Optimal Treatment in Gestational Trophoblastic Disease

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Abstract

Gestational trophoblastic diseases are a heterogenous group of conditions ranging from the benign hydatidiform mole to the malignant choriocarcinoma. Optimal therapy in this group of diseases rest in the correct diagnosis, assessing their risk for malignant behavior using prognostic scoring systems and administering appropriate treatment. Their rarity makes it imperative that these patients are treated in special centres by experts. Benign moles are treated surgically with evacuation of the uterus or hysterectomy. In malignant gestational trophoblastic disease, chemotherapy is the treatment of choice; single agent for non-metastatic and low-risk metastatic disease and combination chemotherapy for high-risk metastatic disease. Judicious use of surgery and radiotherapy in these cases will improve the survival rate. With appropriate treatment, the cure rates approach 100% in the low-risk group and 80% to 85% in the high risk group.

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Introduction

Gestational trophoblastic diseases (GTD) encompass a spectrum of interrelated conditions:

- Hydatidiform mole (HM)
- Invasive mole (IM)
- Choriocarcinoma (CC)
- Placental site trophoblastic tumour (PSTT)

Hydatidiform mole, is essentially a benign condition, but the others can lead to a fatal outcome. Over the last four decades, GTD has developed from one of the most fatal malignancies to one of the most curable, with the advent of effective chemotherapy. Besides chemotherapy, other factors have played a key role in the good prognosis for this disease. These include the development of a very sensitive tumour marker, human chorionic gonadotropin (HCG), for diagnosis and assessment of treatment response; identification of prognostic factors that have been put into a scoring system to individualize treatment; and finally the judicious use of surgery and radiotherapy in addition to chemotherapy for selected patients.

Optimal therapy in GTD requires individualization of treatment based on the pathology of the tumour, sites of metastases and other risk factors. It requires a multimodality approach.

Hydatidiform Mole (HM)

There are two pathological varieties of HM. These are the complete hydatidiform mole (CHM) and the partial hydatidiform mole (PHM). Unlike CHM, the diagnosis of PHM is often made only after evacuation of the uterus when they present as spontaneous abortion or missed abortion. The risk of malignant sequelae is much higher with CHM (15% to 20% compared to less than 5% in PHM). However, their general management is very similar and should be considered clinically in the same category.

After diagnosis of molar pregnancy, the preoperative preparation includes a metastatic screen and stabilization of any associated medical conditions. This involves complete physical examination, chest X-ray, baseline serum HCG, full blood count, and renal and liver function tests. Any anaemia or hypertension should be controlled.

The choice of treatment of molar pregnancy is suction evacuation, followed by sharp curettage. Suction evacuation can be performed for uterus of any size. The suction is performed with an intravenous infusion of oxytocin (30 units at 30 dpm) which is maintained for about an hour after the procedure. Evacuating large uteri can be complicated by the onset of acute respiratory distress syndrome, believed to be due to release of molar tissue into the circulation. Immediate ventilatory supportive therapy can be life saving in this situation.

Hysterectomy with the mole *in situ* is the treatment of choice for older women (40 years and above) especially if the patient wants to be sterilized.[1] The ovaries need not be removed even though theca lutein cysts are present. There is also some evidence that hysterectomy may

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decrease the risk of post molar malignant sequelae. Bahar and colleagues[2] found it to be 10% in those with hysterectomy as compared to 33% in those without. In a much larger series, the risk of malignant sequelae decreased to 3.5% after evacuation with hysterectomy compared to the 20% anticipated with evacuation with a D&C.[3] However it should be emphasized that hysterectomy does not negate the necessity for close follow up with HCG monitoring after evacuation of the mole.

