Distinguished Expert Series

Placental site trophoblastic tumor – a challenging rare entity

B. Piura, *M.D., F.R.C.O.G., Prof.*

Unit of Gynecologic Oncology, Department of Obstetrics and Gynecology, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva (Israel)

Summary

Placental site trophoblastic tumor (PSTT) is a challenging rare variant of gestational trophoblastic disease (GTD) with variable characteristics. Historically, it was first described in 1895 and was considered a benign lesion until Scully and Young recognized its malignant potential in 1981. Current knowledge related to PSTT is largely based on the experience of handling this disease in established trophoblastic disease centers and on the experience of authors who reported small series or singular cases. In contrast to other forms of GTD, it arises from the implantation-site intermediate trophoblast, produces less β-hCG and is less sensitive to chemotheapy. More than half of the patients present with disease confined to the uterus, whereas the remainder present with disease extension beyond the uterus. Because of the relative insensitivity to chemotherapy, simple hysterectomy is the mainstay of treatment. While the outcome of patients with disease confined to the uterus is usually excellent, most patients with disease extension beyond the uterus experience progression of disease and die despite surgery and aggressive chemotherapy. Other important adverse prognostic factors are interval from antecedent pregnancy > 2 years, age > 40 years and mitotic count > 5 mf/10 HPF. Although the ideal chemotherapy regimen for PSTT has yet not been established, it seems that the EP/EMA regimen is the most effective first-line chemotherapy available to date for metastatic and relapsing PSTT. Although PSTT produces less hCG than choriocarcinoma, β-hCG is still the best available serum marker to follow the disease and treatment course of PSTT.

Key words: Intermediate trophoblast; Implantation site; Gestational trophoblastic disease; Hysterectomy; Chemotherapy.

Introduction

Placental site trophoblastic tumor (PSTT) is a rare variant of gestational trophoblastic disease (GTD), with fewer than 250 reported cases to date. In contrast to the more common forms of GTD that originate from the cytotrophoblast and syncytiotrophoblast (hydatidiform mole, invasive mole and choriocarcinoma), PSTT originates from the implantation-site intermediate trophoblast and accounts for about 1% of all GTDs, with an estimated incidence of 1 per 100,000 pregnancies [1-4]. It is believed that the lesion described by Marshand in 1895 as "atypical chorioepithelioma" is in fact the first description in the literature of PSTT [5]. Similar lesions had further been reported and variously called "atypical choriocarcinoma", "syncytioma" and "chorioepitheliosis". These lesions were limited to the placental implantation site with no evidence of local invasion and/or distant metastases, and the patients were cured by curettage alone or simple hysterectomy. Kurman *et al.* [6] adopted in 1976 the term "trophoblastic pseudotumor" for this entity since it seemed to represent an exaggerated placental site reaction rather than a true tumor. However, worrying reports had soon started to appear, like that of Twiggs *et al.* [7], of trophoblastic tumors originating from the placental implantation site with local invasion, spread beyond the uterus and death of the patient. These worrying reports prompted Scully and Young [8] to change in 1981 the name of this tumor to "placental site trophoblastic tumor (PSTT)" to better reflect its potential for malignant behavior. Current knowledge related to PSTT is largely based on the experience of handling this disease in established trophoblastic disease centers [1-4] in the United Kingdom and the United States (Table 1) and on the experience of authors who reported small series or singular cases. Because of the rarity of PSTT, patient accrual occurred over prolonged periods during which treatment approaches and modalities changed. Thus, the understanding of the variable biologic behavior and treatment alternatives of PSTT is still limited and posses a challenge. The aim of the present paper is to revise the up-to-date knowledge related to placental site trophoblastic tumor.

Intermediate trophoblast lesions

Most of the cytotrophoblastic cells differentiate into the syncytiotrophoblast. The syncytiotrophoblast produces and secrets human chorionic gonadotropin (hCG), estrogen and progesterone that are essential for the maintenance and continuation of pregnancy. Nevertheless, some of the cytotrophoblastic cells that are located on the chorionic villi of the

Revised manuscript accepted for publication May 4, 2006

Table 1. — *Data collated from four large series of patients with placental site trophoblastic tumor.*

