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Review Article

Placental site trophoblastic tumor and epithelioid trophoblastic tumor: Clinical and pathological features, prognostic variables and treatment strategy

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HIGHLIGHTS

- Placental Site Trophoblastic Tumor and Epithelioid Trophoblastic Tumor are rare Gestational Trophoblastic Neoplasias.
- Prognostic factors include stage and interval of ≥48 months since antecedent pregnancy.
- Patients diagnosed at early stage should be treated surgically with adjuvant chemotherapy reserved for high risk cases.
- A combination of surgery and chemotherapy is recommended for patients with metastatic disease.

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ABSTRACT

Placental site trophoblastic tumor [PSTT] and epithelioid trophoblastic tumor [ETT] are the rarest gestational trophoblastic neoplasias, developing from intermediate trophoblast of the implantation site and chorion leave, respectively. PSTT and ETT share some clinical-pathological features, such as slow growth rates, early stage at presentation, relatively low βhCG levels and poor response to chemotherapy. The mortality rate ranges from 6.5% to 27% for PSTT and from 10% to 24.2% for ETT. Advanced stage, long interval between antecedent pregnancy and diagnosis, and presence of clear cells are the independent prognostic variables for PSTT, and they may be similar for ETT. Hysterectomy can represent the only therapy for early disease, whereas adjuvant chemotherapy should be reserved to patients with poor risk factors, such as an interval from the antecedent pregnancy >4 years, deep myometrial invasion or serosal involvement. Few cases of fertility-sparing treatment in young women have been reported. An individualized multidisciplinary approach, including chemotherapy and debulking surgery with abdominal and/or extra-abdominal procedures, is warranted for advanced disease. EP/EMA and TP/TE are the preferred regimens in this setting. Immunohistochemistry has sometimes shown expression of EGFR, VEGF, MAPK, PDGF-R and PD-L1, and therefore investigational studies on biological agents targeting these molecules are strongly warranted for chemotherapy resistant-disease.

Contents

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1. Introduction

Gestational trophoblastic disease is a spectrum of benign and malignant gestational lesions consisting of two major groups, which recapitulate the development of early placenta and the implantation site, and include molar lesions, which represent abnormal villous development, and non-molar lesions [1–3]. Non-molar lesions show a relatively wide range of histologic subtypes including benign lesions, such as placental site nodule and exaggerated placental site, and neoplastic tumors, such as choriocarcinoma, placental site trophoblastic tumor [PSTT] and epithelioid trophoblastic tumor [ETT]. Studies on gene expression profiles in different human trophoblastic subpopulations have elucidated the lineage and differentiation of trophoblast and its relation to various intermediate trophoblastic tumors and confirmed histologic classification. Both ETT and placental site nodule are related to the intermediate trophoblast located in the chorion leave of the placental membranes, while PSTT and exaggerated placental site are related to the intermediate trophoblast in the normal implantation site [1,2]. Choriocarcinoma is characterized by syncytiotrophoblast and cytotrophoblast of either villous or non-villous type. Invasive mole, choriocarcinoma, PSTT and ETT are also referred to as gestational trophoblastic neoplasia [GTN] [4–7]. PSTT and ETT represent the rarest GTNs. PSTT was first described by Kurman et al. [8], who analyzed 12 cases of a trophoblastic uterine pseudotumor, and interpreted them as an exaggerated form of syncytial endometritis mimicking a malignant tumor. The lesion could be distinguished from choriocarcinoma by the absence of the dimorphic population of cytotrophoblast and syncytiotrophoblast. This tumor was subsequently renamed PSTT after the demonstration of its potentially malignant behavior [9]. Roughly 725 cases have been described in the literature [10]. ETT is an entity firstly described by Mazur and Kurmar, and further elucidated by Shin and Kurman [11]. Approximately 110 cases have been reported up to date [12].

Roughly 30% of patients with GTNs have metastases at the time of diagnosis, most commonly to the lungs, vagina, liver, and brain [6], and PSTT and ETT have the same metastatic potential of the other types of GTN [12,13]. Consequently, the Federation International of Obstetrics and Gynecology [FIGO] staging system for PSTT and ETT is the same as for the other GTNs [7]. However, the FIGO scoring systems is not a prognosticator system in PSTT and ETT, since it is not correlated with the clinical outcomes.

The prognostic tool of patients with GTNs has drastically changed over the last decades, mainly due to the currently available chemotherapy regimens. In fact, since the introduction of effective chemotherapy regimens, patients with GTNs passed from nearly 100% fatality to nearly 100% cure rates [5].

Patients with low-risk GTN are treated with single-agent methotrexate with folinic acid rescue, or, less frequently, with actinomycin-D [7]. The combination of etoposide, actinomycin D and methotrexate [EMA] alternated with cyclophosphamide and vincristine [CO] is the most frequently adopted regimen for high-risk disease. EMA/CO-resistant patients usually achieve a complete response with etoposide + cisplatin [EP]/EMA or paclitaxel + cisplatin [TP] alternating with paclitaxel + etoposide [TE] or bleomycin + EP [BEP] [4,7].

Given the rarity of PSTT and ETT and the paucity of data reported in the literature, we sought to systematically review the literature, in order to offer a possible algorithm that may help the clinicians in diagnosing and treating patients affected by these very rare diseases.

2. Placental site trophoblastic tumor

2.1. General features

PSTT accounts for 0.2–3% of GTNs with an estimated incidence of 1 in 100,000 pregnancies [7,14–19]. Mean age of patients at diagnosis ranges from 29 to 35 years [12,14–24] (Table 1a). However, anecdotal cases have been reported also in postmenopausal women [17,18]. PSTT is usually preceded by any gestational event after a median interval of 3–-36 months [13–24] (Table 1a). Most antecedent pregnancies consisted of full term or preterm deliveries, but spontaneous abortions and moles are often reported.

