Systematic Review and Meta-Analysis

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Clinical features and management of trophoblastic epithelioid tumors

A systematic review

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Abstract

Background: This study aimed to systematically review the existing literature on epithelioid trophoblastic tumors (ETTs), the rarest type of gestational trophoblastic neoplasia.

Methods: A systematic review according to PRISMA guidelines was performed, using ScienceDirect, Web of Science, and Scopus databases. The only filter used was the English language. Eligibility/inclusion criteria: retrospective observational studies (case reports, case series) including full case description of epithelioid trophoblastic tumor lesions.

Results: Seventy studies were assessed for synthesis, including 147 cases. 66.7% of patients with ETT presented with irregular vaginal bleeding. Pretreatment β-hCG levels ranged up to 1000 mIU/mL in 58.5% patients. Of most patients, 42.2% had stage I disease, 10.9% stage II, 25.2% stage III, and 21.8% of patients had stage IV. The most common sites of metastatic disease were the lungs, followed by the liver and brain. After treatment, complete remission was achieved in 75.5% of patients, partial remission in 10.2% of patients, and 14.3% of patients died. On univariate and multivariate analyses, stage IV disease was an independent prognostic factor for overall and disease-free survival.

Conclusions: Hysterectomy and metastatic lesion resection are essential for controlling ETT. Investigational studies on molecules like EGFR, VEGF, PD-1, CD105, and LPCAT1 are potential therapeutic targets for metastatic ETT.

Abbreviations: 5-FU/MTX = 5-fluorouracil, methotrexate, AP = antecedent pregnancy, BSO = bilateral salpingo-oophorectomy, C/T = carboplatin; paclitaxel, CEC = cyclophosphamide, etoposide, cisplatin, EMA/CO = etoposide, methotrexate, actinomycin-D/ cyclophos-phamide, vincristine, EMA/EP = etoposide, methotrexate, actinomycin-D/etoposide and cisplatin, EP/EMA = etoposide, cisplatin/etoposide, methotrexate, dactinomycin, ETTs = epithelioid trophoblastic tumors, FAEV = 5-fluorouracil, actinomycin-D, etoposide, vincristine, GTN = gestational trophoblastic neoplasia, ICE = ifosfamide; carboplatin, etoposide, LFN = lymphadenectomy, MTS = metastasectomy, NO-CHEMO = no chemotherapy, NOS = no surgery, PICOs = Population, Intervention, Comparison, Outcomes, SPN = spinal surgery, TAH = total abdominal hysterectomy, TE = tumor excision, TIP = paclitaxel, ifosfamide, cisplatin, TP/TE = paclitaxel, cisplatin/paclitaxel, etoposide, USO = unilateral salpingo-oophorectomy, VIP = etoposide, ifosfamide, cisplatin, β-hCG = ß-serum chorionic gonadotropin.

Keywords: cancer, epithelioid trophoblastic tumors, trophoblastic neoplasia

1. Introduction

Epithelioid trophoblastic tumor (ETT) is the rarest subtype of gestational trophoblastic neoplasia (GTN) accounting 1.0%–2.0% of all GTN cases.[1] Shih and Kurtmann first reported on the clinical and pathological features of ETT in 1998, and since 2003 the World Health Organization has accepted the classification of the tumor as a form of GTN.[2,3]

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Data availability statement: All data generated or analysed during this study are included in this published article.

Simple Summary: Epithelioid trophoblastic tumor (ETT) is an extremely rare subtype of gestational trophoblastic neoplasia (GTN), accounting for only 1.0–2.0% of all GTN cases. We investigated the clinical features, treatments, outcomes, and prognostic factors in patients with ETT, and explored potential therapeutic targets, over 23 years (1998–2021). The management of this rare pathology remains a challenge, 47% of patients from reviewed reports have metastases at the time of diagnosis. In this regard, a systematic literature review on the epithelioid trophoblastic tumor was performed to provide useful clinical information about patient characteristics, chemotherapy use, and outcomes.

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ETT can arise from all types of pregnancy, including full-term delivery, miscarriage, ectopic pregnancy, or following a hydatidiform mole. The clinical presentations include mostly, vaginal bleeding and slightly elevated ß-serum chorionic gonadotropin (ß-hCG) levels.

Almost half of the cases occur in the cervix or the lower uterine segment forming a well-defined, expandable mass. The tumor appears as a discrete, nodular, expansile lesion with solid, cystic, and hemorrhagic components. The gross size varies from 0.5 to 5 cm.[4,5] Microscopically the growth pattern of ETT is nodular and well-circumscribed with focally infiltrative at the periphery.[6] The cells are relatively uniform, mononucleate arranged in nests and cords, the predominant cell type being chorionic-type intermediate trophoblast. Also, compared to placental trophoblastic tumors and choriocarcinoma, calcification is common in epithelioid trophoblastic tumors.[6] Mitoses are reported to range from 0-9/10 high-power fields with a mean of 2/10 and the Ki-67/MIB1 proliferative index ranges from 10%–25%.[4] Immunohistochemically, ETT has diffuse expression of HLA-G, p63, inhibin, cyclin E, HSD3B1, GATA3.[6] Other trophoblastic markers including Mel-CAM and hPL are focally positive.[6]

ETT has a high chemo-resistance to single-agent chemotherapy and the need to institute a multiagent treatment is required for poor prognosis and/or metastatic disease, with a mortality rate of 10% to 24%.[2] The current standard of care has focused on total hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy for early-stage disease and resection of residual disease sites (metastasectomy), following the multiagent chemotherapy in metastatic disease. The aims of this systematic review were: (1) to provide and summarize the literature on a rare event on which there is scant data, such as the epithelioid trophoblastic tumor; (2) to provide any information about patient characteristics, chemotherapy use, and outcomes over 23 years (1998–2021).

