

Placental Site Trophoblastic Tumor: Molecular Analysis and Clinical Experience

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ABSTRACT

Placental site trophoblastic tumor is a very rare variant of gestational trophoblastic disease which differs histologically and immunocytochemically from gestational choriocarcinoma. The English language literature includes only 74 reported cases. Seventeen patients have been managed at Charing Cross Hospital with this diagnosis. The median follow-up is 4.6 years, and the 5-year overall survival is 80% (95% confidence interval, 55-93%). Multivariate regression analysis identified an interval of >2 years since the preceding pregnancy as an independent adverse prognostic factor.

Genotypic analysis by PCR allelotyping has confirmed the gestational origin of all 11 tumors successfully studied. More detailed molecular analysis has identified the causative pregnancy for eight tumors. Five were diploid biparental tumors following term pregnancies, and three were androgenetic tumors following monospermic complete hydatidiform moles.

INTRODUCTION

PSTT,² a name proposed less than 20 years ago (1) for a rare variant of gestational trophoblastic disease, is composed of cells resembling intermediate trophoblasts of the placental bed. It consists of a monomorphic population of nonvillous trophoblast-like cells which invade surrounding tissues. The trophoblasts have dense eosinophilic cytoplasm and pleomorphic nuclei and can be mononuclear or multinucleated which form clusters or cords. PSTT produces masses in which necrosis is marked but hemorrhage is less conspicuous in contrast to CC where hemorrhage is prominent. This difference may reflect the reduced tendency for vascular invasion in PSTT where infiltration is chiefly by interstitial invasion. In addition, PSTT differs from CC immunocytochemically because more of the tumor cells express hPL than hCG. This is consistent with the presumed intermediate trophoblastic origin of PSTT, which is a monomorphic tumor, rather than the biphasic cytotrophoblastic

and syncytiotrophoblastic pattern of CC. The less prominent and more variable synthesis of hCG by PSTT makes the serum hCG level a less reliable tumor marker. Furthermore, the natural history of the disease appears to differ from CC in that there is a lower propensity to metastasize, greater lymphatic spread, and variable chemoresistance. For this reason surgery plays a major role in the management of PSTT. A recent review identified 74 cases described in the English language literature. This report covers 17 patients treated at a single institution and adds 10 new cases to the literature (2).

MATERIALS AND METHODS

Between 1975 and 1995, 1351 patients with gestational trophoblastic disease were treated at the Charing Cross Trophoblastic Unit. This includes 17 patients with PSTT. In addition, two PSTT patients, initially diagnosed and treated elsewhere, were referred to Charing Cross at relapse and are excluded from further analysis. The pathological specimens from the patients were reviewed histologically and immunostained for hPL and hCG expression. Since 1989 commercial rabbit primary polyclonal antibodies to hCG and hPL (DAKO Ltd.) have been used for immunostaining but older specimens were stained with polyclonal antisera prepared locally. The medical records of the 17 patients diagnosed and managed at Charing Cross were reviewed for clinical features, extent of disease, WHO prognostic score at presentation (Table 1; Ref. 3), disease management, and outcome including time of last follow-up.

Paired tumor tissue and peripheral blood were available from 13 patients for genotype analysis. Where possible, genetic diagnosis was carried out on DNA prepared from blood samples from the patient, her partner, and from pathological blocks of tissue. Using the PCR, DNA was amplified, as previously described (4), with up to 11 pairs of primers which flank short tandem repeat sequences on different chromosomes. One of each pair of primers was labeled with a blue (FAM), green (HEX), or yellow (TAMRA) fluorescent dye. Products were then separated by electrophoresis in 6% denaturing polyacrylamide gels using a Model 373A automated fluorescent DNA sequencer (Applied Biosystems Ltd., Cheshire, United Kingdom). Using 672 GeneScan software (Applied Biosystems Ltd.), the sizes of fluorescent bands, and hence the polymorphic DNA sequences, could be automatically determined by comparison to a fluorescent-labeled red (ROX) internal size standard.

The log rank method was used to test for the significance of differences in survival distributions (5). The variables found to be significant were put into a stepwise Cox regression model to establish which were independently prognostic (6).