At diagnosis, PSTT is confined to the uterus in approximately two thirds of the cases (range: 41.2–100%) (Table 1b). The most common site of metastasis is the lung, with an incidence at diagnosis of 10–29% [16,22]. Less common sites of metastasis are represented by the liver, brain, spinal cord, ovary/ies, vagina, peritoneum, spleen, and pancreas [20,25,26]. Lan et al. [15] reported lymph nodal involvement in 17 (5.9%) of 286 patients with PSTT reported in their cohort. Stage and age at diagnosis were also correlated in the cohort reported by Chang et al. [20]. In fact, patients with metastatic PSTT were 3-year older ($p = 0.045$). Patients with metastatic disease had also a higher incidence of antecedent term delivery (82% *versus* 57%, $p = 0.043$), and a longer median interval between the antecedent pregnancy and the diagnosis of PSTT (24 months *versus* 12 months, $p = 0.016$) than those with disease confined to the uterus.

2.2. Signs and symptoms

The most common presenting symptom is abnormal vaginal bleeding, occurring in 31.3–79.4%of the cases, followed by amenorrhea [12–14,16–20,22–24] (Table 1b). Rarely the patients may suffer from nephrotic syndrome, virilization, galactorrhea, polycythemia. Back pain, dizziness, headache, and cough may be present as signs of metastatic disease Baseline serum β sub-unit of human chorionic gonadotropin [βhCG] levels are elevated in 77–90% of the cases, but they are usually much lower than those measured in choriocarcinoma [17–23]. In the series of Chang et al. [20], serum βhCG ranged from 1.1 to 8300 mIU/ml at presentation. The measurement of free-βhCG as a proportion of total βhCG could represent a useful biochemical tool for the differential diagnosis of GTN in women with persistent low βhCG levels [12]. Specifically, a proportion of free-βhCG >30% appears to be strongly suggestive of PSTT.

Table 1
Placental site trophoblastic tumor.

a) Patient age and obstetric history

Author	Patient (N)	Time since antecedent pregnancy	Obstetric history	Patient age (years)
Choi [24]	20	≤1 year in 16 pts (80%)	8 term pregnancies 8 abortions 2 molar pregnancies	Mean = 32 (range, 25–53)
Papadopoulos[16]	34	Mean = 3.4 years (95% CI = 1.9–4.9)	18 term pregnancies 5 abortions 7 molar pregnancies	Mean = 33 (95% CI = 25–41)
Baergen [22]	55	Mean = 34 months (range, 5–131)	32 term pregnancies 4 abortions 5 molar pregnancies	Mean = 32 (range, 20–62)
Chang [20]	88			
Non metastatic	61	Median = 12 months (range, 0.25–204)	31 term pregnancies 6 abortions 7 molar pregnancies	Mean = 29 (range,15–52)
Metastatic	27	Median = 24 months (range, 0–480)	18 term pregnancies 2 abortions 2 molar pregnancies	Mean = 32 (range, 21–53)
Zhao [18]	108	≤1 year 74 (69.8%)	67 term/preterm pregnancies 31 abortions 8 molar pregnancies 2 Unknown	Mean = 31.8 (range, 20–63)
Schimd [14]	62	NA	37 term pregnancies 16 abortions 9 molar pregnancies	Mean = 34.6 (range, 28–38)
Hyman [13]	17	Median = 9 months (range, 0–65)	10 term pregnancies 7 abortions	Median = 33 (range, 18–47)
Lee [19]	6	Median = 8 months (range 3–12)	5 term pregnancies 1 unknown	Median = 31 (range, 29–33)
Hassadia [17]	17	Median = 18 months (range,6 months–22 years)	13 term pregnancies 3 abortions 1 unknown	Median = 35 (range, 26–52)
Lan [15]	5	Mean = 3 months (range, 1 month–33 years)	NA	Median = 30 (range, 26–63)
Chen [23]	17	Mean = 14 months (range, 3–36)	15 term pregnancies 1 abortions 1 molar pregnancies	Mean ± SD = 32 ± 4

b) Symptoms and stage at presentation

Author	Patient (N)	Symptoms	Stage at presentation
Choi [24]	20	Abnormal vaginal Spotting or amenorrhea = 19 (95.0%)	I = 17 (85.0%)
Papadopoulos [16]	34	Vaginal bleeding = 27 (79.4%)	I = 15 (44.1%)
Baergen [22]	55	NA	I = 46 (83.6%) II = 1 (1.8%) III = 3 (5.4%) IV = 5 (9.1%)
Chang [20]	88	Vaginal bleeding = 55 (66.5%) Amenorrhea =38 (43.2%)	I = 58 (65.9%) II = 4 (4.5%) III = 10 (11.4%) IV = 11 (12.5%) NA = 5 (5.7%)
Zhao [18]	108	Vaginal bleeding = 77 (71.3%) and/or Amenorrhea = 38 (35.2%)	I = 71 (65.7%) II = 4 (3.7%) III = 31 (28.7%) IV = 2 (1.9%)
Schimd [14]	62	NA	I = 34 (54.8%) II = 5 (8.1%) III = 16 (25.8%) IV = 7 (11.3%)
Hyman [13]	17	Vaginal bleeding = 10 (58.8%) Amenorrhea = 2 (11.7%) Abdominal mass = 2 (11.7%) Back pain = 1 (5.9%) Dizziness = 1 (5.9%) Uterine rupture = 1 (5.9%) Nephrotic syndrome = 1 (5.9%)	I = 7 (41.2%) II = 1 (5.9%) III = 3 (17.6%) IV = 6 (35.3%)
Feltmate [21]	13	Vaginal bleeding = 8 (61.5%) Amenorrhea = 4 (30.8%) Persistent β-hCG = 1 (7.7%)	I = 9 (69.2%) >I = 4 (30.8%)
Lee [19]	6	Amenorrhea = 1 (16.7%) Vaginal bleeding = 5 (31.3%)	I = 6 (100.0%)
Hassadia [17]	17	Vaginal bleeding = 9 (52.9%) Amenorrhea = 4 (23.5%) Uterine rupture = 2 (11.8%)	I = 8 (47.1%) II = 1 (5.9%) III = 5 (29.4%)