2. Materials and Methods

A systematic review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the ScienceDirect, Web of Science, and Scopus databases.

Ethical approval was not required for this study as all the research materials are derived from published studies.

2.1. Eligibility criteria

After an initial review of the literature we noted that no clinical trials have been conducted on patients with ETT. Due to the rarity of this pathology, most of the literature describes case reports which led us to include only these types of papers;

The present review assessed the following PICOs (Population, Intervention, Comparison, Outcomes) questions:

- Population: We included case reports or case series of reproductive age and postmenopausal women diagnosed with epithelioid trophoblastic tumors;
- Intervention: We considered all care interventions including surgery and chemotherapy use;
- Comparison: no comparison expected;
- Outcomes: Our primary outcomes measure was patients and disease characteristics. The secondary outcome was final follow-up health outcomes (alive, recurrence, death).

Eligibility/inclusion criteria: studies including full case description of epithelioid trophoblastic tumor lesions. Exclusion criteria: (1) review articles; (2) research articles without a full case description; (3) reports in a non-English language.

2.2. Information sources and search strategy

We conducted electronic searches for eligible reports within each of the following databases: ScienceDirect, Web of Science, and Scopus (Title/Abstract/Keywords). We searched using the search syntax: "epithelioid trophoblastic tumor" OR "Placental Trophoblastic Tumor" OR "Placental Trophoblastic Tumors" OR "Placental-Site Trophoblastic Tumor" OR "Trophoblastic Tumors".

The process of developing the search strategy consisted of studying several relevant articles to identify records in the databases. Search terms were identified by examining words in titles, abstracts, keywords, and indexing by the subject of these records. A design of a search strategy was drafted using these terms and additional search terms were identified from the results of that strategy.

The only filter used was the English language. Relevant articles were obtained in full-text format and screened for additional references.

2.3. Study selection

Two independent reviewers (IMC and OMG) selected the studies using a 2-steps screening method. At first, the screening of titles and abstracts was performed to assess eligibility and inclusion criteria and exclude irrelevant studies. Afterward, the 2 reviewers evaluated full texts of included articles to assess study eligibility and inclusion criteria and avoid duplications of the included cases. Two other authors (DMS and MF) manually searched reference lists to search for additional relevant publications. CC, LT, and FG checked the data extracted.

2.4. Assessing the risk of bias

The inclusion of only case reports in this review presents a risk of bias. We assessed the methodological quality (risk of bias) of the papers included using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports which consists of 8 yes/no/unclear questions.[7] This is the only tool for assessing the methodological quality of case reports and case series.[8] Two reviewers (FG, LT) assessed the quality of the included studies. Disagreements between reviewers at different stages of the review were resolved by a third reviewer (OMG).

2.5. Data collection process/data items

Data collection was study-related (authors and year of study publication) and case-related (patient characteristics, signs/symptoms at clinical presentation, chemotherapy data, cancer lesion characteristics, treatment, and outcome).

Survival estimates were calculated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression model. All statistical analyses were conducted using the Statistical Package for the Social Sciences (software version 25; IBM Corp., Armonk, NY, USA). A 2-sided P value of $< .05$ was considered statistically significant.

3. Results

3.1. Reports selection

Figure 1 shows the literature review flowchart. We retrieved 375 articles on ScienceDirect, 187 articles on Web of Science and 275 papers on Scopus databases (accessed on 24 August 2021). After duplicates were removed, 334 articles were assessed. Based on the title and abstract, 232 records were excluded.