RESULTS

Clinical Features. The average age of the 17 patients treated at Charing Cross Hospital was 30 years old (range, 19-54; Table 2). The last known antecedent pregnancy was a

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² The abbreviations used are: PSTT, placental site trophoblastic tumor; CC, choriocarcinoma; hPL, human placental lactogen; hCG, human chorionic gonadotrophin; FTND, full-term normal delivery; D&C, uterine dilation and curettage; HPF, high-power field.

Table 1 WHO prognostic scoring index for gestational trophoblastic tumors

	Score			
	0	1	2	6
Age (yr)	<39	>39		
Pregnancy	Mole	Abortion/NK ^a	Term	
Interval (mo)	<4	4-7	7-12	>12
Serum hCG (IU/liter)	10 ³ -10 ⁴	<10 ³	10 ⁴ -10 ⁵	>10 ⁵
Blood groups ABO (F × M)	A × O O × A O × A or NK	B × A or O AB × A or O		
No. of metastases	0	1-4	5-8	>8
Site of metastases	Lung Vagina	Spleen Kidney	Gastrointestinal tract Liver	Brain
Largest mass (cm)	<3	3-5	>5	
No. of prior drugs	0		1	≥2
Total score	Low risk: 0-5 Medium risk: 6-8 High risk: 9+			

^a NK, not known.

Table 2 Clinical features of PSTT patients

Patient (reference)	Survival (yr)	Age (yr)	Interval since pregnant (mo)	Antecedant pregnancy	Serum hCG (IU/liter)	Disease extent outside uterus	WHO score	PSTT known at start	Presenting complaints
1 (11,14)	18.5	20	23	HM ^a	380	Pelvis	10	Yes	Nephrotic syndrome
2 (14)	10.9	32	13	FTND	33	None	11	No	Amenorrhea, hyperprolactinemia, perforated
3 (8)	8.1	28	16	FTND	399	None	13	Yes	PVB
4 (14, 24)	7.9	19	10	HM	634	None	9	No	Amenorrhea, rising hCG post-HM
5 (14)	7.8	30	19	FTND	129	Lung	11	Yes	PVB, perforated uterus
6	6.7	23	40	FTND	20,710	Lung	13	No	PVB
7 (11,14)	5.4 ^b	24	48	FTND	39	None	12	Yes	PVB
8	4.7	54	22	HM	188	None	10	No	PVB, rising hCG post-HM
9 (8,14)	4.6	29	15	HM	41	None	8	No	PVB, rising hCG post-HM
10	4.1	23	15	FTND	36	None	9	Yes	PVB
11	3.2	20	10	MA	816	Lung	11	Yes	PVB, perforated uterus
12 (11,14)	2.7 ^b	39	128	FTND	666	Pelvis	14	Yes	PVB
13	2.4	28	22	FTND	37	None	9	Yes	Amenorrhea
14	2.2	32	5	SB	571	Pelvis	6	Yes	PVB
15	1.8 ^b	41	180	FTND	7538	Lung	17	Yes	PVB, hemoptysis, galactorrhea
16	1.7	25	10	FTND	191	None	6	Yes	PVB
17	0.6 ^b	44	144	FTND	34	Extensive	11	No	PVB, abdominal mass

^a HM, hydatidiform mole; FTND full-term normal delivery; MA, missed abortion; SB, stillbirth; PVB, *per vagina* bleeding.

^b Deceased.

full-term pregnancy (FTND) in 11 (66%) of 17 patients, a hydatidiform mole in 4 (24%) of 17 patients, a missed abortion in 1 (6%) of 17 patients, and a stillbirth in 1 (6%) of 17 patients. The causative pregnancy has been confirmed genetically for all seven tumors with samples available from both parents and for one tumor without a paternal blood sample.

The most common presenting complaint of the 17 patients was menstrual irregularity, which was a presenting complaint in 16 (94%) of 17 patients; the remaining patient presented with nephrotic syndrome. Intermenstrual vaginal bleeding occurred in 13 (76%) of 17 patients, including two patients with rising serum hCG on follow-up after a molar pregnancy and one who also had galactorrhea from hyperprolactinemia and hemoptysis from pulmonary metastases at diagnosis. Three women presented with amenorrhea, including one patient with hyperpro-

lactinemia and one on follow-up after a molar pregnancy. Three women suffered uterine rupture following diagnostic D&C, necessitating emergency hysterectomy.