Author publication year	Feltmate *et al.* [1] 2001	Papadopoulos *et al.* [2] 2002	Hassadia *et al.* [3] 2005	Baergen *et al.* [4] 2006
No. of patients	13	34	17	55
and accrual period	1982 – 1999	1975 – 2001	1984 – 2004	?
Age (years)	Mean, 31.2 (20 – 53)	Mean, 33	Median, 35 (26 – 52)	Mean, 32 (20 – 62)
Type of AP	Full term, 7 (53.8%) TOP, 3 (23.1%) Miscarriage, 2 (15.4%) Mole, 1 (7.7%)	Full term, 18 (52.9%) Mole, 7 (20.6%) Miscarriage, 5 (14.7%) TOP, 2 (5.9%) Stillbirth, 1 (2.9%) Ectopic, 1 (2.9%)	Full term, 13 (76.5%) Miscarriage, 2 (11.7%) TOP, 1 (5.9%) Unknown, 1 (5.9%)	Full term, 46 (83.6%) Mole, 5 (9.1%) Miscarriage, 4 (7.3%)
Interval from AP	Mean, 16.5 months	Mean, 40.8 months	Median, 18 months	Mean, 34 months
Prevailing presenting symptoms	VB, 8 (61.5%) Amenorrhea, 4 (30.8%)	VB, 27 (79.4%) Abdominal pain, 5 (14.7%) Amenorrhea, 2 (5.9%)	VB, 8 (47%) Amenorrhea, 4 (23.5%) Abdominal pain, 2 (12%)	
Stage of disease at presentation	Stage I, 9 (69.2%) Stage II, 4 (30.8%)	Stage I, 15 (44.1%) Stage II, 8 (23.5%) Stage III, 10 (29.4%) Stage IV, 1 (2.9%)	Stage I, 8 (47.1%) Stage II, 1 (5.9%) Stage III, 5 (29.4%) Stage IV, 3 (17.6%)	Stage I, 46 (83.6%) Stage II, 1 (1.8%) Stage III, 3 (5.5%) Stage IV, 5 (9.1%)
Serum hCG (mIU/ml) at presentation	Range, 4 - >2,000 92.3% patients had < 500	Mean, 4,254; Range, 6 – 58,000. 79% patients had < 1000 58% patients had < 500	Median, 13,923; Range, 6 – 107,600. 58.8% patients had <500	Mean, 691; Range, 5 – 7,500.
Mitotic index (mf/10 HPF)	Median, 10 in patients who recurred; Median 2 in patients who did not.	Median, 4.7; Range, 0.6 – 11.3.	Not evaluated.	Mean, 5; Range, 0 – 20.
Treatment	TAH alone, 4 TAH then chemo, 5 Chemo then TAH, 4 Chemo included MAC, EMA, EMA/CO and EP/EMA.	Curettage alone, 2 TAH alone, 8 TAH then chemo, 8 Chemo then TAH, 6 Surgery between chemo, 7 Chemo alone, 1 Not specified , 2 Most common chemo was EMA/CO and EP/EMA	TAH alone, 6 TAH then chemo, 2 Chemo then TAH, 1 Surgery between chemo, 2 Chemo alone, 6 Chemo consisted of variety of regimens including CEC, EMA and EP/EMA.	Curettage alone, 4 Curettage then chemo, 1 Resection, 1 TAH alone, 30 TAH then chemo, 18 TAH then radiation, 1 Chemo consisted of variety of regimens including VIP and EMA/CO.
Outcome	Death rate 5/13 (38.5%)	Death rate, 7/34 (20.6%)	Death rate, 4/17 (23.5%)	Death rate, 8/55 (14.5%)

AP, antecedent pregnancy; TOP, termination of pregnancy; VB, vaginal bleeding; mf/10 HPF, mitotic figures per 10 high power fields; TAH, total abdominal hysterectomy; Chemo, chemotherapy; MAC, methotrexate, actinomycin-D (dactinomycin) and cyclophosphamide; EMA, etoposide, methotrexate and actinomycin-D (dactinomycin); EMA/CO, EMA alternating with cyclophosphamide and oncovin (vincristine); EP/EMA, etoposide and cisplatin alternating with EMA; CEC, cyclophosphamide, etoposide, and cisplatin; VIP, etoposide, ifosfamide and cisplatin.

placenta differentiate into implantation-site intermediate trophoblast and chorionic-type intermediate trophoblast. In contrast to the syncytiotrophoblast, the intermediate trophoblastic cells produce and secrete human placental lactogen (hPL). The inherent capability of the intermediate trophoblastic cells to penetrate the decidua and invade maternal blood vessels facilitates the anchorage of the placenta on the inner uterine wall and enables direct contact of the chorionic villi with the maternal blood. Two neoplastic and two non-neoplasic lesions of the intermediate trophoblast have so far been identified [9]. The two neoplastic lesions are PSTT that originates from the implantation-site intermediate trophoblast and epithelioid trophoblastic tumor (ETT) that originates from the chorionic-type intermediate trophoblast. ETT is a rare tumor that has only recently been recognized [10]. The two non-neoplastic lesions are exaggerated placental site (EPS) which originates from the implantation-site intermediate trophoblast and placental site nodule (PSN) which originates from the chorionic-type intermediate trophoblast.

