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Management and prognostic factors of epithelioid trophoblastic tumors: Results from the International Society for the Study of Trophoblastic Diseases database

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HIGHLIGHTS

- Epithelioid Trophoblastic Tumor (ETT) is an extremely rare potentially high-risk Gestational Trophoblastic Neoplasia.
- ETT patients with advanced-stage disease or an interval of ≥48 months since antecedent pregnancy have poor outcome.
- A surgical approach is recommended for ETT patients with early-stage disease.
- Surgery and multi-chemotherapy is the preferred treatment modality for ETT patients with metastatic disease.
- ETT patients should be treated in a trophoblastic disease center for optimal management.

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ABSTRACT

Objective. Epithelioid Trophoblastic Tumor (ETT) is an extremely rare form of Gestational Trophoblastic Neoplasia (GTN). Knowledge on prognostic factors and optimal management is limited. We identified prognostic factors, optimal treatment, and outcome from the world's largest case series of patients with ETT.

Methods. Patients were selected from the international Placental Site Trophoblastic Tumor (PSTT) and ETT database. Fifty-four patients diagnosed with ETT or mixed PSTT/ETT between 2001 and 2016 were included. Cox regression analysis was used to identify prognostic factors for overall survival (OS).

Results. Forty-five patients with ETT and 9 patients with PSTT/ETT were included. Thirty-six patients had FIGO stage I and 18 had stages II–IV disease. Patients were treated with surgery ($n = 23$), chemotherapy ($n = 6$), or a combination of surgery and chemotherapy ($n = 25$). In total, 39 patients survived, including 22 patients with complete sustained hCG remission for at least 1 year. Patients treated with surgery as first line treatment had early-stage disease and all survived. Most patients treated with chemotherapy with or without surgery had FIGO stages II–IV disease (55%). They underwent multiple lines of chemotherapy. Eleven of them did not survive. Interval since antecedent pregnancy and FIGO stage were prognostic factors of OS ($p = 0.012$; $p = 0.023$ respectively).

Conclusions. Advanced-stage disease and an interval of ≥48 months since the antecedent pregnancy are poor prognostic factors of ETT. Surgery seems adequate for early-stage disease with a shorter interval. Advanced-stage disease requires a combination of treatment modalities. Because of its rarity, ETT should be treated in a centre with experience in GTN.

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1. Introduction

Epithelioid Trophoblastic Tumor (ETT) is an extremely rare form of gestational trophoblastic neoplasia (GTN), first described in 1998 by Shih and Kurman [1]. This unique type of tumor develops in intermediate trophoblastic cells. Intermediate trophoblastic cells can be villous or extravillous in form of implantation-site and chorionic leave type. ETT appears to develop from the chorionic leave type intermediate trophoblast. Tumor like conditions arising from the intermediate trophoblast include benign exaggerated placental site (EPS) and placental site nodule (PSN) and other malignant tumor includes placental site trophoblastic tumor (PSTT). ETT is histologically distinguished from PSTT by its nested well circumscribed nodular growth which is different from the sheet-like and infiltrative growth pattern seen in PSTT [2–4].

ETT is often misdiagnosed as PSTT or choriocarcinoma and can even resemble a squamous cell carcinoma (SCC) [1]. This confusion with SCC occurs because of its frequent involvement of the lower uterine segment or endocervix, its epithelioid histologic appearance and expression of p63 and cytokeratins [5]. In contrast to ETT and other types of trophoblastic neoplasms, p16 is overexpressed in high-risk human papillomavirus (HPV)-related cervical lesions and may help differentiate ETTs from cervical SCC [6]. HPV-ISH (in situ hybridization) may also be used for confirming the diagnosis of HPV-related cervical lesions.