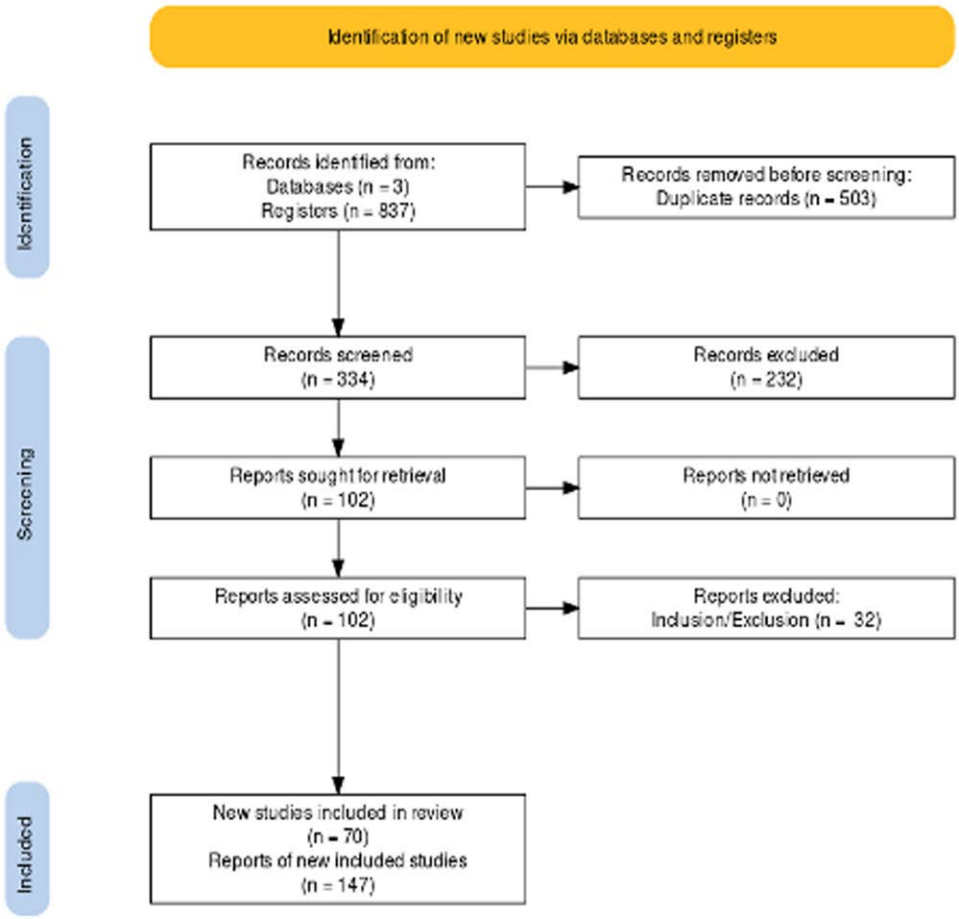

Figure 1. Flowchart of literature review.

Then, the full text of 102 papers was evaluated for eligibility. Based on inclusion and exclusion criteria, 32 articles were further removed. Finally, 70 studies were assessed for qualitative synthesis, including 147 cases.

3.2. Studies characteristics

The main characteristics of the included case reports were reported in Table 1.

3.3. Risk of bias

Fifty-seven case reports scored "yes" for all 8-checklist questions, hence included case report was scored as high quality.

3.4. Clinical presentation

The most common presenting symptom was irregular vaginal bleeding (61.2%), and the antecedent obstetrical event before diagnosis was full-term pregnancy in 91 patients (61.9%) whereas 39 (26.5%) underwent an abortion. Pretreatment serum human chorionic gonadotropin (β-hCG) levels ranged up to 1000 mIU/mL in 86 patients (58.5%),and in 36 patients (24.5%) over 1000 mIU/mL. Most patients (42.2%) had stage I disease; 37 patients (25.2%) had lung metastases (FIGO stage III) and 32 patients (21.8%) had FIGO stage IV disease (Table 2). Most common sites of metastatic disease were the lungs (n = 39), followed by liver (n = 9) and brain (n = 7)

3.5. Poor outcome prediction based on clinical characteristics

Binomial logistic regression was performed to ascertain the effects of clinical characteristics on the likelihood that participants died during follow-up.

The logistic regression model was statistically significant, $\chi 2(4) = 27.40$, $P < .001$.

3.6. Treatment and outcome

All 62 patients (100%) who were included in stage I, achieved complete remission (CR) after treatment. Surgery was used in 96.7% being combined with first-line chemotherapy in 33.9% of cases (21 patients), and the most common regimen used to be EMA/CO (42.7%) (Table 3).

In stage II, 15 patients (93.8%) achieved complete remission (CR), and one patient (6.3%) with partial remission PR). Surgery was performed in all 16 cases. In 13 patients (81.2%) first-line chemotherapy was used combined with surgery and 3 patients (18.7%), needed second-line chemotherapy. The most frequent first-line chemotherapy used, was EMA/CO in 5 patients (31.3%) (Table 4).

In stage III, 30 patients (81.1%) achieved complete remission (CR), 5 patients (13.5%) with partial remission (PR), and 2 patients (5.4%), died of disease. Surgery was performed in 35 patients (94.6%), chemotherapy was used in 30 patients (81.1%), and most used regimens were EMA/CO (33.3%) and EP/EMA (26.6%). Second-line chemotherapy was used in 6 patients (16.2%), with a survey rate of 66.6% (Table 5).

Table 1

Studies characteristics.