Histology, immunohistochemistry and mitotic index

Histologically, the GTDs that arise from the cytotrophoblast and syncytiotrophoblast are characterized by the biphasic proliferation of the cytotrophoblast and syncytiotrophoblast cells. In contrast, PSTT is histologically characterized by the monophasic proliferation of the intermendiate trophoblastic cells [11]. Histologic features of PSTT are: (1) the presence of sheets of large polygonal intermediate trophoblastic cells with irregular hyperchromatic nuclei and dense eosinophilic cytoplasm; (2) the presence of myometrial infiltration with characteristic separation of muscle bundles by tumor cells; (3) the presence of vascular invasion characterized by extensive replacement of blood vessel walls with tumor cells that extend into the vascular lumen from the outside to inside; (4) the presence of abundant extra-cellular eosinophilic fibrinoid material. Baergen *et al.* [4] observed that invasion of more than the inner third of the myometrium ($p = 0.006$), presence of extensive coagulative necrosis ($p = 0.024$) and presence of cells with clear cytoplasm ($p < 0.0005$) are significant adverse prognostic factors.

On immunohistochemical staining, most PSTTs are positive for human placental lactogen (hPL), cytokeratin and α-inhibin and weakly and/or focally positive for β-hCG, placental alkaline-phophatase (PLAP) and epithelial membrane antigen (EMA).

Mitotic activity in PSTT is variable and there is conflicting data as to whether high mitotic count is a significant adverse prognostic factor [3, 12]. Some investigators have noticed that high mitotic count is associated with a worse outcome. Feltmate *et al.* [1] observed that mitotic counts were significantly higher in patients who developed recurrent disease (median, 10 mf/10 HPF) as compared to patients who did not (median, 2 mf/10 HPF) ($p = 0.04$). All patients in their series with a mitotic count ≤ 5 mf/10 HPF did not develop recurrent disease, whereas all recurrences occurred in patients with a mitotic count > 5 mf/10 HPF [1]. Papadopoulos *et al.* [2] found in their series that the median mitotic count was 4.7 mf/10 HPF (range, 0.6 – 11.3 mf/10 HPF), and observed that mitotic count ≤ 5 mf/10 HPF and > 5 mf/10 HPF was associated with a mortality rate of 20% and 33.3%, respectively (the difference is not statistically significant). In a series of 55 patients, Baergen *et al.* [4] observed that the mean mitotic count was 5 mf/10 HPF (range, 0 – 20 mf/10 HPF) and demonstrated that a mitotic count ≤ 2.5, 2.6 – 6 and > 6 mf/10 HPF was associated with a likelihood of survival at 48 months of 100%, 86.3% and 51.9%, respectively ($p = 0.005$). In a separate group of 94 patients collated from the literature, they demonstrated that a mitotic count ≤ 2.5, 2.6 – 6 and > 6 mf/10 HPF was associated with a likelihood of survival at 48 months of 87.4%, 88% and 12%, respectively ($p = 0.0005$) [4].

Age

Most women affected by PSTT are premenopausal and in their third and fourth decade of life. In the series of Feltmate *et al.* [1], Papadopoulos *et al.* [2] and Baergen *et al.* [4], the mean age at presentation was 31.2 (range, 20 – 53) years, 33 years and 32 (range, 20 – 62) years, respectively. In the series of Hassadia *et al.* [3] and Baergen *et al.* [4], the median age at presentation was 35 (range, 26 – 52) years and 31 years, respectively. PSTT is extremely rare in postmenopausal women with only about ten cases reported to date [3, 4, 13]. The oldest patient with PSTT, as reported by Nigam *et al.* [13], was a 63-year-old woman who had been postmenopausal for 12 years. Hassadia *et al.* [3] noticed that age > 40 years is an adverse prognostic factor. In 54 patients in whom age was recorded, Baergen *et al.* [4] demonstrated that age ≤ 35 and > 35 years was associated with likelihood of survival at 48 months of 91.9% and 60%, respectively ($p = 0.025$). In a separate group of 117 patients collated from the literature, they observed that age ≤ 35 and > 35 years was associated with likelihood of survival at 48 months of 86% and 58.6%, respectively ($p = 0.155$, not significant) [4].

Presenting features

The commonest prevailing presenting symptom in patients with PSTT is abnormal vaginal bleeding [1-3, 14]. Of 64 patients collated from three large series in the literature, in which the presenting symptoms were recorded, 43 (67.2%) presented with abnormal vaginal bleeding, ten (15.6%) – amenorrhea and seven (10.9%) – abdominal pain [1-3]. Less common presenting features were fits, hemoptysis, ruptured uterus, nephritic syndrome and enlarged neck lymph node. Interestingly, few patients with PSTT presented with galactorrhea induced by the hPL that is produced and secreted by the intermediate trophoblastic cells [2, 3].