The overall frequency and incidence of ETT worldwide is difficult to assess. Eysbouts et al. reported an incidence of ETT in 0.1 per 100,000 deliveries in the Netherlands during a 20-year study period, representing 2.2% of their reported GTN cases [7]. There have been several case reports and small case series since the initial publication of Shih et al., with a total of approximately 110 reported cases in 2016 [4,8]. Because ETT is rare, knowledge about optimal management, long-term outcome and prognostic factors remains limited. ETT and PSTT are usually treated in the same way, as both tumors have several overlapping features and similarities in behavior [4,9]. An interval of >48 months since antecedent pregnancy was reported as a poor prognostic factor for patients with PSTT [10].

However, some studies failed to demonstrate this prognostic factor in PSTT/ETT. [9,11] The present study is the largest case series of ETT reported in the literature. In this article, we report the common characteristics, potential prognostic factors and effects of current management of 54 patients to optimize the treatment of ETT.

2. Materials and methods

The international PSTT and ETT database (http://stdc.group.shef.ac.uk/psttuhr/), established in 2006, provides demographic, clinicopathological, treatment and outcome data from different countries. Cases can be recorded prospectively and retrospectively. Three hundred forty-one cases were added on the database from patients treated between 2001 and 2016. This database is covered by ethics application reference number REC: 06/MRE04/22. The database was searched for ETT patients. Fifty-seven patients who were diagnosed and registered with ETT or mixed PSTT/ETT between 2001 and 2016 were selected. In 2017 a request was sent to all contributors to update their data and to add follow-up. Patient data was collected on the following items: age, parity, antecedent pregnancy, diagnostic modalities, initial presenting features, hCG pre-treatment concentrations, tumor location(s), and size, histopathological findings, FIGO stage, treatment schedules, and follow-up including recurrence and survival. Three patients were excluded from analysis based on pre-treatment expert histology reviews which reported one case of PSTT, one case of mixed ETT/choriocarcinoma and one case of APSN with just a small possibility of ETT. Histology was reviewed by an expert pathologist in all cases. In total, 54 patients from ten medical centers across seven countries were available for the final analysis (Table 1). Complete sustained remission was defined as monthly non-detectable hCG levels for one full year in those patients where the tumor was secreting sufficient amounts of this hormone to be elevated in serum. In addition, we also counted patients who progressed on imaging, but still had normal hCG. Unfortunately, we did not have imaging on all patients to confirm this. The world data set has no complete dataset to confirm sustained remission.

2.1. Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 22.0 and R software version 3.5.0 with package survival ROC 1.0.3 were used for statistical analyses and graphics. Baseline characteristics were described in patients with ETT and patients with mixed PSTT/ETT separately. In further analyses, we merged these groups together and stated them as ETT patients because of the similar presentation, but analyses were also performed without the mixed PSTT/ETT tumors. Overall survival (OS) was estimated using the Kaplan-Meier method, and differences in survival were analyzed using the log-rank test. Patients with follow-up time missing from the database could not be used for survival analysis. We performed univariable Cox regression analysis to determine which variables were significantly associated with length of survival. The variables which were significantly associated with length of survival at a $p < 0.10$ level of significance, were included in a multivariate regression analysis model to determine whether the interval remained prognostic after correction for other significant variables. Variables were categorized into different groups: age (≤ or >40 years), time since antecedent pregnancy (≤ or > 48 months), tumor size (1–3 cm or > 3 cm), pre-treatment hCG ($<10^3$ or $\geq 10^3$), FIGO stage (stage 1 vs stages II–IV) and ETT versus PSTT/ETT. In addition, a model was built where the time since antecedent pregnancy was not categorized but considered as a continuous variable. In order to relax the assumption of linearity, it was entered into the model as a restricted cubic spline curve. Time-dependent Receiver Operating Characteristic (ROC) curve analysis using Nearest Neighbor Estimation (NNE) was used to evaluate the sensitivity and specificity of the interval since antecedent pregnancy as continuous variable to differentiate between survival or death at 5 years [12]. Patients with an interval longer than the threshold were called positive. The confidence interval of the area under the ROC curve was obtained using the bootstrap method with 2000 replications. The positive predictive value (PPV) and negative predictive value (NPV) were estimated with the Kaplan-Meier method at a cut-off of 48 months and at the optimal cut-off value found by maximizing Youden's index [13].