Other methods of evacuation of the mole with induction of labour with oxytocin or prostaglandin or hysterotomy have been abandoned in most centres. The former method poses a risk of dissemination of the trophoblasts whilst the latter may increase the risk of malignant sequelae as shown by Tow in Singapore.[4]

Special situations

a. *Hydatidiform mole with coexistent fetus*: true twin pregnancy with one viable fetus and another mole is a rare condition. Partial moles or placental haematomas are some times mistaken for this condition. Due to its rarity any recommendation on management is mainly anecdotal. In the biggest series published so far from a single institution, Stellar and colleagues[5] have found that these patients have a higher risk of complications such as pregnancy-induced hypertension and bleeding during pregnancy. They also run the risk of having malignant sequelae requiring chemotherapy. However, a significant proportion did deliver a viable fetus. Thus their recommendation is that while termination of the pregnancy is the preferred option, informed patients desirous of a child may be allowed to progress under close supervision.
b. *Recurrent mole*: The risk of recurrent molar pregnancy is estimated to be between 1% and 2% but it increases dramatically after the second or third molar pregnancy. In a large review of the Sheffield Supraregional Trophoblastic Screening Service, Sharma et al[6] found that 32 out of 4183 patients (0.77%) developed a second molar pregnancy. However, they shared many of the risk factors of the first molar pregnancy. Very recently, a unique strategy has been proposed to prevent recurrence of repeated molar pregnancies.[7] This involves intracytoplasmic sperm injection (ICSI), coupled with preimplantation genetic diagnosis with fluorescence *in situ* hybridization (FISH). In this approach, complete moles that arise from dispermic fertilization are avoided by using ICSI. ICSI is followed by preimplantation selection and discarding of 46,XX embryos. Triploid partial moles are also avoided by confirmation of the diploid status of the embryo by FISH.
c. *Prophylactic chemotherapy*: The use of prophylactic chemotherapy to prevent occurrence of malignant sequelae has been very controversial. Two questions remain unresolved. Should prophylaxis be given to all benign moles after evacuation or only to the high-risk patients? It is known that about 15% to 20% of patients will develop gestational trophoblastic tumour (GTT, see below) following the evacuation of a molar pregnancy. Some high risk factors have been identified which predisposes the patient for developing GTT. These include very high initial HCG values (>1 000 000 miu / ml), uterus larger than 20 weeks, development of pulmonary complications during evacuation, eclampsia, and uterine subinvolution with haemorrhage. In a large study published in 1971, Ratnam et al[8] showed that while prophylactic methotrexate resulted in a non-significant decrease in the incidence of choriocarcinoma following molar evacuation, there was significant drug toxicity with one death. It should be noted that this study used oral methotrexate without folinic acid rescue. Parenteral methotrexate with folinic acid rescue produces very little toxicity. However, more recently, others have found that prophylactic chemotherapy in high risk moles caused a significant decrease in the incidence of post molar GTD but did not eliminate it.[9] Since all post molar GTD can be diagnosed early on regular HCG monitoring, it appears that prophylactic chemotherapy may be most suitable for patients who are unable to come for followup after evacuation of a mole (especially if they are "high-risk") or in places where universal, sensitive HCG monitoring is not available.

Post Mole Surveillance

Serial monitoring of serum HCG is the best way to detect malignant sequelae early. Routine chest X-ray at every visit is not warranted unless the HCG value rises. Usually, the author recommends weekly serum beta HCG monitoring until the levels become negative and then monthly for 6 months. It is very rare for malignant GTD to occur after 6 months of normal HCG levels. In most patients, the HCG levels become negative within 8 to 12 weeks after evacuation of the mole. If the values remain persistently high or plateau for more than 3 weeks, then the patient is considered to have malignant gestational trophoblastic disease. In the absence of vaginal bleeding, routine re-curettage of the uterus need not be performed. If there is vaginal bleeding, transvaginal ultrasonography is very useful to diagnose either residual molar tissue in the uterine cavity or presence of myometrial nodules (see below).

Malignant GTD

This term includes three main types of diseases: invasive mole (IM), choriocarcinoma (CC) and gestational trophoblastic tumour (GTT). The first two are histological diagnoses. Patients should be labelled as having

these disease entities only if histological proof is available. However, these diagnoses are difficult to make either because a hysterectomy is needed to confirm tissue diagnosis or the disease is at inaccessible sites for biopsy. In fact, in most cases, the diagnosis of malignant GTD is made on the basis of raised serum HCG values with or without radiological evidence. This group of patients is classified as having GTT. The clinical management of all these entities are almost the same with chemotherapy as the first line treatment. For the purpose of this review they will be discussed together and differences for certain situations will be highlighted. Another very rare entity, placental site trophoblastic tumour (PSTT), which can behave either in a benign or malignant fashion, will be discussed separately.