Extent of disease at presentation

The International Federation of Gynecology and Obstetrics (FIGO) anatomical staging system of GTD has been adopted for PSTT [15] (Table 2). More than half of the patients with PSTT present with disease confined to the uterus (Stage I) [1-4]. Of 119 patients with PSTT collated from four large series in the literature, 78 (65.5%) presented with disease confined to the uterus (Stage I), 14 (11.8%) – disease extension to the pelvis (Stage II), 18 (15.1%) – lung metastases (Stage III), and nine (7.6%) – metastases in other sites (Stage IV) [1-4]. The most common site of metastasis was the lung; however, metastases to the scalp, brain, liver, spleen, bowel, pancreas, kidney, adjacent pelvic organs, and vagina have also been reported [4, 12, 16].

Extent of disease at presentation is the most important prognostic factor. Patients with disease confined to the uterus have an excellent outcome with survival rates about 95%, whereas approximately 70% of patients presenting with disease beyond the uterus have progression of disease and die despite surgery and aggressive multi-drug chemotherapy [1-4]. Hassadia *et al.* [3] observed in a series of 17 patients the following mortality rates in relation to extent of disease at presentation: Stage I – 0/8 (0%), Stage II – 1/1 (100%), Stage III – 1/5 (20%), and Stage IV – 2/3 (66.6%). In a series of 55 patients, Baergen *et al.* [4] observed the following mortality rates: Stage I – 3/46 (6.6%), Stage II –

Table 2. — *FIGO anatomical staging of GTD.*

Stage	Extent of disease
I	Disease confined to the uterus
II	Disease extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
III	Disease extends to the lungs, with or without known genital involvement
IV	All other metastatic sites

0/1 (0%), Stage III – 1/3 (33.3%), and Stage IV – 4/5 (80%). They demonstrated that Stage I-II and III-IV was associated with likelihood of survival at 48 months of 92.3% and 0%, respectively ($p < 0.0005$) [4]. In a separate group of 117 patients collated from the literature, they observed that Stage I-II and III-IV was associated with likelihood of survival at 48 months of 91% and 40.7%, respectively ($p < 0.0005$) [4].

Antecedent pregnancy

In contrast to choriocarcinoma, in which the antecedent pregnancy is hydatidiform mole in 50% of the cases, abortion or ectopic pregnancy – 25% and full-term pregnancy – 25%, most PSTTs occur after a full-term normal delivery [1-4]. The type of the antecedent pregnancy in 119 patients with PSTT collated from four large series in the literature was a full-term pregnancy in 84 patients (70.6%), miscarriage – 13 (10.9%), complete hydatidiform mole – 13 (10.9%), termination of pregnancy – six (5%), stillbirth – one (0.8%), ectopic pregnancy – one (0.8%), and unknown – 1 (0.8%) [1-4]. The commonest sex of the fetus/infant resulting from the antecedent pregnancy was female [3]. In 42 patients in whom type of antecedent pregnancy was recorded, Baergen *et al.* [4] observed that PSTT after full-term pregnancy and molar pregnancy was associated with likelihood of survival at 48 months of 76.7% and 100%, respectively ($p = 0.256$, not significant). In a separate group of 74 patients collated from the literature, they observed that PSTT after a full-term pregnancy is a significant adverse prognostic factor ($p = 0.046$) [4]. Palmieri *et al.* [17] have recently described a rare case of PSTT occurring after evacuation of a partial hydatidifrom mole. Of much interest is that if data from the genetic origins of choriocarcinomas are extrapolated, the immediate prior pregnancy is not necessarily the one that gives rise to the PSTT [18].

Lengthening of the interval from the antecedent pregnancy has been shown to be associated with worsening of the prognosis [2-4]. Papadopoulos *et al.* [2] found that the mean interval from antecedent pregnancy was 3.4 years and observed that an interval ≤ 2 and > 2 years was associated with a mortality rate of 0% and 64%, respectively, and an interval ≤ 4 years and > 4 years was associated with a mortality rate of 0% and 100%, respectively. Hassadia *et al.* [3] found that the median interval from antecedent pregnancy was 18 months (range, 6 months – 22 years) and showed that interval ≤ 2 and > 2 years was associated with a mortality rate of 10% and 42.8%, respectively, and interval ≤ 4 years and > 4 years was associated with a mortality rate of 8.3% and 60%, respectively. Feltmate *et al.* [1] found that the mean interval from antecedent pregnancy was 16.5 months (range, 2 weeks – 5 years). They observed that in patients who developed recurrent disease the mean interval was 27 months, whereas in patients who did not develop recurrent disease the mean interval was 9.9 months [1]. In 38 patients in whom interval from antecedent pregnancy was recorded, Baergen *et al.* [4] observed that the mean interval from antecedent pregnancy was 34 (median, 18; range, 5 – 131) months and demonstrated that an interval ≤ 2 and > 2 years was associated with a likelihood of survival at 48 months of 92.3% and 48.2%, respectively ($p = 0.014$). In a separate group of 89 patients collated from the literature, they demonstrated that an interval ≤ 2 and > 2 years was associated with a likelihood of survival at 48 months of 82.1% and 52.2%, respectively ($p = 0.029$) [4]. There are only a few cases reported in the literature with an interval from the antecedent pregnancy longer than ten years; Nigam *et al.* [13] reported a patient with an interval of 17 years, NcLellan *et al.* [19] – 18 years, and Hassadia *et al.* [3] – 22 years. Hence, it has been suggested that PSTT may remain dormant for long periods [13].