3. Results

3.1. Description of patients

Patient characteristics of the included 54 patients are presented in Table 2. Histology showed ETT in 45 cases and mixed PSTT/ETT in 9

Table 1
Contributing countries ISTTD PSTT and ETT database.

Country	Number of ETT patients[a] (%)
United Kingdom	29 (53%)
France	10 (18%)
The Netherlands	7 (13%)
United States of America	3 (6%)
Canada	3 (6%)
Denmark	1 (2%)
Australia	1 (2%)

[a] Including mixed PSTT/ETT patients. ETT, epithelioid trophoblastic tumor; PSTT, placental site trophoblastic tumor.

cases. There were no differences in patient characteristics between the ETT and mixed PSTT/ETT group. Most patients were diagnosed before the age of 50 years, with a range of 17 to 54 years. Irregular vaginal bleeding was the most common initial presenting feature. The interval from the end of the antecedent pregnancy and date of diagnosis was >12 months in 44 patients, including 21 patients presenting >48 months after delivery. The majority of patients had disease confined to the uterus (FIGO stage I) upon presentation. Median pre-treatment hCG concentration of all patients was low with an extensive range. Serum hCG pre-treatment concentration was normal (≤4 IU/L or less) in 23 patients, albeit measured by different assays. In stages I and II disease, pre-treatment hCG concentrations were between <2 and 15 IU/L ($n = 25$). In stage ≥III patients, hCG pre-treatment concentration was increased for all patients, except one (median 10.494 IU/L, range 29–500,000 IU/L).

Table 2
Patient characteristics.

Patients ($n = 54$)			
		ETT $N = 45$	PSTT/ETT ($N = 9$)
Age	Years (SD)	38.3 (7.1)	37.2 (7.0)
Gravida	Median (range)	2 (1–8)	3 (2−13)
Parity	Median (range)	2 (0–6)	2 (1–9)
Antecedent pregnancy	N (%)		
Term		28 (62%)	7 (78%)
Hydatidiform mole		8 (18%)	0 (0%)
ToP/Miscarriage		6 (13%)	2 (22%)
Ectopic pregnancy		1 (2%)	0 (0%)
Unknown		2 (4%)	0 (0%)
Interval between diagnosis and antecedent pregnancy	N (%)		
<4 months		2 (4%)	0 (0%)
4–6 months		2 (4%)	1 (11%)
7–12 months		2 (4%)	0 (0%)
13–48 months		19 (42%)	4 (44%)
>48 months		17 (38%)	4 (44%)
Unknown		3 (7%)	0 (0%)
FIGO stage	N (%)		
Stage I		30 (67%)	6 (67%)
Stage II		3 (7%)	1 (11%)
Stage III		5 (11%)	2 (22%)
Stage IV		7 (16%)	0 (0%)
Pre-treatment hCG IU/L	Median (range)	29 (<2–500.000)	2 (<2–33,327)
Tumor size cm	Median (range)	4 (0.5–14.0)	5 (0.2–11.0)
Lymphovascular space invasion (LVI)	N (%)		
LVI		2 (4%)	2 (22%)
No LVI		17 (38%)	5 (56%)
No hysterectomy		10 (22%)	1 (11%)
Unknown		16 (36%)	1 (11%)
Myometrial invasion			
Inner half		7 (16%)	2 (22%)
Outer half without serosal invasion		2 (4%)	0 (0%)
Outer half with serosal invasion		5 (11%)	4 (44%)
No myometrial invasion		4 (9%)	1 (11%)
No hysterectomy		10 (22%)	1 (11%)
Not documented		17 (38%)	1 (11%)
Metastases at time of diagnosis	N (%)		
Not present		30 (67%)	6 (67%)
Present	N (%)	15 (33%)	3 (33%)
Lung		4	2
Liver		3	0
Pelvic disease[a]		4	1
Other[b]		6	0
Initial presenting features	N (%)		
Vaginal bleeding		23 (51%)	7 (78%)
Abdominal pain		6 (13%)	0 (0%)
Abnormal ultrasound		3 (7%)	0 (0%)
Raised hCG		13 (29%)	1 (11%)
Other[c]		11 (24%)	5 (56%)

ETT, epithelioid trophoblastic tumor; PSTT, placental site trophoblastic tumor; ToP, termination of pregnancy.