The histological diagnosis of PSTT had been established before initial treatment in 12 of 17 patients but was not suspected in 5 of 17 patients. The latter five patients included three patients with previous molar pregnancies and rising serum hCG levels, one patient requiring emergency hysterectomy for uterine rupture, and one patient treated initially for presumed metastatic CC.

Sites of Disease. The extent of the disease at presentation was confined to the uterus in eight patients and extended within the pelvis only in another three patients. Pulmonary metastases were the sole site of distant disease in five patients while one patient had extensive disease within the pelvis including inva-

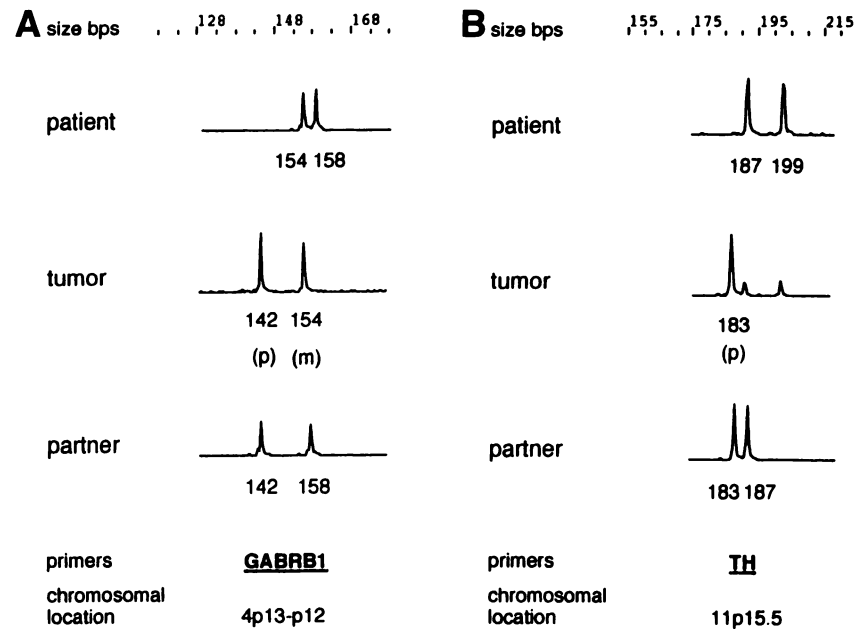


Fig. 1 PCR alleotype analysis of PSTT. **A**, microsatellite polymorphisms detected following PCR amplification with fluorescent-labeled primers for the tetranucleotide repeat GABRB1 (22) in a postterm PSTT with a maternal (*m*) and paternal (*p*) contribution to the genome. **B**, microsatellite polymorphisms detected following PCR amplification with fluorescent-labeled primers for the tetranucleotide repeat TH (23) in a postmole PSTT, which is androgenetic in origin, being homozygous for one of the paternal (*p*) alleles.

sion of local muscle, iliac and para-aortic lymph nodes, pulmonary metastases and supraclavicular lymph node metastases.

Serum hCG Levels. Although all 17 patients had raised serum hCG levels, the median serum hCG at presentation was 191 IU/liter (range, 33–20,710 IU/liter). The serum level of hCG was not of prognostic importance and did not accurately reflect the tumor burden in these patients.

Prognostic Scores at Diagnosis. The risk category for all patients at presentation was calculated according to the WHO trophoblastic disease prognostic scoring (Table 1; Ref. 3). The average prognostic score at presentation was 11 (range, 6–17). Two patients were in the low-risk category (<6), 4 patients in the medium group (6–9), and 11 patients in the high-risk group (>9). The WHO prognostic score at presentation did not correlate with the outcome, and the role of this risk assessment in PSTT is far more limited than in CC.

Histology. The histopathological features of the tumors were reviewed by F. J. P. The median mitotic count per for the specimens was 2.7 (range, 0.6–11.3), and five tumors had >5 mitoses/HPF. Immunocytochemical analysis for hPL and hCG expression was performed for all but one tumor where there was insufficient material. More tumor cells expressed hPL than hCG in 15 (88%) cases, while hCG-positive cells dominated in only 2 (12%) tumors.