Study ID	Year	Study design	Symptoms	Primary Tumor Location	Stage	Outcome
Fang et al	2014	Case report	Vaginal bleeding	Uterine	I	Remission
Saeeda Almarzooqi et al	2014	Case series	Vaginal bleeding	Uterine	I	Remission
McGregor SM et al	2020	Case report	Vaginal bleeding	Uterine	I	Remission
Mma E et al	2015	Case series	Vaginal bleeding (both cases)	Uterine (both cases)	I (1st case); IV (2nd case)	Remission (1st case); died of disease (2nd case)
Zhou F et al	2017	Case report	Asymptomatic	Uterine	I	Remission
Lo C et al	2006	Case report	Vaginal bleeding	Uterine	I	Remission
ZHabg Di et al	2020	Case report	Vaginal bleeding	Uterine	I	Remission
Manoharan J et al	2016	Case report	Abdominal pain	Uterine	I	Remission
Moutte A et al	2013	Case series	Vaginal bleeding- 3 cases; abdominal pain: 2 cases; asymptomatic-2 cases	Uterine: 6 cases; vagina-1 case	I: 5 cases; II: 1 case; III: 1 case	Remission
Davis M et al	2015	Case series	Vaginal bleeding	Uterine	I: 1 case; III-2 cases; IV: 3 cases	Remission (4 cases); partial remission (2 cases-stage 4)
Qi Li et al	2007	Case series	Vaginal bleeding (all)	Uterine	I (2 cases); IV (1 case)	Remission (2 cases: stage 1); Died of disease (1 case: stage 4)
Shih M et al	1999	Case series	Vaginal bleeding (11 cases); abdominal pain (1 case); asymptomatic (2 cases)	Uterine (13 cases); bowel (1 case)	I (10 cases); III (3 cases); IV (1 case)	Remission -12 cases; partial remission: 2 cases (1 case: stage III, 1 case: stage iv)
Yang J et al	2019	Case series	Vaginal bleeding (14 cases); others (6 cases); asymptomatic (1 case)	Uterine (all)	I (8 cases); II (3 cases); III (6 cases); IV (4 cases)	Remission (15 cases); partial remission: 3 cases (2 cases: stage 3; 1 case: stage 4); died of disease: 3 cases (stage 4)
Trujilo A et al	2017	Case series	Vaginal bleeding (1 case); asymptomatic (1 case)	Uterine	I	Remission
Venken P et al	2006	Case report	Vaginal bleeding	Uterine	I	Remission
Takekawa Y et al	2010	Case report	Vaginal bleeding	Uterine	I	Remission
Coulson L et al	2000	Case report	Vaginal bleeding	Uterine	I	Remission
Scott E et al	2012	Case report	Abdominal pain	Uterine	I	Remission
Ohya A et al	2017	Case report	Vaginal bleeding	Uterine	I	Remission
Stanculescu R et al	2016	Case report	Asymptomatic	Uterine	I	Remission
Park JW et al	2016	Case report	Vaginal bleeding	Uterine	I	Remission
Kurt S et al	2021	Case report	Vaginal bleeding	Uterine	I	Remission
Sung WJ et al	2013	Case series	Vaginal bleeding	Uterine	I	Remission
Sobecki-Rausch J et al	2018	Case series	Vaginal bleeding (3 cases); asymptomatic (1 case); others (1 case)	Uterine (4 cases); lung (1 case)	I (1 case); III (3 cases); 4 (1 case)	Remission: 4 cases; died of disease: 1 case (stage4)
Zhang X et al	2015	Case report	Vaginal bleeding	Uterine	I	Remission
Shen X et al	2011	Case series	Abdominal pain (3 cases); vaginal bleeding (5 cases); asymptomatic (1 case)	Uterine (all)	I (1 case); II (2 cases); III (2 cases); IV (4 cases)	Remission -4 cases (1: stage 1; 2: stage 2; 1 stage 3); died of disease -5 cases (1: stage 3; 4: stage 4)
Qian XQ et al	2020	Case report	Vaginal bleeding	Uterine	I	Remission
Fadare O et al	2006	Case series	Vaginal bleeding (3 cases); asymptomatic (2 cases)	Uterine (2 cases); cervix (2 cases); ovarian (1 case)	I (1 case); II (2 cases); III (2 cases)	Remission (4 cases); partial remission (1 case: stage 2)
Li J et al	2011	Case series	Asymptomatic (2 cases); vaginal bleeding (5 cases)	Uterine	I (4 cases); III (2 cases); IV (1 case)	Remission (6 cases); died of disease (1 case: stage 3)
Jiang F et al	2018	Case report	Vaginal bleeding	Recto-uterine pouch	I	Remission
Li J et al	2019	Case report	Vaginal bleeding	Uterine	III	Remission
Meydanli MM	2002	Case report	Vaginal bleeding	Uterine	I	Remission
Yigit S et al	2020	Case report	Vaginal bleeding	Uterine	I	Remission
Black K.A et al	2021	Case report	Vaginal bleeding	Uterine	II	Remission
Phippen NT et al	2010	Case report	Abdominal pain	Cervix	II	Remission
Vemula S et al	2015	Case report	Abdominal pain	Cervix	II	Remission
Kuo KT et al	2004	Case report	Vaginal bleeding	Uterine	II	Remission
Parker A et al	2003	Case report	Abdominal pain	Fallopian tube	II	Remission
Zhao J et al	2013	Case report	Asymptomatic	Vagina	II	Remission
Khunamornpong S et al	2011	Case report	Abdominal pain	Ovarian	II	Remission
Choi MC et al	2019	Case report	Asymptomatic	Uterine	II	Remission
Kavurmacı Ö et al	2018	Case report	Asymptomatic	Uterine	III	Remission
Kim JH et al	2017	Case report	Abdominal pain	Abdominal	III	Remission
Jiang L et al	2017	Case report	Vaginal bleeding	Fallopian tube	III	Remission

(*Continued*)

Table 1

(*Continued*)

Study ID	Year	Study design	Symptoms	Primary Tumor Location	Stage	Outcome
Lewin SN et al	2009	Case series	Asymptomatic (1 case); vaginal bleeding (2 cases)	Uterine (1 case); lung (2 cases)	III (all cases)	Remission (all cases)
Abrão FC et al	2011	Case report	Vaginal bleeding	Lung	III	Partial remission
Lei W	2018	Case report	Asymptomatic	Uterine	III	Remission
Okereke IC	2014	Case report	Vaginal bleeding	Uterine	III	Partial remission
Li JW et al	2019	Case report	Asymptomatic	Lung	III	Remission
Fénichel P et al	2014	Case report	Vaginal bleeding	Ovarian	III	Remission
Ahn HY et al	2013	Case report	Asymptomatic	Lung	III	Remission
Urabe S et al	2007	Case report	Others	Lung	III	Remission
Kageyama S et al	2016	Case report	Abdominal pain	Uterine	III	Remission
Luo R et al	2016	Case report	Asymptomatic	Vagina	III	Remission
Kim J et al	2013	Case report	Abdominal pain	Uterine	IV	Remission
Nakamura B et al	2021	Case report	Abdominal pain	Uterine	IV	Remission
Bell S et al	2021	Case report	Asymptomatic	Abdominal soft tissue	IV	Partial remission
NoH et al	2008	Case report	Abdominal pain	Uterine	IV	Partial remission
Andriani A et al	2021	Case report	Abdominal pain	Abdominal soft tissue	IV	Remission
Macdonald M et al	2010	Case series	Vaginal bleeding	Uterine	IV	Died of disease: case; partial remission: 1 case
Dobrosavljevic A et al	2019	Case report	Abdominal pain	Uterine	IV	Died of disease
Jordan S et al	2011	Case report	Abdominal pain	Cervix	IV	Died of disease
Chohan M et al	2004	Case report	Others	Spine	IV	Died of disease
Kodey PD et al	2014	Case report	Vaginal bleeding	Uterine	IV	Died of disease
Gil F et al	2019	Case report	Vaginal bleeding	Vulvar	IV	Died of disease
Shet T et al	2008	Case report	Vaginal bleeding	Uterine	IV	Died of disease
Madhu B et al	2012	Case report	Abdominal pain	Liver	IV	Partial remission
Hsiue EHC et al	2017	Case report	Abdominal pain	Uterine	IV	Died of disease
Mahmood H et al	2016	Case report	Vaginal bleeding	Ovarian	IV	Partial remission