[a] Metastases in vagina, cervix, broad ligament, adnexa.

[b] Lymph nodes, kidney, spleen, rectus abdominis muscle, intra-abdominal mass.

[c] One or more initial presenting features of: abdominal distention (n = 4), vaginal discharge (n = 3), abnormal cervical smear (n = 2), cough, malaise, breathlessness, lymphadenopathy, hot flushes, chest pain, swollen leg, back pain, post coital bleeding, secondary amenorrhea, chest infection, abdominal mass, fever (cough, …, fever n = 1).

3.2. Diagnostic evaluation

The diagnosis ETT or mixed PSTT/ETT was established following: hysterectomy ($n = 32$), biopsy/excision of an extra-uterine lesion ($n = 9$), uterine evacuation ($n = 7$), endometrial biopsy ($n = 4$), cervical biopsy ($n = 1$) or cervical conization (n = 1). The primary tumor site was the uterus ($n = 43$), the cervix ($n = 2$) or extrauterine without uterine involvement (n = 9). These extrauterine lesions were present in the lungs (n = 3), rectus abdominis muscle (n = 2), liver (n = 1), axillary lymph node (n = 1) or were intra-abdominal (n = 2). The original histology differed from the final diagnosis by an expert pathologist in 18 cases (33%, 18/54). Original histology varied between ETT, PSTT, choriocarcinoma, cervical cancer (squamous cell carcinoma, glassy cell carcinoma), endometrial cancer, poorly differentiated carcinoma, mixed mullerian tumor, mixed PSTT/ETT, mixed atypical placental side nodule/ETT or mixed atypical placental side nodule/complete mole. Twelve uterine tumors had metastases at time of diagnosis including lung ($n = 3$), pelvic disease ($n = 6$) or multiple sites, ≥2, (n = 3).

3.3. Treatment

Surgery is the cornerstone of treatment and indeed, 23 patients (43%, 23/54) underwent surgery alone as first line treatment and 25 patients (46%) in combination with chemotherapy. Six patients received only chemotherapy (11%). As expected, almost all patients in the surgery group had FIGO stage I disease (96%, 22/23) (Fig. 1). First line surgery consisted of a total abdominal hysterectomy ($n = 43$), excision of an extra-uterine lesion (n = 4) or endometrial resection ($n = 1$). Thirty-six stage I patients underwent a total abdominal hysterectomy (TAH) and detailed information was present in 31 patients. TAH with bilateral salpingo-oophorectomy (BSO) was performed in 9 patients, and TAH without BSO in 20 patients. Pelvic lymph node dissections (LND) were performed in 9 patients, iliac lymph node dissection in 1 and pelvic and para-aortic lymph node dissection in 1, all negative for tumor. A radical hysterectomy without BSO was performed in 2 patients, both without parametrial invasion.

Thirty-one patients underwent chemotherapy and 18 different chemotherapy regimens were used. Most common first line chemotherapy regimens included: etoposide + methotrexate + actinomycin-D/etoposide + cisplatin (EMA/EP, $n = 12$); EMA/cyclophosphamide + vincristine (EMA/CO, $n = 5$) and paclitaxel + etoposide/paclitaxel + cisplatin (TE/TP or PAC-E/PAC-PLAT, $n = 4$). Median number of chemotherapy lines during treatment was 2 (range 1–9, $n = 31$). The majority of patients treated with chemotherapy had FIGO stages II–IV disease (55%, 17/31).