Molecular Genetics. Paired tumor and blood samples were available for 13 patients. In addition, paternal samples were available for seven cases (Fig. 1). Two cases without paternal samples yielded inconsistent results which could not be interpreted. In both cases, the tumor blocks were more than 12 years old and had been multiply handled over the years, which could have introduced contamination. The results on the seven patients with paternal samples available included four biparental tumors and three androgenetic posthydatidiform molar tumors. For the latter tumors, at least five informative polymorphisms

for which the paternal DNA is heterozygous were examined. In all three tumors these polymorphisms were homozygous, and the tumors are therefore more likely to be derived from mono-spermic rather than dispermic complete hydatidiform moles. For six cases, no paternal material was available and two of these were uninterpretable. The remaining tumors were all gestational; however, further interpretation was difficult because the tumor samples contained high proportions of reactive maternal cells and no paternal DNA samples were available. Two of these cases containing few contaminating host cells could be identified as heterozygous tumors consistent with a biparental origin. The genotypic analysis has not identified any tumor as deriving from pregnancies other than the antecedent pregnancy ascertained from the history.

Treatment Outcome. One patient with nonmetastatic histologically confirmed PSTT declined a hysterectomy, went into spontaneous remission, and has had two normal subsequent pregnancies (Table 3). All 16 of the remaining patients had a hysterectomy either at diagnosis or subsequently. Two patients had a hysterectomy as the sole treatment (one as an emergency following uterine rupture at D&C) and went into complete remission. Three were treated initially with chemotherapy for gestational trophoblastic disease but subsequently underwent a hysterectomy for the development of drug resistance. Five patients had an initial hysterectomy (two following uterine rupture) followed by chemotherapy. Four were treated for PSTT at presentation with chemotherapy followed by hysterectomy. Two were treated with chemotherapy for metastatic disease at presentation. Three patients received radiotherapy for PSTT: two in a palliative context to sites of drug-resistant disease and one as adjuvant treatment following surgery.

Four patients have died of disease progression. The median follow-up for all 17 patients is 4.6 years, and the 5- and 10-year survival rates are 80% (95% confidence

Table 3 Histological features and treatment of PSTT patients

Patient	Survival (yr)	Mitoses/HPF	hPL > hCG + vecells	Treatment	Response
1	18.5	1.3	Yes	Ac ^a /CO Hysterectomy and LSO	NC CR
2	10.9	1.4	Yes	Hysterectomy	CR
3	8.1	2.1	Yes	Hysterectomy and iliac lymphadenectomy	CR
4	7.9	1.3	Yes	Adjuvant EMA/CO MTX, HuMMP, EMA/CO, EP/EMA Hysterectomy	NE all NC CR
5	7.8	5.0	Yes	Adjuvant EP/EMA Emergency hysterectomy for perforation	NE NE
6	6.7	1.0	Yes	Postoperative EMA/CO EMA/CO	PR CR
7	5.4 ^b	5.2	Yes	Relapsed EMA/CO Hysterectomy MTX, EA	CR NE NC
8	4.7	0.6	Yes	Hysterectomy and iliac lymphadenectomy Relapsed at 4 years after surgery and POMB/EMA EMA/CO	CR PD MR
9	4.6	2.7	Yes	Hysterectomy MTX, EMA/CO	CR NC
10	4.1	11.3	Yes	Hysterectomy	CR
11	3.2	3.7	No	D&C only	Spontaneous CR
12	2.7 ^b	4.7	Yes	Emergency hysterectomy for perforation EMA/CO Hysterectomy and BSO CHAMOCA, EP/CO	NE PR PR PR
13	2.4	1.5	Yes	Relapse CHAMOCA, EP/CO, and surgery Hysterectomy	PD CR
14	2.2	8.0	N/D	EMA/CO	NC
15	1.8 ^b	7.6	No	Hysterectomy and BSO EMA/CO	CR CR
16	1.7	2.5	Yes	Relapsed thoracotomy EP/EMA, 5FU, Cisplat/Taxol EMA/CO	PD NC NC
17	0.6 ^b	2.8	Yes	Hysterectomy EMA/CO, EP/EMA Laparotomy, irradiation	CR NE PD NE

^a Ac, actinomycin D; BSO, bilateral salpingo-oophorectomy; D&C, uterine dilation and curettage; CR, complete remission; PR, partial response; MR, mixed response; NC, no change; PD, progressive disease; NE, not evaluable; N/D, not done; CO, cyclophosphamide and vincristine; EMA, etoposide, methotrexate, and actinomycin D; MTX, methotrexate; HuMMP, hydroxyurea, methotrexate, and 6-mercaptopurine; EP, etoposide and cis-platinum; EA, etoposide and actinomycin D; POMB, cis-platinum, vincristine, methotrexate, and bleomycin; CHAMOCA, hydroxyurea, vincristine, methotrexate, cyclophosphamide, actinomycin D, and adriamycin; 5FU, 5-fluorouracil; Cisplat/Taxol, paclitaxel and cis-platinum.

