostly methotrexate resistant, needing multidrug primary therapy such as vincristine, actinomycin D, and cyclophosphamide that are used typically for managing germ

![Image](https://example.com/fig7.jpg)

Fig. 7 Choriocarcinoma with metastatic lymphangitis carcinomatosis in 28-year-old woman. (A) Radiograph of the chest shows irregular reticulonodular opacities in both lungs. (B, C) Axial contrast-enhanced computed tomography (CECT) and fusion positron emission tomography (PET)/computed tomography (CT) images of the pelvis show the residual malignancy in the uterus as a hypoattenuating lesion with peripheral hypermetabolic areas.

![Image](https://example.com/fig8.jpg)

Fig. 8 Stage IV choriocarcinoma in a 26-year-old woman with liver metastases. (A) Split screen grayscale and color Doppler ultrasound of the pelvis shows heterogeneously hyperechoic lesion with internal vascularity in an enlarged uterus. (B) Grayscale ultrasound image shows multiple well-defined hyperechoic vascular liver metastases.

![Image](https://example.com/fig9.jpg)

Fig. 9 Choriocarcinoma and its mimics in patients of childbearing age. Sagittal contrast-enhanced computed tomography (CECT) images showing enlarged uterus with heterogeneously enhancing lesions. (A) Choriocarcinoma. (B) Invasive mole. (C) Uterine fibroid with sarcomatous changes. (D) Carcinoma cervix invading the uterus. (E) Uterine leiomyosarcoma.
cell tumors. It is imperative to distinguish between these two entities, as they significantly differ in management and prognosis.

Complications of Choriocarcinoma

The commonest complication of choriocarcinoma is hemorrhage, either from the primary in the uterus or from metastases. Life-threatening uterine hemorrhage may occur in patients with choriocarcinomas due to direct vascular invasion or uterine perforation and approximately 2% of patients with uterine AVMs may also develop fatal hemorrhage. Asymptomatic vascular malformations can be monitored noninvasively by Doppler US or CECT/MRI. They can undergo spontaneous regression, but rare symptomatic cases presenting with uncontrolled bleeding require uterine artery embolization or hysterectomy. Touhami et al in a systematic review on the management of AVMs in GTNs have observed that uterine artery embolization was successful only in 85% of cases, whereas hysterectomy, uterine artery ligation, and laparoscopic resection of uterine AVM were successful in 100% of cases. In patients presenting with active bleeding from metastatic sites involving the vagina, lungs, liver, and brain, catheterization with selective angiographic embolization can be performed.

Management and Follow-Up

Hysterectomy is the treatment of choice in patients with disease confined to the uterus, though it does not obviate the need for chemotherapy. Chemotherapy with preservation of uterus is advised in reproductive aged patients wishing to retain fertility. Based on risk stratification, patients with low-risk disease are usually treated with single-agent chemotherapy, methotrexate being the first-line drug. Patients with high-risk disease and those refractory to the single drug methotrexate therapy require multidrug combination therapy using methotrexate, actinomycin D, etoposide, cyclophosphamide, and vincristine. Metastasectomy is considered in patients with persistent oligometastatic disease and those with large volume of tumor burden. Thoracotomy with wedge resection of pulmonary lesions is indicated in isolated persistent lung metastases that are refractory to treatment. Whole brain radiotherapy may be indicated in patients with high-risk disease and brain metastases.

Serial monitoring of βhCG is advised for the assessment of treatment response as decrease in the serum βhCG level precedes radiographic tumor regression. Asymptomatic residual lesions found on imaging does not need treatment in patients with normal βhCG, because changes on imaging lag behind the clinical and biochemical response. Posttreatment changes on US include decrease in uterine size, vascularity, anechoic cystic spaces, and myometrial invasion. Similar reduction in uterine volume, vascularity, and myometrial heterogeneity is also noted on MRI, but restoration of normal zonal anatomy may take 6 to 9 months after normalization of the βhCG levels. The approach to the diagnosis and management in suspected cases of choriocarcinoma is summarized in Fig. 11.

In approximately 12.5% of patients with high-risk choriocarcinomas, recurrence may be seen. Patients with high volume of tumor burden at initial presentation and those with inadequate initial therapy are at increased risk of recurrence. Post successful remission, the risk of recurrence reduces with time and is around 1% after 1 year.

The overall survival for choriocarcinoma at the present time approaches 100% with cure rates of 100% for low-risk groups and 80 to 90% for high-risk groups even in the presence of metastatic disease or resistance to first- or second-line chemotherapies. Salvage therapy with surgical resection of resistant foci of disease and platinum-based drug regimens are found to improve the long-term survival in patients with advanced and refractory disease. Death is exceptional and usually occurs secondary to hemorrhagic complications or pulmonary insufficiency.
Conclusion

Choriocarcinoma is a rare GTD associated with fatal outcomes in patients with delayed diagnosis and inadequate management. Lung lesions antecede all other distant metastases in the evolution and progression of metastatic choriocarcinoma; hence, CECT of the chest should be recommended in all high-risk patients, as early detection of distant metastases makes significant difference in the survival rates. US with color Doppler, CT, and MRI complement each other, and more than one study is recommended simultaneously during the evaluation, staging, and surveillance of choriocarcinoma.

Ethical Approval
The study was approved by the Institutional Ethics Committee, Basavatarakam Indo American Cancer Hospital & Research Institute (Reference No: IEC/2022/160).

Author Contributions
A.M. and V.K. researched the literature and conceived the study. A.M. wrote the first draft of the manuscript. All the authors reviewed and edited the manuscript and approved the final version of the manuscript.

Funding
None.

Conflict of Interest
None declared.

References