Table 1 (*continued*)

b) Symptoms and stage at presentation

Author	Patient (N)	Symptoms	Stage at presentation
Chen [23]	17	Abdominal pain = 2 (11.8%) Enlarged neck node = 1 (5.9%) Amenorrhea = 2 (11.8%) Vaginal bleeding = 10 (58.8%) Amenorrhea and bleeding 5(29.4%)	IV = 3 (17.6%) I = 15 (88.2%) III = 2 (11.8%)

c) Survival by stage

Author	Patient (N)	Stage (N)	Clinical outcome
Schimd [14]	62	I (34)	10-Year OS = 90% p = 0.001
		II (5)	10-Year OS = 52%
		III–IV (23)	10-Year OS = 49%
Zhao [18]	108	I (71)	Mean OS = 171.3 months p = 0.003
		II (4)	Mean OS = 43 months
		III (31)	Mean OS = 123.8 months
		IV (2)	Mean OS = 9.5 months
Chang [20]	88	I–II (62)	OS = 93.5% p < 0.0001
		III–IV (21)[a]	OS = 33.3%
Hyman [13]	17	I–III (11)	2-Year OS = 100% (p = 0.009)
		IV (6)	2-Year OS = 33%
Hassadia [17]	17	I (8)	Alive with NED = 8/8[b]
		II–IV (9)	Alive with NED = 4/9[c]

Legend: N, number; 95% CI, 95% confidence interval; NA, not available; SD, standard deviation; β-hCG, β-human chorionic gonadotropin; OS, overall survival; NED, no evidence of disease.
[a] Sufficient information for staging not available for 5 patients.
[b] After a follow-up ranging from 3 months to 11 years.
[c] After a follow-up ranging from 2.5 years to 11 years.

2.3. Pathologic features

The cells of PSTT resemble the cell population arising from the blastocyst which infiltrate the endometrium and the surrounding myometrium in early gestation [24]. Differently to the normal implantation site which is confined to the inner third of the myometrium, PSTTs are more invasive [22]. Macroscopically, these tumors form solid, tan-yellow, soft and fleshy masses which can be polypoid (Fig. 1), and can invade the perimetrium and parauterine tissues. Areas of hemorrhage and necrosis may also occur. Microscopically, sheets, nests and rows of uniform tumor cells infiltrate the myometrium, typically replacing the wall of the vessels with fibrinoid deposits (Fig. 2). Tumor cells are rounded or polygonal, and more rarely spindled, with eosinophilic cytoplasm and irregular hyperchromatic nuclei [11,21,22,26]. Multinucleated cells are not uncommon and show the eosinophilic cytoplasm and nuclei similar to mononuclear cells. However, mixed forms with choriocarcinoma and PSTT may rarely occur.

Immunohistochemical markers of implantation trophoblasts such as human Placental Lactogen [hPl], Mel-CAM (CD146), CD10, HLA-G, and Mucin-4 are positive in tumor cells, whereas hCG and placental alkaline phosphatase [PLAP] are detected in a small proportion of cells [12,25,27]. P63, a transcription factor belonging to the p53 family [28], and SALL4, a transcription factor displaying essential functions in embryonic stem cells, are not expressed in this tumor [29]. Ki-67 labelling index usually ranges from 8 to 20%. Positive p53 immunostaining was noted in 6 (100%) of the 6 patients with recurrent/metastatic PSTT *versus* only one (16.7%) of the 6 patients with disease confined to the uterus ($p = 0.015$), which suggested a possible role of p53 in tumor progression [30]. Lan et al. [15] described a strongly positive staining for Epidermal Growth Factor Receptor [EGFR] and Vascular Endothelial Growth Factor [VEGF], and negative staining for HER2/neu and CD117 in all the 5 patients with PSTT who were tested. In early and term normal placenta, immunohistochemical Programmed Death –Ligand1 [PD-L1] expression was found to be high in the outer surface of syncytiotrophoblast, undetectable in the cytotrophoblast, and very weak and focal or undetectable in the intermediate trophoblast [31]. In the same study, strong and diffuse PD-L1 immunoreactivity was detected in 7/7 (100%) complete moles, 22/30 (73.3%) choriocarcinomas, but only in 2/6 (33.3%) PSTTs. In the other 4 PSTTs immunoreactivity was weak and focal or undetectable. The phosphorylated form of Mitogen- Activated Protein Kinase [MAPK] was found in cells from 84% of PSTTs, but not in healthy intermediate trophoblastic cells, whereas the total concentration of MAPK was similar in these two cellular types, which suggested that MAPK activation was probably due to epigenetic events [28].

2.4. Diagnostic imaging features

The reliability of the different imaging techniques in the diagnosis of PSTT is debated. Ultrasound [US] may identify a solid mass within the endometrial cavity or in the myometrium with more or less prominent blood vessels on color Doppler imaging, whereas in other cases US evidences only an enlarged heterogeneous uterus with echogenic foci and cystic areas of hemorrhage [32,33]. Brand and Coakley [32] failed to detect PSTT by trans-vaginal or -abdominal US in 2 cases, whereas the tumor was barely visible during intraoperative ultrasound in another one case. Zhou et al. [33] suggested that PSTT can present three different sonographic patterns. Type 1 appears as a heterogeneous solid mass in the uterine cavity with minimal to moderate vascularization. Type 2 consists of a heterogeneous solid mass in the myometrium with minimal to high vascularization. Type 3 presents as a lacunar–like lesion with cystic areas in the myometrium, and high vascularization at color doppler. MRI features are not specific as well. In the study by Brandt and Coakley [32], all 3 PSTTs were isointense as compared to myometrium on T1-weighted imaging, and isointense to slightly hyperintense on T2-weighted imaging. In one case a central area of lower signal intensity was seen, in one case a central focus was detected that did not enhance with gadolinium, and in another one MRI findings resembled those of cervical cancer.

The staging of PSTT needs extensive imaging procedures, including chest and abdominal CT, MRI of the brain and the pelvis, and whole body positron emission tomography (PET), which are useful to assess the extent and the metastatic spread of the disease [6,7,12,34]. However, the choice of the imaging techniques to use should be left to discretion of the provider and presenting symptoms.