^b Deceased.

interval, 55–93%) and 69% (95% confidence interval, 40–88), respectively (Fig. 2).

Prognostic Factors Predicting Outcome. Log rank univariate survival analysis was used to test for the significance of differences in survival distributions. No significant difference was demonstrated according to age at presentation (<30 years versus >30 years, *P* = 0.10), nature of previous pregnancy (FTND versus hydatidiform mole, *P* = 0.18), or serum hCG level at presentation (<200 IU/liter versus >200 IU/liter, *P* = 0.94). A knowledge of the histology at the onset of treatment was not of prognostic value (*P* = 0.12). The extent of disease at presentation was also not of prognostic importance (uterine versus metastatic, *P* = 0.25), nor was the prognostic score (0–9 versus >9, *P* = 0.22). The interval between the implicated pregnancy and the diagnosis was however significant for survival. An interval of >2 years was an adverse prognostic feature (*P* = 0.001; Fig. 3).

In this series, the mitotic counts (*P* = 0.36) were not of

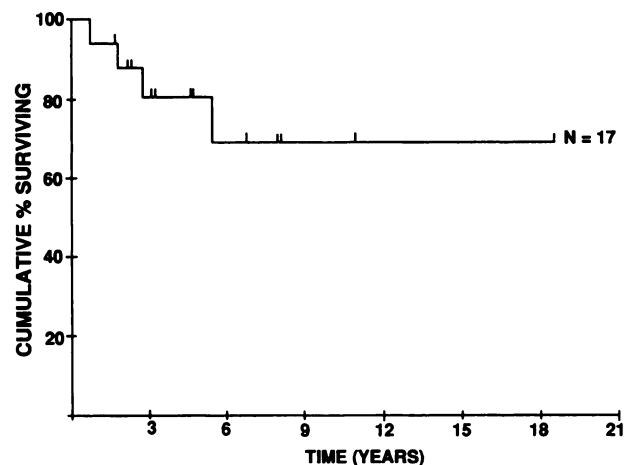


Fig. 2 Overall survival plot for PSTT patients.

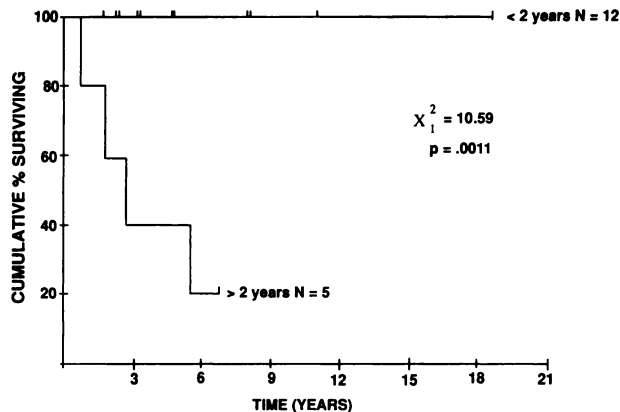


Fig. 3 Overall survival plot for PSTT patients according to the interval from the preceding pregnancy.

prognostic significance. The tumors in which more cells stained for hPL than hCG had a similar prognosis ($P = 0.25$).

The variables found to be significant at $P \leq 0.15$ were put into a stepwise Cox regression model to establish which were independently prognostic. In this model, an interval of >2 years since the last pregnancy ($P = 0.0015$) was an independent poor prognostic factor.