Human chorionic gonadotropin

In GTDs that originate from the cytotrophoblast and syncytiotrophoblast, the syncytiotrophoblast produces and secretes vast amounts of β-hCG and serum β-hCG levels strongly correlate with the volume and malignant behavior of the tumor. Thus, in GTDs that originate from the cytotrophoblast and syncytiotrophoblast, β-hCG is a perfectly reliable serum marker for monitoring the response to treatment and follow-up of the disease course. In PSTT, the intermediate trophoblastic cells produce and secrete mainly human placental lactogen (hPL) and scant amounts of β-hCG. Hence, serum β-hCG levels do not usually correlate with the burden or malignant behavior of PSTT. In addition, the detection and measurement of serum hPL is a much-complicated procedure that is not available in most institutions. However, although serum β-hCG levels do not exactly reflect the burden or malignant behavior of PSTT, most relapses of PSTT are associated with a rise in the serum β-hCG level. Thus, although PSTT produces less hCG than choriocarcinoma, β-hCG is still the best available serum marker to follow the disease and treatment course of PSTT [4, 14].

Most patients with PSTT present with serum β-hCG level < 500 mIU/ml [1-4, 14]. Feltmate *et al.* [1] observed in a series of 13 patients that serum β-hCG levels ranged from 4 to > 2,000 mIU/ml, with 92.3% of the patients presenting with serum β-hCG levels < 500 mIU/ml. They have consequently concluded that serum β-hCG levels in PSTT correlate neither with the burden nor with the malignant behavior of the disease and thus appear to have a diminished predictive value [1]. Papadopoulos *et al.* [2] observed in a series of 34 patients that the mean serum β-hCG level was 4,254 mIU/ml (range, 6-58,000 mIU/ml); 79% and 58% of the patients presented with serum β-hCG levels < 1,000 mIU/ml and < 500 mIU/ml, respectively. Hassadia *et al.* [3] demonstrated in a series of 17 patients that the median serum β-hCG level was 13,923 mIU/ml (range, 6-107,600 mIU/ml); 58.8% of the patients presented with serum β-hCG levels

< 500 mIU/ml. They observed that a serum β-hCG level at presentation ≥ 10,000 mIU/ml is an adverse prognostic factor [3]. In 42 patients in whom the maximum serum β-hCG level was recorded, Baergen *et al.* [4] observed that the maximum serum β-hCG level ranged from 5 to 7,500 (mean, 691) mIU/ml and that the maximum serum β-hCG level < 1000 mIU/ml and > 1000 mIU/ml was associated with a likelihood of survival at 48 months of 85.2% and 45%, respectively (p = 0.034). In a separate group of 83 patients collated from the literature, they observed that the maximum serum β-hCG level < 1000 mIU/ml and > 1000 mIU/ml was associated with a likelihood of survival at 48 months of 79.6% and 43.3%, respectively (p = 0.037) [4].

Treatment

Since PSTT is less sensitive to chemotherapy than other forms of GTD and since most patients with PSTT present with disease limited to the uterus, hysterectomy is the primary mode of therapy in PSTT [3, 20]. Of 119 patients collated from four large series in the literature, 48 (40.3%) had hysterectomy alone, 33 (27.7%) – hysterectomy then chemotherapy, 11 (9.2%) – chemotherapy then hysterectomy, nine (7.6%) – hysterectomy between chemotherapy, one (0.8%) – hysterectomy then radiotherapy, six (5%) – curettage alone, one (0.8%) – curettage then chemotherapy, one (0.8%) – resection of tumor alone, seven (5.9%) – chemotherapy alone, and two (1.7%) – treatment not specified [1-4]. Overall, 102 (85.7%) patients underwent hysterectomy and 61 (51.3%) received chemotherapy [1-4]. In a separate group of 170 patients collated from the literature in whom information on treatment was available, Baergen *et al.* [4] observed that 139 (81.8%) had hysterectomy and 31 (18.2%) underwent curettage only or conservative resection. Seventy-six (44.7%) of these 170 patients were also treated with some form of chemotherapy, an additional seven (4.1%) with chemotherapy and radiation, and three (1.8%) received supplemental radiotherapy [4].