In stage IV, 4 patients (12.5%) achieved complete remission (CR), 9 patients (28.1%) achieved partial remission, and 19 patients (59.4%), died of disease. Surgery was performed in 26 patients (81.25%), chemotherapy was used in 31 patients (96.9%), and the most used regimens were EMA/CO (40.6%) and FAEV (25%). Second-line chemotherapy was used in 14 patients (43.7%), with the most common regimen EMA/CO, used in 6 patients (42.8%), and 9 patients (64.2%) failed to survey second-line chemotherapy (Table 6).

Regardless of the stage of the disease, patients with the onset of the disease more than 48 months after the previous pregnancy had a mortality of 20% (n = 12/48), compared with a

Table 2

Characteristics of 147 patient diagnosed with epithelioid trophoblastic tumor (ETT).

Parameters	No. of patients, N (%)
Age	
<40 y	88 (59.9%)
>40 y	59 (40.1%)
Symptoms	
Vaginal bleeding	90 (61.2%)
Abdominal pain	36 (24.5%)
Asymptomatic	21 (14.3%)
AP outcome	
Full-term birth	91 (61.9%)
Abortion	39 (26.5%)
Molar pregnancy	9 (6.1%)
Ectopic pregnancy	1 (0.7%)
Interval to AP	
<48 months	77 (52.4%)
≥48 months	60 (40.8%)
No data	10 (6.8%)
ß-HCG	
<100 mIU/mL	50 (34.0%)
100-1000 mIU/mL	36 (24.5%)
≥1000 mIU/mL	36 (24.5%)
No data	25 (17.0%)
FIGO Stage	
I	62 (42.2%)
II	16 (10.9%)
III	37 (25.2%)
IV	32 (21.8%)

AP = antecedent pregnancy, ß-hcg = ß human chorionic gonadotrotropin.

Table 3

Treatment and outcomes in 62 patients included in stage I of the disease.

Treatment	Total no. of patients/%
Surgery	
TAH	22/35.5%
TAH/BSO	18/29%
TAH/BSO/LFN	11/17.7%
TAH/BSO/MTS	1/1.6%
TE	8/12.9%
NOS	2/3.2%
First-line chemotherapy	
EMA/CO	9/14.5%
FAEV	5/8.1%
TP/TE	1/1.6%
EMA/EP	2/3.2%
EP/EMA	1/1.6%
MTX	2/3.2%
MTX-FA	1/1.6%
NO-CHEMO	41/66.1%
Total with chemotherapy	21/33.9%

BSO = bilateral salpingo-oophorectomy, EMA/CO = etoposide, methotrexate, actinomycin-D/cyclophos-phamide, vincristine, EMA/EP = etoposide, methotrexate, actinomycin-D/etoposide and cisplatin, EP/EMA-etoposide = cisplatin/etoposide, methotrexate, dactinomycin, FAEV = 5-fluorouracil, actinomycin-D, etoposide, vincristine, LFN = lymphadenectomy, MTS = metastasectomy, NO-CHEMO = no chemotherapy, NOS-no surgery, TAH = total abdominal hysterectomy, TE = tumor excision, TP/TE = paclitaxel, cisplatin/paclitaxel, etoposide.

Table 4

Treatment and outcomes in 16 patients included in stage II of the disease.

Treatment	Total no. of patients/%	Total remission no. of patients /%	Partial remission no. of patients/%
Surgery			
TAH	3/18.8%	3/100%	–
TAH/BSO	6/37.5%	5/83.3%	1/16.7%
TAH/BSO/LFN	2/12.5%	2/100%	–
TAH/BSO/MTS	1/6.3%	1/100%	–
TE	3/18.8%	3/100%	–
USO	1/6.3%	1/100%	–
First-line chemotherapy			
EMA/CO	5/31.3%	–	–
FAEV	4/25.0%	–	–
EMA/EP	2/12.5%	–	–
5FU/MTX	1/6.3%	–	–
BEP	1/6.3%	–	1/100%
Second-line chemotherapy			
EMA/CO	1/6.3%	1/100%	–
TIP	1/6.3%	1/100%	–
Pembrolizumab	1/6.3%	1/100%	–

BSO = bilateral salpingo-oophorectomy, EMA/CO = etoposide, methotrexate, actinomycin-D/cyclophos-phamide, vincristine, EMA/EP = etoposide, methotrexate, actinomycin-D/etoposide and cisplatin, LFN = lymphadenectomy, NO-CHEMO = no chemotherapy, NOS-no surgery, TAH = total abdominal hysterectomy, TE = tumor excision, USO-unilateral salpingo-oophorectomy.

mortality of 10.4% (n =8/77) in patients with disease's onset at less than 48 months (chi-square value = 2.498, P = .114). No significant statistical difference in survival distribution was observed (log rank= 3.033, P = .08). A statistically significant difference was observed in cumulative survival between stages of the disease with a log rank= 76.384 (Figs. 2,3).