2.5. Prognosis

The mortality rate of women with a diagnosis of PSTT ranges from 6.5% to 27% [14,18,21,22]. Schmid et al. [14] retrospectively identified 62 cases of PSTT among 35.550 women with gestational trophoblastic disease assessed at two UK referral centers (Weston Park Hospital, Sheffield and Charing Cross Hospital, London) between 1976 and 2006. In this series, the 10-year disease free survival [DFS] and 10-year overall survival [OS] were 70% and 73%, respectively. Zhao et al. [18] analyzed 108 patients with PSTT from eight Chinese centers between 1998 and 2013, and reported that 93 (86.1%) were alive without disease [NED], 8 (7.4%) were alive with disease and 7 (6.5%) died of PSTT or secondary diseases. Baergen et al. [22], who conducted a clinical-pathological study of 55 cases diagnosed in United States and 180 cases reviewed from the literature, reported a 4-year OS ranging from 80% to 86%.

Data regarding the prognostic relevance of different clinical-pathological variables are not conclusive. At univariate analysis, advanced stage [13,14,17,18,21,22], presence and number of distant metastases [14,16], long interval between antecedent pregnancy and diagnosis of PSTT [14,16,18,22], older age [14,22], deep myometrial invasion [22], high mitotic index [14,21,22], presence of necrosis [18,22], presence of cells with clear cytoplasm [22] and elevated βhCG levels [14,22] have been reported as associated with lower DFS and OS. Advanced stage [18,22], long interval between antecedent pregnancy and diagnosis of PSTT [14], and presence of clear cells [22] were independent poor prognostic variables at multivariable analysis.

Schmid et al. [14] found that 10-year OS ranged from 90% for stage I to 49% for stage III-IV ($p = 0.001$), and Zhao et al. [18] reported that mean OS ranged from 171.3 months for stage I, to 9.5 months for stage IV ($p = 0.003$), and that uterine size and the maximum lesion diameter had no significant impact on the clinical outcome (Table 1c). Baergen et al. [22] noted that >90% of stage I patients were alive at 48 months *versus* only 41% of those with stage III-IV disease. All cases confined to the inner third of the myometrium had a favorable outcome, whereas recurrence or metastasis developed in 15% of cases involving the outer half of the myometrium. It is noteworthy that 50% of the patients with tumor involving the serosa died of their disease.

In the series of the New England Trophoblastic Disease Center [NETDC], 3/9 (33.3%) patients diagnosed in stage I relapsed *versus* 2/3 patients (66.6%) who presented with metastases [21]. In the experience of the Charing Cross Hospital on 34 patients with PSTT, lung metastases and an antecedent pregnancy interval ≥ 4 years were risk factors for death, whereas women with no extra-pelvic disease or a pregnancy interval < 4 years had 100% OS [16]. The analysis of Schmid et al. [14] confirmed that a cut-off value of 48 months since antecedent pregnancy could differentiate between patients with good or bad prognosis. Of the 14 patients who died, 13 had an interval ≥ 48 months since the antecedent pregnancy, and only one patient had a shorter interval (hazard ratio [HR] = 93.1, $p < 0.0001$). Conversely, in the small series of Hyman et al. [13], the 2-year OS was similar in the 10 patients with an interval from the antecedent pregnancy <12 months, and in the 7 with longer interval (78% *versus* 69%, $p = 0.284$).

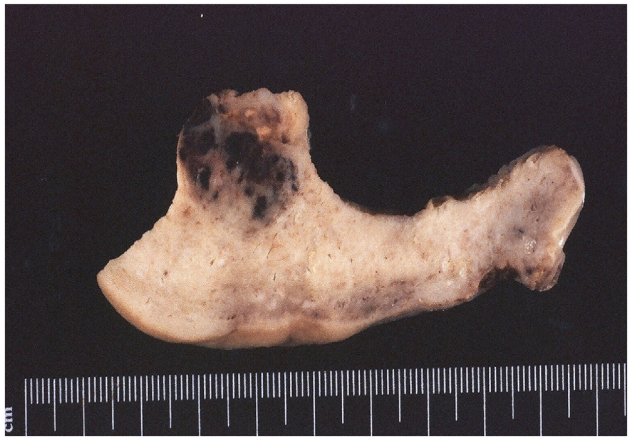

Fig. 1. Placental Site Trophoblastic Tumor presenting as a polypoid mass infiltrating the myometrium.

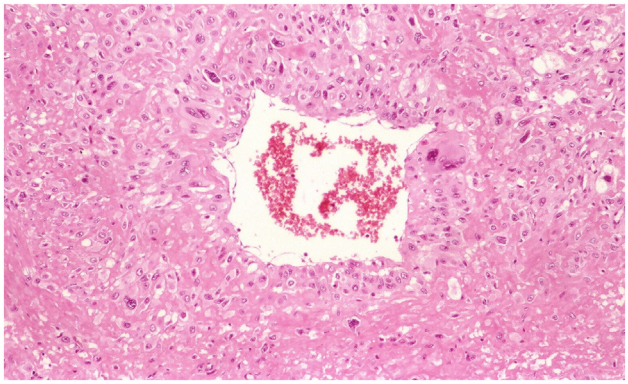

Fig. 2. Microscopic features of Placental Site Trophoblastic Tumor: sheets, nests and rows of uniform tumor cells that infiltrate the myometrium, and replace the wall of vessels with fibrinoid deposits.

Older age was associated with an unfavorable outcome in some series [14,23] but not in others [13,20,21].

The presence of tumor cells with clear cytoplasm was an independent poor prognostic variable in the series of Baergen et al. [22]. Moreover, these authors reported an OS of 94–100% for cases with no or minimal necrosis *versus* 64–75% for those with intense necrosis.

The prognostic value of mitotic index and baseline serum βhCG levels is of uncertain significance. Baergen et al. [22] reported that OS ranged from 88% to 100% among patients with a mitotic count <2.5 mitoses/10 high power fields [HPF] *versus* 48% to 52% among those with a mitotic count >6 mitoses/10 HPF. Feltmate et al. [21] noted that mitotic count was higher in patients who developed recurrent disease compared to those who did not (10 *versus* 2 mitoses/10 HPF, $p = 0.04$), and that women with a mitotic count <5 mitoses/10 HPF did not experience any recurrence. Increasing mitotic index was a poor prognostic variable for OS on univariate but not on multivariable analysis in the series reported by Schmid et al. [14], whereas this variable had no prognostic relevance in the Chang et al. [20] cohort.