Majority of cases of malignant GTD follow molar pregnancies. However, it is important to realize that gestational choriocarcinoma can be derived from normal term pregnancies, spontaneous abortions and ectopic pregnancies. Malignant GTD following non-molar gestation may present with non gynaecological symptoms like haemoptysis or stroke depending on the site of the disease. Often a high index of suspicion is needed to make the diagnosis. Any woman in the reproductive age group presenting with unusual symptoms or metastatic disease without a known primary must be suspected of having GTD. A simple serum HCG may be all that is needed to clinch the diagnosis.

Optimal therapy in malignant GTD depends on proper classification of the patient according to the prognosis. Failure to do this may result in inappropriate treatment with high risk of failure. Three main systems are used for classifying patients: a clinical classification (Table I) used mainly in the USA, the World Health Organization (WHO) prognostic scoring system (or its modifications) (Table II) and the International Federation of Gynecology and Obstetrics (FIGO) staging system (Table III). The author's own preference is for the clinical classification, as it is simpler. Soper et al[10] in a retrospective analysis evaluated the clinical prognostic factors in 455 patients according to the three classification systems. They found all three systems equally efficient in identifying low risk patients but the clinical classification of poor prognostic metastatic disease had the highest sensitivity for including patients that failed therapy.

Briefly, patients with non-metastatic disease and good prognosis metastatic disease have very favourable outcomes with single agent chemotherapy, whereas, those

TABLE I: PROGNOSTIC GROUP CLINICAL CLASSIFICATION: NIH CLASSIFICATION OF GESTATIONAL TROPHOBLASTIC DISEASE

I. Non-metastatic GTD: no evidence of disease outside uterus

II. Metastatic GTD
   A. Low-risk group
      1. short duration (last pregnancy <4 months)
      2. low pretreatment HCG titre (<100 000 IU/24 h urine or <40 000 mIU/ml serum)
      3. no metastasis in brain or liver
      4. no prior chemotherapy
      5. antecedent pregnant event is not a term delivery (mole, ectopic pregnancy, spontaneous abortion)
   B. High-risk group
      1. long duration (last pregnancy >4 months)
      2. high pretreatment HCG titre (>100 000 IU/24 h urine or >40 000 mIU/ml serum)
      3. brain or liver metastases
      4. significant, unsuccessful chemotherapy
      5. term pregnancy

NIH: National Institute of Health
GTD: gestational trophoblastic disease
HCG: human chorionic gonadotrophin

TABLE II: WORLD HEALTH ORGANIZATION PROGNOSTIC INDEX SCORE FOR GESTATIONAL TROPHOBLASTIC DISEASE

Risk factor	0	1	2	4
Age	≤39	>39		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	
Interval[a]	<4	4 to 6	7 to 12	>12
Human chorionic gonadotrophin (HCG) (IU/L)[b]	$<10^3$	-10^4	-10^5	$>10^5$
ABO blood groups		O x A	AB	B
(female x male)		A x O		
Largest tumour mass, including uterine (cm)		3-5	>5	
Site of metastases		Spleen	GI tract	Brain
Number of metastases		1-4	5-8	>8
Prior chemotherapy			Single drug	Two or more

[a] Interval = time (months) between end of antecedent pregnancy and start of chemotherapy
[b] Immediate pre-therapy plasma HCG level

Risk groups:
≤4 low-risk group
5 to 7 middle-risk group
≥8 high-risk group

with poor prognostic metastatic disease should be treated with multi-agent chemotherapy.

Chemotherapy in Non-metastatic GTD

The treatment of choice for non-metastatic GTD is single agent chemotherapy. The limited role of surgery in this situation will be discussed later. The drugs of choice for single agent therapy have been methotrexate (MTX) and actinomycin-D (ACT-D). Several protocols are used (Table IV), all producing 100% remission rates. The choice of protocol in any centre is mainly one of familiarity. An optimal regimen should maximize response rate while minimizing morbidity. ACT-D is the appropriate drug for patients with compromised liver and renal functions. Patients who fail to respond to one single agent are switched to the other single agent. Patients who develop resistance to both drugs are then changed to combination chemotherapy used for "poor-prognosis" patients.