4. Discussion

Follow-up information was available in 119 patients. The mean follow-up was 20.6 months (median, 12 months; range, 1–180 months). Overall survival is 85.7%, with a 75.5% disease-free survival, and 21 patients died 14.3%. Stage IV appeared most important poor prognostic factor.

The reports included in this review showed a median age of patients with ETT of 30 years. Other studies showed that ETT occurs in women between 15 and 48 years of age with a mean of 36.1 years.[9] By dividing the patients into 2 age groups, according to the FIGO classification, we showed that the incidence of ETT is more frequent in women under 40 years of age compared to those over 40 years of age. Classically, it is considered that ETT occurs in women of childbearing age, usually after a normal pregnancy.[10] In addition, the time from gestation to presentation varies, reporting intervals from 1 year to 18 years.[4] However, recent reports describe cases of ETT, one with an aggressive spread in the abdomen and pelvis, in a 68-year-old woman, 30 years after the last birth, and one in a 53-year-old woman, 25 years after spontaneous delivery.[5,10]

In addition, we showed that an interval ≥48 months, from the last known/presumed pregnancy, is a predictor of poor outcome with 12 patients (20.0%) who died. Other studies demonstrated that an interval of ≥48 months from the antecedent pregnancy was associated with a 100% death rate, independent of the stage.

Diagnosis of ETT remains a challenge due to its rarity and diverse presentations, which can lead to potential mismanagement and delay in treatment. In line with previous studies, irregular vaginal bleeding was the most common symptom of ETT (59.9%), in our study.[11]

ETT can develop after any antecedent pregnancy event, in the present study, 61.9% of such events were full-term pregnancies, comparable to a mean of 65.0%, in the literature.[3,4]

Table 5

Treatment and outcomes in 37 patients included in stage III of the disease.

Treatment	Total no. of patients/%	Total remission no. of patients/%	Partial remission no. of patients/%	Death of disease no. of patients/%
Surgery				
TAH	2/5.4%	1/50.0%	–	1/50.0%
TAH/BSO	3/8.1%	1/33.3%	2/66.7%	–
TAH/BSO/LFN	5/13.5%	3/60.0%	2/40.0%	–
NOS	2/5.4%	1/50.0%	1/50.0%	–
MTS	11/29.7%	11/100%	–	–
TAH/BSO/MTS	10/27.0%	9/90.0%	–	1/10%
TE/MTS	3/8.1%	3/100%	–	–
O/MTS	1/2.7%	1/100%	–	–
Total	37/100%	30/81.1%	5/13.5%	2/5.4%
First line chemotherapy				
EMA/CO	10/27.0%	8/80.0%	–	2/20.0%
FAEV	6/16.2%	4/66.7%	2/33.3%	–
TP/TE	3/8.1%	3/100%	–	–
EMA/EP	1/2.7%	–	1/100%	–
EP/EMA	8/21.6%	7/87.5%	1/12.5%	–
MTX	1/2.7%	1/100%	–	–
BEP	1/2.7%	1/100%	–	–
NO-CHEMO	7/18.9%	6/85.7%	1/14.3%	–
Total	37/100%	30/81.1%	5/13.5%	2/5.4%
Second-line chemotherapy				
NO-CHEMO	31/83.8%	28/90.3%	3/9.7%	–
EMA/CO	2/5.4%	–	2/100%	–
TIP	1/2.7%	–	–	1/100%
TP/TE	1/2.7%	1/100%	–	–
BEP	1/2.7%	–	–	1/100%
ICE	1/2.7%	1/100%	–	–

5 = FU/MTX -5-fluorouracil, methotrexate, BEP = bleomycin, etoposide, cisplatin, BSO = bilateral salpingo-oophorectomy, C/T = carboplatin, paclitaxel, CEC = cyclophosphamide, etoposide, cisplatin, EMA/CO = etoposide, methotrexate, actinomycin-D/cyclophosphamide, vincristine, EMA/EP = etoposide, methotrexate, actinomycin-D/etoposide and cisplatin, EP/EMA = etoposide, cisplatin/ etoposide, methotrexate, dactinomycin, FAEV = 5-fluorouracil, actinomycin-D, etoposide, vincristine, ICE = ifosfamide, carboplatin, etoposide, LFN = lymphadenectomy, MTS = metastasectomy, NO-CHEMO = no chemotherapy, NOS = no surgery, SPN = spinal surgery, TAH = total abdominal hysterectomy, TE = tumor excision, TIP = paclitaxel, ifosfamide, cisplatin, TP/TE = paclitaxel, cisplatin/paclitaxel, etoposide, USO = unilateral salpingo-oophorectomy, VIP = etoposide, ifosfamide, cisplatin.

Table 6

Treatment and outcomes in 32 patients included in stage IV of the disease.