Schmid et al. [14] reported that increasing serum βhCG levels correlated with a worse OS on univariate analysis ($p = 0.0276$) but not on multivariable analysis. In other studies βhCG levels had no prognostic implications [13,18,20].

2.6. Treatment

Total hysterectomy is the treatment of choice for early stage, because of the relative chemoresistance of the disease [4,5,7,11,13,15,16,18–20,35,36]. Grossly uninvolved ovaries can be left in place in young women, because ovarian metastases are uncommon and oophorectomy does not seem to improve survival [19]. Lymphadenectomy can be performed in presence of deep myometrial invasion or macroscopically suspicious nodes.

Stage I patients who underwent hysterectomy experienced long-term OS rates ranging from 90% to 100% in most series [10,13,14,17–22]. Adjuvant chemotherapy did not seem to offer any significant benefit in this clinical setting. A review of 60 patients with stage I disease treated with either surgery alone or surgery plus chemotherapy, reported 10-year OS rates of 96.7% and 79.1% ($p = 0.199$), respectively [10]. On the other side, Schmid et al. [14] noted that the 3 patients with stage II disease who underwent surgery and chemotherapy were

alive without evidence of disease at publication, while the 2 patients with stage II who underwent surgery alone developed a recurrence of their disease.

Although randomised trials have not been performed because of the rarity of this tumor, adjuvant chemotherapy is usually suggested for patients with either an interval from the antecedent pregnancy >4 years or those with deep myometrial invasion or serosal involvement or high mitotic index or for those with stage II disease [12,14]. European Society of Medical Oncology [ESMO] guidelines currently advocate 8 weeks of adjuvant EP/EMA or TP/TE when indicated [7].

Feltmate et al. [21] analyzed 13 hysterectomized patients with PSTT, 8 of whom had received adjuvant chemotherapy. Only one of the 4 patients who underwent chemotherapy within one week of surgery developed a recurrence, while all the 4 patients who started chemotherapy after 3 or more weeks after surgery experienced a recurrence. These data suggest that adjuvant chemotherapy, when indicated, should be administered soon after surgery.

Very few data are available about fertility-sparing treatment in young patients with PSTT apparently confined to the uterine body [18,36–38]. The treatment consisted of hysteroscopic or transabdominal focal uterine resection with or without chemotherapy. Zhao et al. [18] reported that 23 of the 108 patients with PSTT in their cohort had a conservative management, and only one patient in the conservative group died of disease. A successful pregnancy was achieved in 7 patients: 6 women had full-term deliveries with healthy babies, whereas the last patient was lost at follow-up after the second trimester. A systematic review of literature from 1996 to 2017 analyzed 5 case reports and 3 retrospective studies on this issue [38]. Twelve patients underwent laparotomy with local uterine resection, but this surgical approach failed in 5 of them and a definitive treatment with total hysterectomy was then performed. Five patients were successfully treated with a combination of individualized surgery and systemic and/or intrauterine arterial infusion of chemotherapy.

A fertility-sparing approach can be taken into consideration in highly selected young women who strongly desire to preserve the childbearing potential and who have disease confined to the uterus without poor prognostic factors. A close monitoring of post-surgical serum βhCG level is warranted. If the βhCG levels do not normalize, or subsequently rise, total hysterectomy is warranted, even in absence of detectable uterine disease at radiological examinations [37].

The treatment of advanced PSTT with chemotherapy alone is unsuccessful. A long- term control of the disease can only be obtained with an individualized multimodality approach consisting of a combination of chemotherapy and surgery [12,21,23,26,28]. EMA/CO and even more EP/EMA and TP/TE are the preferred regimens that must be continued for 8 weeks after normalization of βhCG levels [5,7]. Surgical resection of residual lesions after chemotherapy should be performed whenever possible [12,14].

Schmid et al. [14] reported 23 patients with stage III-IV PSTT. A long-term disease control was achieved in 2/8 (25.0%) patients treated with chemotherapy alone, 8/14 (57.1%) patients who underwent chemotherapy and surgery, and in the patient treated by surgery alone. These authors detected viable tumor cells on final pathology in several patients who underwent resection of persistent disease after chemotherapy. Patients with unresectable, persistent or recurrent PSTT should receive additional chemotherapy with the same salvage regimens employed for the other types of GTN, such as PEB, ifosfamide + carboplatin + etoposide [ICE], etoposide + ifosfamide + cisplatin [VIP], 5-fluorouracil + actinomycin-D [FA], floxuridine + actinomycin-D + etoposide + vincristine [FAEV], and high dose chemotherapy with peripheral blood stem cell support [4,7,12]. Individualized radiotherapy can be sometimes considered. An increased risk of second malignancies, and especially of leukemia, has been reported after EMA/CO administration [18,39].

3. Epithelioid trophoblastic tumor

3.1. General features

ETT is the rarest variant of GTN. Different presentations have been reported: isolated uterine or cervical disease, isolated extra-uterine disease, or primary uterine tumor with metastatic disease [12,40]. The uterine corpus is the primary site of ETT (40%), followed by the uterine cervix (31%); extra-uterine sites are represented more frequently by the lung (19%), and more rarely by the small bowel, vagina, fallopian tube/s, broad ligament, and gallbladder. Median age at presentation ranges from to 33 to 40 years in most series, but some postmenopausal women with ETT have been reported [41–48] (Table 2). ETTs develop more commonly after a mean interval of 76 months (range: 2–-300 months) from a gestational event, represented by a term delivery (approximately in 43% of the cases), a molar pregnancy (39%), or an abortion (18%) [12,44,48] (Table 2). However, some cases have been reported without any antecedent pregnancy related.

3.2. Signs and symptoms

Patients often have symptoms similar to those of PSTT [40,44,46]. Abnormal vaginal bleeding is the most frequent complaint at time of presentation (57–67% of the cases), followed by amenorrhea, abdominal pain, and abdominal bloating. Extra-uterine or metastatic disease at presentation can be detected in 25–42% of the cases [43,49]. Although patients with extra-uterine ETT may be asymptomatic, some women may experience metastasis-related symptoms, such as dyspnea, shortness of breath and hemoptysis [48,49]. Nephrotic syndrome and virilization are seldom detected. ETTs have been occasionally detected during a laparotomy or laparoscopy performed for presumed abdominal neoplastic mass or ectopic pregnancy [49,50].