Most of these regimes are given over 5 days with courses being repeated every 12 to 14 days until the HCG levels return to normal and usually a further two courses are given. Two unique regimes evaluated by the Gynecologic Oncology Group (GOG) in USA need serious consideration. These are the weekly MTX and the fortnightly ACT-D protocols. These single dose protocols were developed in the search for more efficient, less expensive and yet, safe treatments. In fact the GOG considers the fortnightly ACT-D as its regimen of choice for non-metastatic and "good prognosis" metastatic GTD.[11] However, some authors have expressed reservation about the use of this regime for GTD arising after non molar gestations.[1] The author uses weekly MTX as his first choice.

About 85% of patients achieve cure with the initial chemotherapy. The remaining patients obtain complete cure with additional chemotherapy or surgery in selected cases.

TABLE III: INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS (FIGO) STAGING FOR GTD

Stage I	Strictly confined to uterine corpus
Stage II	Extends outside the uterus, but limited to genital structures
Stage III	Extends to the lungs with or without genital tract involvement
Stage IV	All other metastatic sites

Substages assigned to each stage as follows:
A: no risk factor present
B: one risk factor
C: two risk factors

Risk factors used to assign substages:
1. pre-therapy serum HCG >100 000 mIU/ml
2. duration of disease >6 months

GTD: gestational trophoblastic disease
HCG: human chorionic gonadotrophin

Surgery in Non-metastatic GTD

Before the introduction of effective chemotherapy, surgery was the only viable option for treatment in this condition. Nowadays, surgery is used under the following conditions: a) if the patient requests for sterilization, a hysterectomy may be performed and this alone may be curative in many cases of invasive moles; besides, it may reduce the amount of chemotherapy that need to be given; b) if the disease is resistant to single agent chemotherapy, a hysterectomy may help to avoid change to the more toxic combination chemotherapy regimes.

In many cases of non-metastatic GTD, the uterine lesion, be it invasive mole or choriocarcinoma, is often a localized nodule. The diagnosis can be quite easily made with transvaginal, high resolution, ultrasonography. The addition of colour flow Doppler increases the sensitivity. In such cases, where the patient is young and wants to maintain her reproductive function, resection of the nodules alone combined with single agent chemotherapy is curative.[12]

Management of Low-risk/Good-Prognosis Metastatic GTD

This is very similar to that of non-metastatic GTD. The response to single agent chemotherapy is similar and patients who fail initial therapy with one agent can be salvaged with the alternative single agent or combination chemotherapy. The indications for hysterectomy are the same as above.

Management of High-risk/Poor-Prognosis Metastatic GTD

Multiagent chemotherapy is the treatment of choice in this group. Several drug combinations have been tried but currently the most widely used combination is the so-called EMA-CO regime (Table V). This regime, a modification of the older and more complicated Bagshawe's CHAMOCA regime, contains the three most effective drugs against trophoblasts, namely, methotrexate, actinomycin-D and etoposide. The remission rates for this regime, in previously untreated patients, are in the region of 80% to 85%. The higher rates are often achieved by adjuvant therapy including surgery and radiotherapy. In the largest series reported, using this regime, Bower et al[13] published their results of 272 consecutive patients with high risk GTD, treated with

TABLE IV: CHEMOTHERAPY PROTOCOLS FOR NON-METASTATIC AND LOW-RISK METASTATIC GTD

1. Methotrexate 0.4 mg/kg i.v. or i.m. every day x 5 days; repeat every 12 to 14 days (7 to 9 days window)
2. Methotrexate 1 mg/kg i.m. on days 1, 3, 5, 7; folinic acid 0.1 mg/kg i.m. on days 2, 4, 6, 8; repeat every 15 to 18 days (7 to 10 days window)
3. Methotrexate 40 mg/m^2 i.m. weekly
4. Actinomycin D 10 to 13 ug/kg i.v. every day x 5 days; repeat every 12 to 14 days (7 to 9 days window)
5. Actinomycin D 1.25 mg/m^2 i.v. every 14 days