3.4. Outcome

Median follow-up time of the survivors was 17.5 months (IQR 7.75–-44.50 months). There were two patients whose follow-up time was missing from the database. In total, 39 patients were alive with no evidence of disease, 4 patients were alive with disease, 10 patients died of disease, and 1 patient died of multiple pulmonary embolisms during the course of adjuvant chemotherapy. All patients who underwent surgery as first line treatment were in remission ($n = 23$). However, one of these patients relapsed 4 times and was alive with disease on the date of last contact. Patients treated with chemotherapy with or without

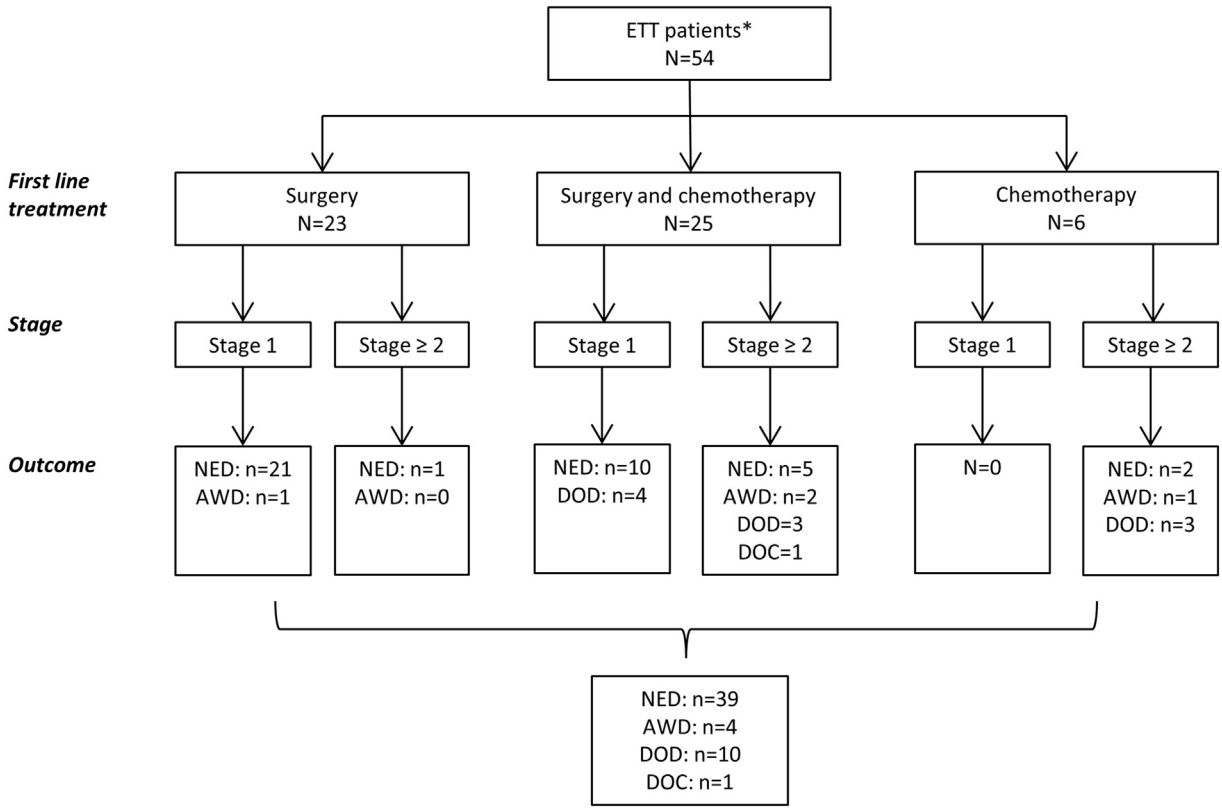

Fig. 1. Flow-chart treatment and outcome. *Including 9 mixed PSTT/ETT patients. AWD, alive with disease; DOC, dead of other cause; DOD, dead of disease; ETT, epithelioid trophoblastic tumor; NED, no evidence of disease; PSTT, placental site trophoblastic tumor.