ETT, that is frequently present in the lower uterine segment or cervix, is sometimes misdiagnosed as primary carcinoma of the uterine cervix [11,12,43]. Serum βhCG levels widely range from 12 to 148,460 mIU/ml, but are usually slight to moderately elevated (665–2500 mIU/ml) [42].

3.3. Pathologic features

Unlike PSTT, which is a typical tumor of the uterine corpus, ETT is commonly found in the uterine cervix (31%) and in extra-uterine localizations, particularly in the lung (19%). Macroscopic features clearly depend by the site and the diameter of the lesions, that may range from 0.5 to 14.8 cm [12,40,42,43,51,52]. Microscopically, ETT resembles an epithelial malignant tumor, particularly squamous cell carcinoma. Cords, nests, and sheets of monotonous eosinophilic cells are associated with extensive geographic necrosis and deposits of hyaline-like material (Fig. 3). The mitotic count ranges from 0 to 12 mitoses/10 HPF, with a mean value of 2 mitoses/10HPF. The mitotic count correlates to the values of Ki-67, that may range from 2 to 3 to 77%, with a mean value of 15–18% [11,44,49–51]. Tumor cells show a differentiation similar to the citotrophoblast of the chorion leave. At immunohistochemistry, ETT cells present a positive staining for inhibin-α, cytokeratin 18, cytokeratin AE1/AE3, epithelial membrane antigen [EMA], E-cadherin, prolyl 4-hydroxylase, and EGFR, and a focal positivity for hCG, hPL, PLAP and Mel-CAM [11,12,41,42,45,48–51]. Positive staining for p63 and its truncated isoform p40 is useful for differentiating ETT from PSTT, but not from squamous cell carcinoma [44,49,53]. SALL4 was not expressed in 1 ETT and in 2 mixed PSTT and ETT in which it was tested [29]. Cyclin-E was found to be expressed in ETT, but not in the intermediate trophoblastic cells of the chorion leave [28]. Positive immunostaining for EGFR, VEGF receptor [VEGF-R], and platelet-derived growth factor receptor [PDGF-R] was detected in a mixed trophoblastic tumor that included ETT, PSTT and a focal area of choriocarcinoma [54]. PD-L1 immunoreactivity was strong and diffuse in 4 (28.6%), weak and

focal in 4 (28.6%) and undetectable in 6 (42.8%) of the 14 ETTs in which it was tested [31].

Since tumor cells can replace the endocervical surface epithelium and the hyaline-like matrix can resemble keratin, ETT can be sometimes misdiagnosed as squamous cell carcinoma of the uterine cervix [12,29,43,52]. Inhibin-α and cytokeratin 18 should be expressed in ETT, but not in squamous cell carcinoma, and it may help in the differential diagnosis. Moreover, the presence of decidualized stromal cells, and the absence of intercellular bridges between the neoplastic cells, should suggest a diagnosis of ETT [51].

Diagnostic imaging features.

3.4. Diagnostic imaging features

Pelvic US performed by experienced physicians may help in discriminating ETT from other types of GTN [6,53]. Specific features include a well-circumscribed border with hypoechogenic halo in the gray-scale. This feature was reported in all the 12 patients (100%) diagnosed with ETTs, one of the 21 (4.8%) with PSTT, and one of the 16 cases (6.3%) with invasive mole or choriocarcinoma ($p < 0.001$) [53]. The well-defined border reflects the expansile growth pattern, that forms interfaces between the tumor and the surrounding fibers, whereas the hypoechogenic halo may correlate with the dilated lymphatic and blood vessels adjacent to tumor borders. ETT shows more neovascularization (doppler signal) at the periphery of the tumor than in the intratumoral area, in contrast with the other types of GTN, that present minimal, moderate or remarkable neovascularization within the tumor but not on the surface.

MRI and CT are more reliable than US for both differentiating ETT from other types of GTN or from other uterine tumors, and assessing the extra-uterine extension and metastatic spread of the disease [6,7,45]. The tumor can appear as a well-circumscribed mass hyper-intense on T2-weighted images, isointense on T1-weighted images, and heterogeneously enhanced after gadolinium administration.

The staging of ETT includes chest and abdominal CT and PET, which are useful to assess the extent and the metastatic spread of the disease. PET/CT is also useful for the evaluation of the response to the treatments, and for the detection of recurrences [6,7,55].

3.5. Prognosis

From a prognostic standpoint, ETT has a biological behavior very similar to that of PSTT, but data on this issue are very scanty [7]. The clinical course of ETT is difficult to predict: the risk of metastatic spread at time of diagnosis is 25%, and the overall risk of death is 10–24.2% [12,42,44,49]. The analysis of 62 cases of patients with ETT reviewed by Zhang et al. [42], revealed that 19 (30.6%) patients experienced a recurrence, and 15 (24.2%) died after a median follow-up of 22 months (range: 1–192 months).

The prognostic variables of ETT may be similar to those described for PSTT. In the study of Zhang et al. [42], FIGO stage was the only significant prognostic factor for OS. Multifocal lesions in bulky uterus, full-thickness myometrial invasion and uterine serosal involvement were associated with unfavorable clinical outcome in the 9 patients with ETT assessed by Shen et al. [56].

An interval from the antecedent pregnancy >4 years was a bad prognosticator in the study by Davis et al. [43]. Between the 7 cases of ETT included in the NETDC database from 1998 to 2014, all the patients with an interval following the prior pregnancy >4 years had stable or progressive disease despite intensive chemotherapy. Conversely, Zhang et al. [42] failed to detect a prognostic value for the time from the precedent gestation. The association between high mitotic index and clinical outcome is debated [20,51,57,58]. In a series of 5 cases by Fadare et al. [57], the only patient who died of metastatic disease had a mitotic count of 48 mitoses/10 HPF, which was superior to all the other patients. Conversely, a patient reported by Sung et al. [58] with 36 mitoses/10 HPF and MIB-1 labeling index of 36.1% did not experience any recurrence during the 8 years of follow-up.