Table 3. — *EMA CO chemotherapy.*

	EMA
Day 1	Etoposide (VP-16) 100 mg/m² in 200 ml NaCl 0.9% by a 30-minute intravenous infusion. Actinomycin-D (Dactinomycin) 0.5 mg in 150 ml NaCl 0.9% by a 5-minute intravenous infusion. Methotrexate 100 mg/m² in 150 ml NaCl 0.9% by a 5-minute intravenous infusion followed by methotrexate 200 mg/m² in 1,000 ml dextrose 5% by a 12-hour intravenous infusion.
Day 2	Etoposide (VP-16) 100 mg/m² in 200 ml NaCl 0.9% by a 30-minute intravenous infusion Actinomycin-D (Dactinomycin) 0.5 mg in 150 ml NaCl 0.9% by a 5-minute intravenous infusion. Folinic acid (leucovorin, rescue factor) 15 mg by either intramuscular injection or oral tablets every 12 hours for four doses beginning 24 hours after start of methotrexate.
	CO
Day 8	Vincristine (oncovin) 1 mg/m² in 150 ml NaCl 0.9% by a 5-minute intravenous infusion. Cyclophosphamide (endoxan, cytoxan) 600 mg/m² in 150 ml NaCl 0.9% by a 30-minute intravenous infusion

Chemotherapy is given on days 1, 2 and 8 of every 14 days. Every 14-day cycle is accepted as one course. Day 15 is day 1 of the next course.

Table 4. — *EP EMA chemotherapy.*

	EP
Day 1	Etoposide (VP-16) 150 mg/m² in 500 ml NaCl 0.9% by a 60-minute intravenous infusion Cisplatin 75 mg/m² in 3,000 ml NaCl 0.9% by a 12-hour intravenous infusion
	EMA
Day 8	Etoposide (VP-16) 100 mg/m² in 500 ml NaCl 0.9% by a 60-minute intravenous infusion Actinomycin-D (Dactinomycin) 0.5 mg in 150 ml NaCl 0.9% by a 5-minute intravenous infusion Methotrexate 300 mg/m² in 1,000 ml NaCl 0.9% by a 12-hour intravenous infusion. Folinic acid (leucovorin, rescue factor) 15 mg by either intramuscular injection or oral tablets every 12 hours for four doses beginning 24 hours after start of methotrexate

Chemotherapy is given on days 1 and 8 of every 14 days. Every 14-day cycle is accepted as one course. Day 15 is day 1 of the next course.

Treatment of disease confined to the uterus (Stage I)

Simple hysterectomy is the primary mode of treatment in disease confined to the uterus [3, 20]. Ovarian micrometastases from disease apparently limited to the uterus is rare (3%); thus, preservation of grossly normal ovaries at the time of hysterectomy in premenopausal women who wish to preserve ovarian function is reasonable [3, 14]. Moreover, there are few reports of young women with PSTT localized within the uterine cavity that were successfully treated with either curettage alone or open resection of the intrauterine tumor [4, 12, 21, 22]. The role of adjuvant chemotherapy after surgery for disease confined to the uterus has yet not been established and remains controversial [1, 12]. Kim [9] has advised hysterectomy plus peri-operative single-agent chemotherapy (e.g., methotrexate or actinomycin-D). Other authors have recommended the administration of early adjuvant multidrug chemotherapy, such as EMA/CO (Table 3) or EP/EMA (Table 4), after hysterectomy for disease confined to the uterus in patients with any of the following high-risk factors: interval from antecedent pregnancy > 2 years and mitotic count > 5 mf/10 HPF [1, 14, 16, 21]. It has been shown that patients who received chemotherapy < 1 week after hysterectomy were less likely to recur than patients who received chemotherapy > 1 week after hysterectomy [1]. The prognostic significance of other factors such as large volume of intrauterine disease, deep myometrial invasion, and vascular space involvement has yet not been established.