TABLE V: COMBINATION CHEMOTHERAPY PROTOCOL FOR HIGH-RISK GESTATIONAL TROPHOBLASTIC DISEASE

EMA-CO regime		
Course 1: EMA		
Day 1	Etoposide (VP-16)	100 mg/m^2 i.v. infusion in 250 ml saline over 30 minutes
	Actinomycin D	0.5 mg i.v. push
	Methotrexate	100 mg/m^2 i.v. push 200 mg/m^2 i.v. infusion over 12 hours
Day 2	Etoposide	100 mg/m^2 i.v. infusion in 250 ml saline over 30 minutes
	Actinomycin D	0.5 mg i.v. push
	Folinic acid	15 mg i.m. every 12 hours, 4 doses beginning 24 hours after starting methotrexate
Course 2: CO		
Day 8	Cyclophosphamide	600 mg/m^2 i.v. in saline
	Vincristine	1.0 mg/m^2 i.v. push

EMA-CO. The cumulative 5-year survival rate is 86.2%. No deaths from GTD occurred later than 2 years after the start of EMA-CO. Significant adverse prognostic factors included, the presence of liver metastases, brain metastases, antecedent term pregnancy and a prolonged interval from antecedent pregnancy at time of diagnosis. A total of 213 patients (78%) achieved complete remission while 47 patients (17%) developed drug resistance to EMA-CO. Of these, cisplatin-based therapy and surgery salvaged 33 patients (70%). Eleven patients (4%) died early during therapy. Of much significance was the finding of second malignancy developing in patients treated with EMA-CO. Two developed acute myeloid leukaemia, two developed cervical cancer and one developed gastric adenocarcinoma. The offending agent seems to be etoposide, especially in relation to developing leukaemia.[14]

Salvage therapy for patients who failed EMA-CO has not been very successful, but various other drugs have been used, including, cisplatin, ifosfamide and paclitaxel in combination with the usual drugs.

The impact of long-term chemotherapy on fertility and fetal malformations has been a major concern. Several studies have been reassuring. In the longest follow up published from a single centre, Song et al[15] reported on the outcome of 265 patients given chemotherapy between 1959 through 1980. By the end of 1985, 205 patients had become pregnant, with a total of 355 pregnancies. The rates of fetal wastage, malformations, twin pregnancies, and neonatal and infant deaths did not deviate from normal. Cytogenetic study of the peripheral lymphocytes of 94 children revealed no increase of chromosomal aberrations. Berkowitz et al[16] summarized the post-chemotherapy fertility from five different centres; 77.5% of the patients had live births and only 2% had fetal abnormalities.

Special situations

a. Central nervous system (CNS) metastases

The presence of CNS metastases has always been considered as a very high risk factor in all classification systems. However, its treatment is still subject to some controversy. Firstly, there is some doubt as to whether prophylactic treatment to prevent cerebral metastases is important. While most centres do not practice it, the Charing Cross group from London, gives intrathecal methotrexate to all patients with multiple pulmonary metastases.[17] Secondly, the role of adjuvant whole brain radiation appears uncertain. Many centres give elective whole brain irradiation of about 3000 rads in 10 fractions combined with systemic chemotherapy.[18] But, the Charing Cross group again differs by giving only systemic chemotherapy together with intrathecal methotrexate. It is well known that chemotherapy can cause cerebral haemorrhage because of necrosis of these highly vascular tumours. Since irradiation is thought to be haemostatic and tumoricidal, the combination of these two modalities may be the therapy of choice. The role of surgery in CNS metastases will be discussed below.

b. Hepatic metastases

Primary involvement of the liver by metastases carries a poor prognosis with survival rates of 40% to 50%. It is dismal if they occur during chemotherapy. The optimal therapy is not established. While combination chemotherapy is often used, adjuvant radiation has been used by some.[19] These vascular lesions can bleed profusely and selective hepatic embolization has been used to control haemorrhage.[20]

c. Vaginal metastases

These classically appear in the anterior vaginal wall below the urethral opening. The metastases may result from invasive mole or choriocarcinoma. They are highly vascular and often the nodule is the "tip of the iceberg" with a large underlying vascular lesion. Chemotherapy is the treatment of choice. In resistant cases where surgery is contemplated, the author recommends selective embolization of the main vascular supply before attempting removal.

Surgery in High-risk Metastatic GTD

The role of surgery in metastatic GTD lies mainly in the control of complications that result from the disease or chemotherapy such as haemorrhage or infection. However, judicious use of surgery, in extirpating the sites of disease, can not only be life saving but may also reduce the amount of chemotherapy given and decrease the chance of drug resistance.