Patient age, tumor size, and serum βhCG levels do not seem to correlate with the clinical outcome, whereas the prognostic relevance of p53 expression is still uncertain [20,42,59].

3.6. Treatment

The therapeutic planning of ETT, which is relatively chemoresistant, is similar to that of PSTT. Hysterectomy is the cornerstone of treatment when the disease is confined to the uterus, whereas a multimodality approach is needed for advanced disease [4,5,7,12,40,42–44,45,48,49]. Rodriguez-Truillo et al. [44] described two cases of cervical ETT in postmenopausal women who underwent primary surgery. The first

Table 2
Epithelioid trophoblastic tumor: patient age and obstetric history.

Author	Patient number	Time since antecedent pregnancy	Obstetric history	Patient age
Sobecki-Rausch [46]	5		1 term pregnancies 2 abortions 2 unknown	Mean = 38 years
Rodriguez-Trujillo [44]	2	33 years 30 years	1 term pregnancies 1 abortions	63 years 57 years
Ohya [45]	1	33 years	4 term pregnancies 1 abortions	56 years
Tse [47]	5	Median = 31.8 months	1 ectopic pregnancy 3 abortions 1 molar pregnancies Unknown	Median = 32.5 years (range, 20–50)
Zhang [42]	78	36 (0–300 months)	4 term pregnancies 23 abortions 15 molar pregnancies 2 ectopic pregnancies 34 unknown	Mean ± SD = 37.1 ± 8.7 years
Coulson [51]	1	17 years	1 molar pregnancy	66 years
Kuo [41]	1	10 years	1 gestational Trophoblastic Neoplasia	41 years
Davis [43]	7	Mean = 104 months (range, 12–264)[a]	4 term pregnancies 2 molar pregnancies	mean = 39.7 years (range, 31–51)

Legend: SD, standard deviation.
[a] 6 patients had a documented antecedent pregnancy.

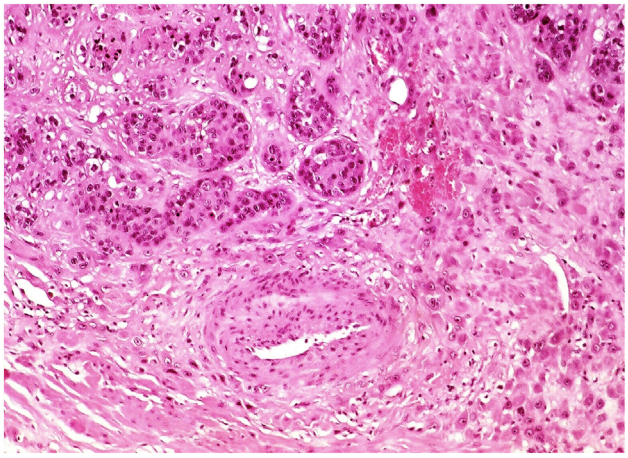

Fig. 3. Microscopic features of Epithelioid Trophoblastic tumor: cords, nests, and sheets of monotonous eosinophilic cells are associated with extensive geographic necrosis and deposits of hyaline-like material.

remained disease-free and died 5 years later for a rectal adenocarcinoma, and the second was alive with no evidence of disease (NED) at time of publication. In the series of Davis et al. [43] 3 patients with ETT confined to the uterus underwent hysterectomy, followed by EP/EMA in one case. Two patients were alive (NED) after 23 and 40 months respectively. The last one developed lung and vaginal metastases within 3 months. Similarly to PSTT, adjuvant chemotherapy with EP/EMA or TE/TP for 8 weeks can be proposed to patients with poor risk factors. These include an interval from the antecedent pregnancy >4 years, presence of multifocal lesions in a bulky uterus, a deep myometrial invasion, or an involvement of the uterine serosa [7,12,43,56].

Data on fertility-sparing treatments in patients with ETT are even rarer than in those with PSTT. Tse et al. [47] reported the case of a 25-year old woman who underwent an emergency laparotomy for an acute abdominal pain and a posterior uterine cystic lesion discovered at US. A cystic mass over the posterior uterine serosa, extending from the uterine fundus to the pouch of Douglas, was detected and excised, with a final diagnosis of ETT. Hysterectomy was not performed and adjuvant chemotherapy was not given. The patient was still alive (NED) and delivered two full-term babies 4 and 7.5 years after the diagnosis. Another case of a successful fertility- sparing treatment in a 32-year-old woman has been reported [59]. She underwent laparoscopy for a suspicious ectopic pregnancy, and a 2 cm mass in the uterine cornual region was found and removed. Serum βhCG increased 4 weeks later and then the patient underwent unsuccessful adjuvant single-agent chemotherapy with methotrexate. MRI and PET/CT revealed a high signal intensity focus in the myometrium and multiple lung nodules, and the histopathological review of the first excised specimen showed an ETT mixed with choriocarcinoma. The patient achieved a complete serological and radiological response after 6 cycles of EMA and she had regular menses with NED 26 months after chemotherapy. Conversely, Davis et al. [43] reported of two patients with ETT who refused hysterectomy.