Treatment of disease extension beyond the uterus (Stage II-IV)

Patients with disease extension beyond the uterus cannot be cured by surgery alone and adjuvant treatment with multi-drug chemotherapy is required [3]. However, the ideal chemotherapy regimen for metastatic and relapsing PSTT has yet not been established [3]. Felmate *et al.* [1] reported that chemotherapy in their series included MAC (methotrexate, actinomycin-D and cyclophosphamide), EMA, EMA/CO and EP/EMA. They have observed that patients who received chemotherapy < 1 week after hysterectomy were less likely to recur than patients who received chemotherapy > 1 week after hysterectomy [1]. Papadopoulos *et al.* [2] reported that the commonest chemotherapy regimens in their series were EMA/CO and EP/EMA. They have suggested that the EP/EMA regimen is the most effective chemotherapy regimen available to date for metastatic and relapsing PSTT [2]. Hassadia *et al.* [3] reported that chemotherapy in their series consisted of a variety of regimens including CEC (cyclophosphamide, etoposide, and cisplatin), EMA and EP/EMA, and that some of their patients treated with EP/EMA developed drug-resistant disease and required salvage with another chemotherapy regimen. It has been suggested that EMA alone (without CO or EP) as first-line chemotherapy is active against PSTT and that the CEC regimen may have a place in the salvage treatment of EMA-resistant disease [3]. Metastatic disease is not necessarily a contraindication to surgery; sometimes, aggressive surgical management of chemotherapy-resistant metastatic disease may be beneficial for young patients with an otherwise poor prognosis [3,23]. Radiation therapy has been employed in the palliative setting but is not a primary modality of treatment [3].

Outcome

Although most patients with PSTT present with disease confined to the uterus and cured with simple hysterectomy, approximately 30% of patients present with disease extension beyond the uterus. Patients with disease confined to the uterus have an excellent prognosis with survival rates about 95%, whereas approximately 70% of patients presenting with disease extension beyond the uterus have progression of disease and die despite surgery and aggressive multi-drug chemotherapy [1-4]. Of the 119 patients collated from four large series in the literature, 24 (20.2%) died of disease overall, with a death rate in each individual series ranging from 14.5% to 38.5% [1-4].

Conclusions

Placental site trophoblastic tumor (PSTT) is a challenging rare variant of gestational trophoblastic disease (GTD) with variable characteristics. Historically, it was first described in 1895 and was considered a benign lesion until Scully and Young recognized its malignant potential in 1981. Current knowledge related to PSTT is largely based on the experience of handling this disease in established trophoblastic disease centers and on the experience of authors who reported small series or singular cases. Patient accrual, however, occurred over prolonged periods during which treatment approaches and modalities changed. In contrast to other forms of GTD, it arises from the implantation-site intermediate trophoblast, produces less β-hCG and is less sensitive to chemotherapy. More than half of the patients present with disease confined to the uterus, whereas the remainder present with disease extension beyond the uterus. Because of the relative insensitivity to chemotherapy, simple hysterectomy is the mainstay of treatment. While the outcome of patients with disease confined to the uterus is usually excellent, most patients with disease extension beyond the uterus experience progression of disease and die despite surgery and aggressive chemotherapy. Other important adverse prognostic factors are interval from antecedent pregnancy > 2 years, age > 40 years and mitotic count > 5 mf/10 HPF. The prognostic significance of other factors such as type of antecedent pregnancy, serum β-hCG level at presentation, maximum serum β-hCG level, extent of myometrial invasion, volume of intrauterine disease, vascular space involvement, extent of tumor necrosis and presence of cells with clear cytoplasm has yet not been established. Although the ideal chemotherapy regimen for PSTT has yet not been established, it seems that the EP/EMA regimen is the most effective first-line chemotherapy available to date for metastatic and relapsing PSTT. Although PSTT produces less hCG than choriocarcinoma, β-hCG is still the best available serum marker to follow the disease and treatment course of PSTT. Since the rarity of PSTT limits our understanding of its biologic behavior and treatment alternatives, the reporting of further cases of PSTT should be encouraged. Analysis of information obtained from series of patients with PSTT and even singular cases forms an important source of knowledge for future research and treatment recommendations of this entity.

References

[1] Feltmate C.M., Genest D.R., Wise L., Bernstein M.R., Goldstein D.P., Berkovitz R.S.: "Placental site trophoblastic tumor: a 17-year experience at the New England Trophoblastic Disease Center". *Gynecol. Oncol.*, 2001, *82*, 415.

[2] Papadopoulos A.J., Foskett M., Seckl M.J., McNeish I., Paradinas F.J., Rees H., Newlands E.S.: "Twenty-five years' clinical experience with placental site trophoblastic tumors". *J. Reprod. Med.,* 2002, *47,* 460.

[3] Hassadia A., Gillespie A., Tidy J., Everard J., Wells M., Coleman R., Hancock B.: "Placental site trophoblastic tumour: Clinical features and management". *Gynecol. Oncol.,* 2005, *99*, 603.