DISCUSSION

PSTT may follow either a normal full-term delivery or a hydatidiform mole and by comparison with CC; the causative pregnancy may not be the immediately antecedent pregnancy (4). Karyotypic characterization carried out on three tumors in the literature revealed that all were diploid (7); similarly, flow cytometry suggested that three of three PSTTs were diploid in one study (8) and that three of four in a second series were diploid and one tetraploid (9). The genetic origins of PSTT were first established using RFLP analysis. This methodology demonstrated that PSTT may have a biparental genotype originating from a normal conceptus or an androgenetic genotype following a complete hydatidiform mole (10). Subsequently, the biparental origin of a case of PSTT was shown by PCR genotyping (11). In this series, microsatellite genotyping has been employed to confirm that PSTT may arise following either a biparental conception or an androgenetic molar pregnancy. In all 11 cases analyzed a gestational origin was confirmed. Furthermore, in this small series genetic characterization was achieved in eight cases: three were shown to derive from molar and five from biparental pregnancies in accordance with the clinical histories. In contrast, a retrospective survey of 602 women requiring chemotherapy for gestational trophoblastic tumors revealed that 83% followed molar pregnancies and only 17% followed a live birth or nonmolar abortion (12).

The clinical features of PSTT at presentation differ from those associated with CC. There appears to be less propensity to metastasize, and hence fewer patients present with nongynecological symptoms. In addition, the cytotrophoblastic cells express hPL and may cause hyperprolactinemia, resulting in amenorrhea and/or galactorrhea. However, serum hPL has been measured in only four cases and was not elevated (2); therefore,

it is unlikely to be a valuable tumor marker in PSTT. Furthermore, PSTT may present with nephrotic syndrome, and this has been described in six cases including the patient in this series (13, 14). It is thought that the tumor produces factors causing chronic intravascular coagulation, leading to glomerular fibrinogen deposition, and serological evidence of disseminated intravascular coagulopathy was found in some patients (14).

Although a repeat D&C before starting treatment for women with hydatidiform moles and rising hCG levels might lead to earlier diagnosis of PSTT, this approach is usually impractical, and in this series there was no difference in the outcome in patients in whom the histology was established prior to the onset of therapy. The approach in our unit is to repeat the D&C in cases where there is unexpected drug resistance.

The most significant clinical prognostic factor in this small series of patients (although it is the largest single institution series currently in the literature) is the interval between the last known antecedent pregnancy and the diagnosis. Four of the five patients in whom the interval was >2 years have died, but all 12 of the remaining patients are alive. Similarly, an interval of ≥ 2 years was found in all 10 fatal cases reported out of a collected series of 43 patients reviewed in 1988 (7). Furthermore, in the recent review of all patients in the English literature, the mean interval from the last known pregnancy was 23 months for 44 living patients and 53 months for 11 deceased patients (2). In this series, 4 of 5 patients with intervals ≥ 2 years presented with pelvic extension or metastatic disease compared to 4 of 12 where the interval was <2 years. The more advanced disease at presentation of the tumors with intervals ≥ 2 years may account in part for their worse prognosis, although the presence of metastases was not a poor prognostic variable in our series. In addition, the late presentation of some tumors may reflect biological differences between tumors or altered host responses to these tumors. This may account for their worse prognosis.

The most important prognostic feature was the mitotic rate in tumors in one series (7), and the overview of all cases confirmed that the mean mitotic count was significantly higher in the deceased patients than in the survivors (2). However, in our series of 17 treated patients, 2 of 5 with >5 mitoses/HPF have died compared with 2 of 12 with <5 mitoses/HPF, and there is no difference in the overall survival by this parameter.

The optimal approach to the management of PSTT remains surgical for localized disease. In one review, it was suggested that chemotherapy failed to control disease in any of 43 cases (7), that responses at best were partial and of short duration (months), and therefore should be reserved for postoperative recurrences. However, in our experience, patients can respond to chemotherapy. This includes one patient who achieved complete remission of pulmonary metastases with chemotherapy (16). A similar response to chemotherapy in a patient with pulmonary metastases of PSTT has since been described (17).

The use of irradiation has been reported in two cases following the development of drug-resistant nodal metastases. This approach achieved clinical remission in both cases but was presumed to be palliative only (18, 19). Three patients were treated with irradiation at Charing Cross Hospital, one in an adjuvant setting. One patient received palliative irradiation to alleviate hematuria from bladder invasion with some success,

and the other patient received radiotherapy to para-aortic disease without evidence of response.

The appropriate follow-up for PSTT differs from other gestational trophoblastic disease variants. Serum hCG is a less sensitive tumor marker in PSTT and late recurrences are more common [in one case in this series after 4 years and one in the literature after 5 years (20)]. In view of this, follow-up with clinical evaluation as well as serological examination is necessary for at least 5 years, especially since these tumors may fail to secrete hCG at relapse even in the presence of an extensive tumor burden (21).

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