Surgical excision of a solitary pulmonary nodule, not

responding to chemotherapy, is the classical example of the main role of surgery in metastatic GTD. Thoracotomy is the most commonly performed surgical procedure, next to hysterectomy, in GTD. Timely intervention by thoracotomy in resistant pulmonary metastatic nodules can salvage most patients as shown in this author's experience (Table VI).[21] Two points need emphasis before embarking on thoracotomies. Firstly, diagnosis of solitary nodule should not be made on a plain chest X-ray alone, but only after a CT scan of the thorax, as the former can miss multiple micrometastases. Secondly, in the presence of a satisfactory HCG regression, the decision to intervene surgically should not be based on radiographic tumour regression alone as this may lag far behind the HCG response. The following criteria have been shown to be good predictors of successful outcome after pulmonary resection: the patient is a good surgical candidate; the primary uterine malignancy must be controlled; there must be no other evidence of systemic metastases; radiographic evidence of a solitary pulmonary lesion; and persistent HCG level must be less than 1000 mIU / ml despite prolonged chemotherapy.[22]

TABLE VI: CLINICAL FEATURES IN 13 PATIENTS WITH THORACOTOMY IN GESTATIONAL TROPHOBLASTIC DISEASE

Number of patients	13
Lung metastases alone	7
Associated lesions	
Uterus	3
Others	3
Interval between diagnosis and surgery (months)	
2 to 4	8
5 to 7	3
9	2
Histology of lung metastases	
Choriocarcinoma	7
Undetermined	6
Second thoracotomy	1
Two-year survival status	
Alive	11
Dead	2*

* cause of death: cerebral haemorrhage
(Table adapted from reference 21)

Solitary cerebral metastases are best treated surgically before starting chemotherapy as these may haemorrhage with the initiation of chemotherapy. For this reason, it is suggested that surgery be considered at the outset if the metastasis is isolated, superficial and if surgery is not going to induce major neurologic deficit.[17]

Follow Up of Malignant GTD

This forms an integral part in the optimal management of GTD. The earlier the malignant transformation or recurrence is detected the better the prognosis. Besides clinical examination, all patients should have weekly HCG estimation until the levels return to normal. Thereafter, HCG estimation is done at monthly intervals. In low-risk disease, this is carried on for a year. In high-risk patients, this should be performed for at least 2 years. During this period of monitoring, it is important to prescribe effective contraception, as a rise in HCG from a pregnancy will confuse the situation.

Recurrent Disease

This is defined as re-elevation of normalized HCG values or the appearance of new metastases after primary remission. It is estimated to occur in about 5% of low-risk GTD and in about 20% of high-risk GTD. Majority of recurrences occur within the first year of follow up.

Salvage therapy in recurrent disease depends on the type of previous chemotherapy and patient's fitness. There is no role for single agent chemotherapy in these situations. Combination chemotherapy with agents like PVB (cisplatin, vinblastine, bleomycin)[23] and ICE (ifosfamide, carboplatin, etoposide)[24] have been used. The prognosis depends on the interval for recurrence and the site(s) of recurrence.

Placental Site Trophoblastic Tumour (PSTT)

First described in 1976 as "trophoblastic pseudotumor", PSTT is a very rare neoplasm of the intermediate trophoblast. Less than 100 cases have been reported in the literature. It may occur after any gestation, but the antecedent pregnancy may be remote. The behaviour of the tumour is unpredictable. In some cases it behaves in a benign fashion whereas in others, it can be very malignant with wide spread metastases. These tumours secrete varying amounts of HCG and the level of the hormone does not correlate with the tumour volume or its prognosis. The intermediate cells produce mainly human placental lactogen (HPL) but it does not appear to be a useful tumour marker. The diagnosis is often made after a dilatation and curettage.

The optimal therapy in these patients is not clear. While curettage seems to be curative in some patients, most authors currently recommend a total hysterectomy in non metatstatic disease. For metastatic disease, there is currently no effective chemotherapy as these cells seem to be less responsive to drugs.

Conclusion

The optimal management of gestational trophoblastic disease depends on prompt diagnosis, correct stratification of the risk category and appropriate treatment using various modalities such as chemotherapy and surgery. As it is an uncommon disease, it is best that all patients

be referred to experts in referral centres familiar with their management. It is this expertise that has converted an almost uniformly fatal disease into a very curable one.

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