[4] Baergen R.N., Rutgers J.L., Young R.H., Osann K., Scully R.E.: "Placental site trophoblastic tumor: A study of 55 cases and review of the literature emphasizing factors of prognostic significance". *Gynecol. Oncol.,* 2006, *100,* 511.
[5] Shih I-M., Mazur M.T., Kurman R.J.: "Gestationanl trophoblastic disease and related lesions". In: Kurman R.J. (ed.). "Blaustein's Pathology of the Female Genital Tract", 5th edition, New York, Berlin, Heidelberg, Springer-Verlag, 2002, 1193.
[6] Kurman R.J., Scully R.E., Norris H.J.: "Trophoblastic pseudotumor of the uterus. An exaggerated form of "synctial endometritis" simulating a malignant tumor". *Cancer,* 1976, *38,* 1214.
[7] Twiggs L.B., Okagaki T., Phillips G.L., Stroemer J.R., Adcock L.L.: "Trophoblastic pseudotumor – evidence of malignant disease potential". *Gynecol. Oncol.,* 1981, *12*, 238.
[8] Scully R.E., Young R.H.: "Trophoblastic pseudotumor: a reappraisal". *Am. J. Surg. Pathol.,* 1981, *5,* 75.
[9] Kim S.J.: "Placental site trophoblastic tumor". *Best Pract. Res. Clin. Obstet. Gynecol.,* 2003, *17*, 969.
[10] Shih I.M., Kurman R.J.: "Epithelioid trophoblastic tumor: a rare neoplasm distinct from choriocarcinoma and placental site trophoblastic tumor simulating carcinoma". *Am. J. Surg. Pathol.,* 1998, *22*, 1393.
[11] Shih I.M., Kurman R.J.: "The pathology of intermediate trophoblastic tumors and tumor-like lesions". *Int. J. Gynecol. Pathol.,* 2001, *20,* 31.
[12] Machtinger R., Gotlieb W., Korach J., Fridman E., Apter S., Goldenberg M., Ben-Baruch G.: "Placental site trophoblastic tumor: outcome of five cases including fertility preserving management". *Gynecol. Oncol.,* 2005, *96,* 56.
[13] Nigam S., Singhal N., Gupta S.K., Chhabra D., Manaktala U.: "Placental site trophoblastic tumor in a postmenopausal female – A case report". *Gynecol. Oncol.,* 2004, *93*, 550.
[14] Dainty L.A., Winter W.E., Maxwell G.L.: "The clinical behavior of placental site trophoblastic tumor and contemporary methods of management". *Clin. Obstet. Gynecol.,* 2003, *46,* 607.
[15] FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia. *Int. J. Obstet. Gynecol.,* 2002, *77,* 285.
[16] Guvendagguven E.S., Guven S., Esinler I., Ayhan A., Kucukali T., Usubutun A.: "Placental site trophoblastic tumor in a patient with brain and lung metastases". *Int. J. Gynecol. Cancer,* 2004, *14*, 558.
[17] Palmieri C., Fisher R.A., Sebire N., Lindsay I., Smith J.R., McGluggage W.G. *et al.*: "Placental site trophoblastic tumor arising from a partial hydatidifrom mole". *Lancet,* 2005, *355,* 688.
[18] Moore-Maxwell C.A., Robboy S.J.: "Placental site trophoblastic tumor arising from antecedent molar pregnancy". *Gynecol. Oncol.,* 2004, *92*, 708.
[19] McLellan R., Buscema J., Currie J.L., Woodruff J.D.: "Placental site trophoblastic tumor in a postmenopausal woman". *Am. J. Clin. Pathol.,* 1991, *95,* 670.
[20] Metindir J., Pak I., Ozdilekcan C., Eren E.: "Chemoresistant placental site trophoblastic tumor with hilar lymph node metastasis: an unusual site of involvement". *Gyncol. Oncol.,* 2005, *96,* 552.
[21] Sakhel K., Khalil A., Kaspar H., Azar G., Mansour A., Nassar A.: "Placental site trophoblastic tumor in a patient with secondary infertility and radiological findings consistent with a leiomyoma: a case report". *Int. J. Gynecol. Cancer,* 2004, *14,* 694.
[22] Tsuji Y., Tsubamoto H., Hori M., Ogasawara T., Koyama K.: "Case of PSTT treated with chemotherapy followed by open uterine tumor resection to preserve fertility". *Gynecol. Oncol.,* 2002, *87,* 303.
[23] Ajithkumar T.V., Abraham E.K., Rejnishkumar R., Minimole A.L.: "Placental site trophoblastic tumor". *Obstet. Gynecol. Surv.*, 2003, *58,* 484.

Address reprint requests to:
B. PIURA, M.D., F.R.C.O.G.
Unit of Gynecologic Oncology
Department of Obstetrics and Gynecology
Soroka Medical Center
and Faculty of Health Sciences
Ben-Gurion University of the Negev
P.O. Box 151
84101 Beer-Sheva (Israel)