Treatment	Total no. of patients/%	Total remission no. of patients/%	Partial remission no. of patients/%	Death of disease no. of patients/%
Surgery				
TAH	5/15.6%	1/20.0%	–	4/80.0%
TAH/BSO	7/21.9%	–	2/ 28.6%	5/71.4%
NOS	6/18.8%	0/0.0%	1/16.7%	5/83.3%
MTS	3/9.4%	–	2/66.7%	1/33.3%
TAH/BSO/MTS	9/28.1%	3/ 33.3%	3/33.3%	3/33.3%
TE/MTS	1/1/3.1%	–	1/100%	–
SPS	1/3.1%	–	–	1/ 100%
Total	32	4/ 12.5%	9/ 28.1%	19/ 59.4%
First-line chemotherapy				
EMA/CO	13/40.6%	1/7/7%	3/23.1%	9/69.2%
FAEV	8/25.0%	–	1/12.5%	7/87.5%
EMA/EP	5/15.6%	1/20.0%	4/80.0%	–
EP/EMA	3/ 9.4%	1/33.3%	1/33.3%	1/33.3%
NO-CHEMO	1/3.4%	1/100%	–	–
BEP	1/3.1%	-	–	1/100%
CEC	1/3.1%			1/100%
Second-line chemotherapy				
NO-CHEMO	19/ 59.4%	4/21.0%	4/21.0%	11/57.9%
EMA/CO	6/18.8%		1/16.7%	5/83.3%
TIP	1/3.1%	–	–	1/100%
Pembrolizumab	2/ 6.3%	–	2/100%	–
BEP	1/3.1%		1/100%	
VIP	1/3.1%		1/100%	
C/T	2/6.3%		–	2/100%

5 = FU/MTX -5-fluorouracil, methotrexate, BEP = bleomycin, etoposide, cisplatin, BSO = bilateral salpingo-oophorectomy, C/T = carboplatin, paclitaxel, CEC = cyclophosphamide, etoposide, cisplatin, EMA/CO = etoposide, methotrexate, actinomycin-D/cyclophosphamide, vincristine, EMA/EP = etoposide, methotrexate, actinomycin-D/etoposide and cisplatin, EP/EMA = etoposide, cisplatin/ etoposide, methotrexate, dactinomycin, FAEV = 5-fluorouracil, actinomycin-D, etoposide, vincristine, ICE = ifosfamide, carboplatin, etoposide, LFN = lymphadenectomy, MTS = metastasectomy, NO-CHEMO = no chemotherapy, NOS = no surgery, SPN = spinal surgery, TAH = total abdominal hysterectomy, TE = tumor excision, TIP = paclitaxel, ifosfamide, cisplatin, TP/TE = paclitaxel, cisplatin/paclitaxel, etoposide, USO = unilateral salpingo-oophorectomy, VIP = etoposide, ifosfamide, cisplatin.

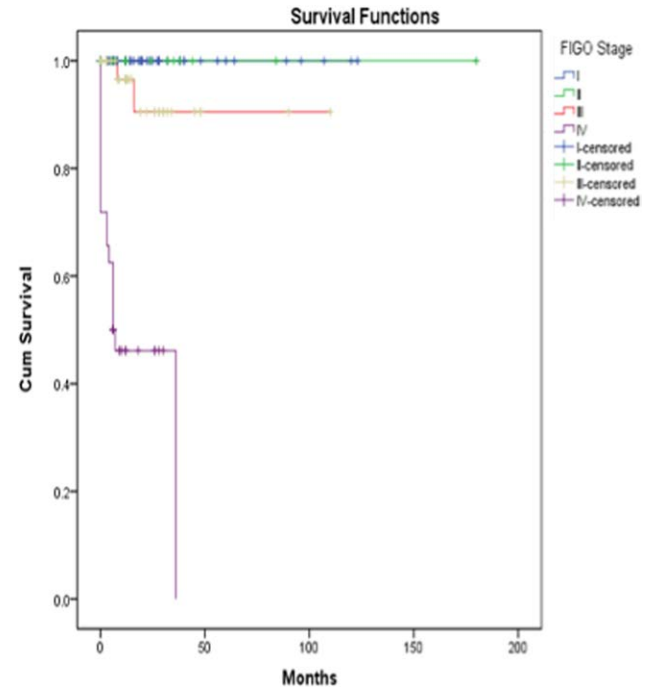

Figure 2. Cumulative survival in women with ETT, depending on FIGO stage of the disease. ETT = epithelioid trophoblastic tumor.

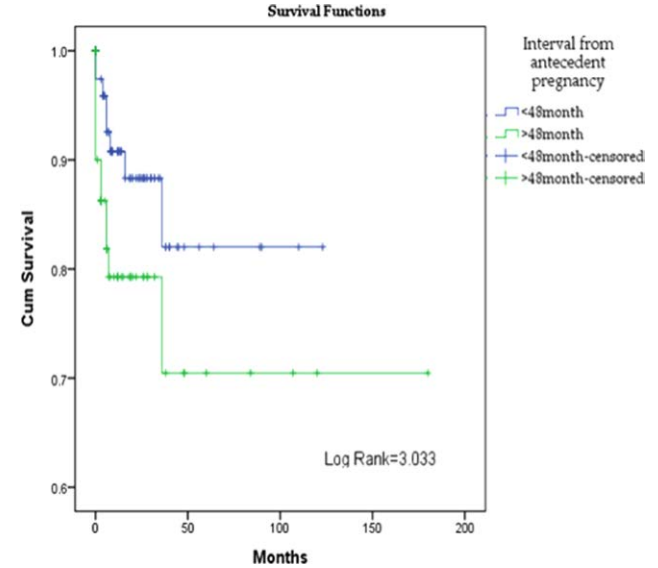

Figure 3. Cumulative survival in women with ETT, depending on the time between previous pregnancy and the onset of the disease. ETT = epithelioid trophoblastic tumor.