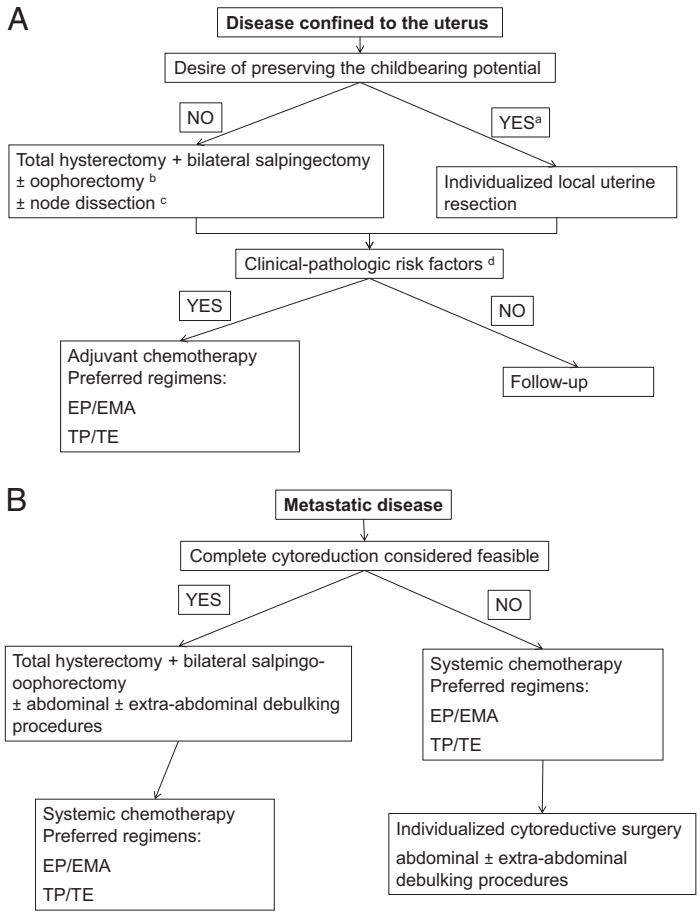

Fig. 4. Treatment algorithm for PSTT and ETT in patients with disease confined to the uterus (4A) and in patients with metastatic disease (4B). a) highly selected cases after exhaustive discussion and counseling b) oophorectomy can be avoided in premenopausal women with macroscopically uninvolved ovaries c) pelvic/aortic lymphadenectomy or sentinel node biopsy can be performed in PSTT patients with deep myometrial invasion (on preoperative imaging or intraoperative examination of uterine specimen) or suspicious nodes (on preoperative imaging or surgical exploration) d) interval from antecedent pregnancy >4 years; multifocal lesions in a bulky uterus; deep myometrial invasion; serosal involvement Legend; PSTT, placental site trophoblastic tumor; EP, etoposide + cisplatin; EMA, etoposide + actinomycin D + methotrexate; TP, paclitaxel + cisplatin; TE, paclitaxel + etoposide.

One had a subsequent spontaneous abortion followed by cervical recurrence, and the other one developed lung metastasis. Therefore, the safety of fertility-sparing treatment in ETT is still unproven.

Complete surgical resection, within a multimodality approach including chemotherapy, seems to be even more critical for advanced ETT than for advanced PSTT [5,7,12,40,42,43,46,48,49]. The surgical management of extra-uterine disease must be individualized and could include radical procedures such as bowel resection/s, upper abdominal procedures and extra-abdominal procedures, such as lung resection and excision of brain metastasis in highly selected cases. For instance, Lei et al. [48] performed a thoracoscopic lower left lobectomy combined with mediastinal lymphadenectomy for a metastatic ETT in the lung. The patient was disease-free at a short follow up of 3 months. Kim et al. [49] reported the case of a 42-year-old woman with pelvic masses and abdominal pain. Laparotomy revealed that the distal sigmoid colon was perforated with a fistula with a right-side pelvic mass. Three additional nodules were detected in the sigmoid mesentery and in the terminal ileum. The mass with the distal sigmoid colon fistula was removed through Hartmann's procedure, and also the other abdominal lesions were excised. The pathological diagnosis was ETT. The patient, who had no adjuvant treatment because of postoperative low serum βhCG and negative CT scan, was alive (NED) 9 months later. Sobecky et al. [46] reported 5 cases of ETT, of which 4 had lung metastases. All 5 women underwent hysterectomy, 3 had also resection of the metastatic pulmonary disease, and the 4 women with lung metastases received adjuvant platinum/etoposide-based chemotherapy. All 5 women were alive (NED) at publication.

In conclusion, surgery should be considered as the primary approach to patients with ETT. For those with extra-uterine disease, multiple surgical procedures (even extra-abdominal procedures) may be required to achieve tumor control. EMA/CO, and even more EP/EMA and TP/TE are the most commonly used regimens for metastatic disease. Patients with unresectable, persistent or recurrent disease should undergo the same salvage chemotherapy regimens proposed for refractory PSTT [4,5,7,12,60]. Chemoembolization can be useful for the management of complications, such as a life-threatening uterine hemorrhage, or for the treatment of liver metastases [6,60].

4. Conclusions

The presence of GTN, including PSTT or ETT, should be taken into consideration in any fertile age woman with abnormal vaginal bleeding and raised serum βhCG, especially after an antecedent pregnancy event. When the pathologic report is suggestive of PSTT or ETT, the specimen should be reviewed by a referent pathologist, and the diagnosis needs to be confirmed [5]. These tumors share some clinical-pathological features, such as slow growth rates, early stage at presentation, relatively low βhCG levels, and poor response to chemotherapy. ETT may be sometimes misdiagnosed as a squamous cell carcinoma of the uterine cervix.

Hysterectomy represents the therapeutic approach when the disease is confined to the uterus. Adjuvant chemotherapy is usually recommended to patients with poor prognostic factors (Fig. 4A). A fertility-sparing approach in young women who wish to preserve their childbearing potential, should be considered only in accurately selected patients, after an adequate and extensive counseling. An individualized multidisciplinary approach, including chemotherapy and debulking surgery with abdominal and extra-abdominal procedures when required and feasible, is indicated for metastatic disease (Fig. 4B).

Future improvements in the management of patients with these rare diseases require a better understanding of the biology of PSTT and ETT. For instance, expression of EGFR, VEGF, VEGF-R, MAPK, PDGF-R and PD-L1 has been shown in PSTT and ETT. Therefore, investigational studies on biological agents targeting these molecules and pathways are strongly warranted, especially in chemotherapy-resistant disease [15,28,31,54]. In the same direction, the International Society for the Study of Trophoblastic Disease has launched a database to collect clinical and pathological information on these tumors, with the aim to implement the knowledge on their biological behavior, and possibly to better plan a personalized therapeutic approach (https://pstt.shef.ac.uk/) [7,43].

The authors declare no conflict of interest.

Author contributions

GA – collected articles and conceived and prepared the manuscript (general features, signs and symptoms, diagnostic imaging features, prognosis, treatment).

CS: collected articles and prepared the manuscript (pathologic features).

GME: participated in manuscript preparation.

AGD: discussed the concept and supervised the manuscript preparation.

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