In 80% of the patient with ETT is detectable mild to moderate elevation of serum hCG of less than 2500 mIU/mL.[5] In the present study, 86 patients (58.5%) had β-hCG levels ≤ 1000 IU/L. In previous studies, patients with ETT had slightly increased levels of β-hCG ≤ 1000 IU/L (55.2%).[12]

Approximately 30.0% of patients reportedly presented with metastatic disease at diagnosis.[3,11] The uterus is the most common primary site of ETT but may occur at extra-uterine locations, including the fallopian tube, ovary, and pelvic peritoneum, while the lung is the most common extra-uterine site of metastasis, accounting for 19.0% of cases.[5,13] In our review 72 patients (48.9%) presented with metastatic disease at diagnosis. The most common extra-uterine site of

metastasis is the lung (26.5%), follow by the liver (6.1%), and brain (4.8%). Surgical resection is the primary treatment modality and is important for ETT present with non-metastatic disease[1]. Our reviewed data have shown that 41 patients (66.1%) were in stage I of the disease. Previous studies have shown that patients with diseases limited to the uterus could be cured by hysterectomy without adjuvant chemotherapy.[14] Surgery is also important for eradicating metastatic disease and drug-resistant residual disease.[14,15] Our results showed that 90.5% of patients with advanced-stage disease underwent multiple surgical procedures, including hysterectomy and resection of isolated tumors.

Regarding chemotherapy, it was used in 33.4% of patients in stage I, 81.3% of patients in stage II, 81% of patients with stage III, and 97% of patients in stage IV. Chemotherapy alone is inadequate for advanced-stage and metastatic or locally advanced disease, together with surgery plays an important role in the management of ETT patients. The most used regimens of first-line chemotherapy were EMA/CO (39%), FAEV (24.2%), EP/EMA (13%), and EMA/EP (10.5%). The first-line chemotherapy successful was complete remission (60%), partial remission (24.2%), and no response (15.8%). The most used regimen EMA/CO efficiency was complete remission (56.8%), partial remission (24.3%), and no response (18.9%). In stage III 2 patients died, the first-line chemotherapy used was EMA/CO, and 8 patients achieved complete remission. Stage IV is a poor prognostic factor, 19 patients (59.3%) died of the disease. The failure of first-line chemotherapy was 5 patients EMA/CO, 6 patients FAEV, 1 patient BEP, and one patient EMA/EP. Second-line chemotherapy was successfully for 6 patients 2 EMA/CO, one BEP, one VIP, and 2 pembrolizumab. First-line chemotherapy with complete remission was achieved by 3 patients, one EMA/CO, one EP/EMA, and one EMA/EP. The treatment of patients with stage IV or metastatic ETT remains a challenge. Ghorani et al found that pembrolizumab (a humanized monoclonal antibody against PD-1) was effective in patients with no response to chemotherapy.[16] Veras et al reported that 8 of 14 patients with ETT had detectable levels of PD-L1 in their tumors.[17] In our study, 3 patients received second-line chemotherapy with pembrolizumab, 1 in stage II who achieved complete remission, and 2 patients in stage IV, with partial remission, who are alive with disease. Cho et al in their study, analyzed 4 cases of ETT, for differential gene expression, pathway alteration, and PD-L1 expression level.[18] A variable high expression level of PD-L1, with PI3K-alternated pathways, was found in those tumors, which suggested pembrolizumab, an anti-PD-1 drug, is effective for resistant chemotherapy in epithelioid trophoblastic tumors. High levels of EGFR expressions have been detected in epithelioid trophoblastic tumors.[19] The anti-EGFR regimen has become a target-based treatment for various malignant diseases. Drugs that target EGFR, including cetuximab, and gefitinib, can produce benefits for patients with ETT, in combination with chemotherapy used. Mutational analyses of the EGFR and PI3K pathway, together with their gene-expresso levels, are essential for treatment development, and optimal therapeutic effects. Frijstein et a. report a conducted study on 32 patients and evaluated the effect of high-dose-chemotherapy (HDC) with peripheral blood stem cell support (PBSCS) on survival patients with refractory response to chemotherapy.[20] The results show that HDC can be beneficial for some patients who have failed adjuvant treatment for poor-prognosis ETT. Oliver et al, using RNA-sequentially analysis in 5 patients with ETT, found LPCAT1-TERT fusion proteins that can positively modulate cell proliferation.[21] These findings could have potential diagnostic, prognostic, and therapeutic relevance. New therapeutic regimens are needed to reduce the toxic effects associated with current chemotherapyThis study has a few limitations. First, due to the rarity of this pathology, we had to include only case report papers in the review, which increases the risk of bias. Also due to the small number of cases, we cannot make recommendations on the treatment of this pathology.

5. Conclusions

Surgery combined with chemotherapy is recommended for patients with metastatic disease. Despite the rarity of ETT with a small number of cases in analyses, it is difficult to establish a management strategy for patients with this disease. In our opinion, the future treatment of ETT could be by immunotherapy, investigational studies on biological agents targeting molecules like EGFR, VEGF, PD-1, PD-L2, CD-105, and LPCAT1 are required, especially in resistant chemotherapy disease.

Author contributions

Conceptualization: CC, FG, and AM; methodology: MF and OMG; software: LT and DMS; formal analysis: IMC; investigation: OMG, FM, and IMC; data curation: OMG and IMC; writing–original draft preparation: CC and LT; writing–review and editing: IS and FG.; visualization: IS; supervision: AM.

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