surgery had a less favorable outcome as 11 of them did not survive (Fig. 1; Supplementary Fig. S1). Four stage I patients treated with adjuvant chemotherapy died of disease, with an interval between 56 and 202 months since antecedent pregnancy (1 interval unknown). Seventeen patients had no evidence of disease after chemotherapy with or without surgery. Most of them were treated with EP-EMA ($n = 9$). The other 8 patients were treated with TE/TP ($n = 2$), methotrexate/folinic acid (MTX/FA) (n = 2), actinomycin + cisplatin + etoposide (APE), EMA, EMA/CO, and EMA + intrathecal MTX + TE/TP. Stage IV patients had the worst outcome: 4 out of 7 patients died of disease and the other 3 patients were alive with disease (Fig. 1). Forty-four patients were in remission after first line treatment, but 9 of them relapsed (20%). The 35 patients who achieved complete remission and did not relapse had a median follow-up of 15 months (IQR 7–40 months). Twenty-two patients had a complete sustained hCG remission for at least 1 year. In 13 patients, no recurrence occurred but follow-up was less than 1 year. Five out of 6 relapsed patients had a complete remission that sustained for more than 1 year, however 3 relapse dates were missing. Six patients had a partial response and 3 patients had progressive disease and died despite further therapy. Subsequent therapies were administered in all patients with relapse, partial response or progressive disease and included chemotherapy, surgery, immunotherapy, radiotherapy and/or stereotactic radiosurgery. Eleven patients underwent 1 or more surgical procedures after primary treatment. These surgical procedures included removal of one solitary metastasis ($n = 10$), pelvic exenteration ($n = 5$) and debulking surgery for recurrent disease (n = 1). Anterior, posterior and total pelvic exenterations were performed in 1, 2 and 2 patients, respectively.

3.5. Prognostic factors of Overall Survival (OS)

Kaplan Meier analyses showed that interval since antecedent pregnancy (Fig. 2) and FIGO stage (Fig. 3) were significant prognostic factors ($p = 0.002$, and $p = 0.021$ respectively). Other variables such as age, pre-treatment hCG, tumor size and histologic appearance of ETT vs PSTT/ETT were not significant factors for the prognosis of patients with ETT ($p > 0.05$). As expected, patients with FIGO stages II–IV had a worse OS (HR = 4.6; $p = 0.035$) compared to patients with FIGO stage I disease in the univariable analysis. Also, patients with an interval since antecedent pregnancy of >48 months had a poor OS (HR = 13.3; $p = 0.015$) compared to those with an interval ≤ 48 months. Both stage and interval remained significantly associated with OS in the multivariable analysis (Table 3). Sensitivity analysis excluding patients with mixed PSTT/ETT tumors ($n = 9$) showed no significant differences in outcome.

There was a significant association between interval since antecedent pregnancy and OS ($p = 0.028$), which was significantly non-linear ($p = 0.009$) which means that the association between interval and the (log) hazard of death is not a straight line (Supplementary Fig. S2). The ROC curve of OS at 5 years showed that a cut-off point of around 48 months since antecedent pregnancy could differentiate between patients' probability of OS (<48 months) or death (≥48 months) with 86% sensitivity and 76% specificity (i.e. False Positive Rate (FPR) of 24%). The area under the ROC curve was 0.828 (95% CI 0.640–0.954) (Supplementary Fig. S3). In addition, we used the Kaplan-Meier method and found that in the subgroup of patients with interval < 48 months, only seven were at risk and no events were observed beyond 5 years. Therefore the estimated NPV at 5 years would be 100% but the confidence interval could not be calculated. The PPV was 53% (i.e. 100% minus the survival at 5 years, Fig. 2). We attempted to identify an optimal cutoff point from the ROC curve by considering Youden's index which attained its maximum of 0.657 at a cut-off point of 38.8 months with 97% sensitivity and 69% specificity (i.e. FPR of 31%). Of the 27 patients with interval < 38 months, no-one had an event. The corresponding Kaplan-Meier curves showed therefore a NPV of 100%, and a PPV of 46% (i.e. 100% minus the survival at 5 years, see Supplementary Fig. S4).

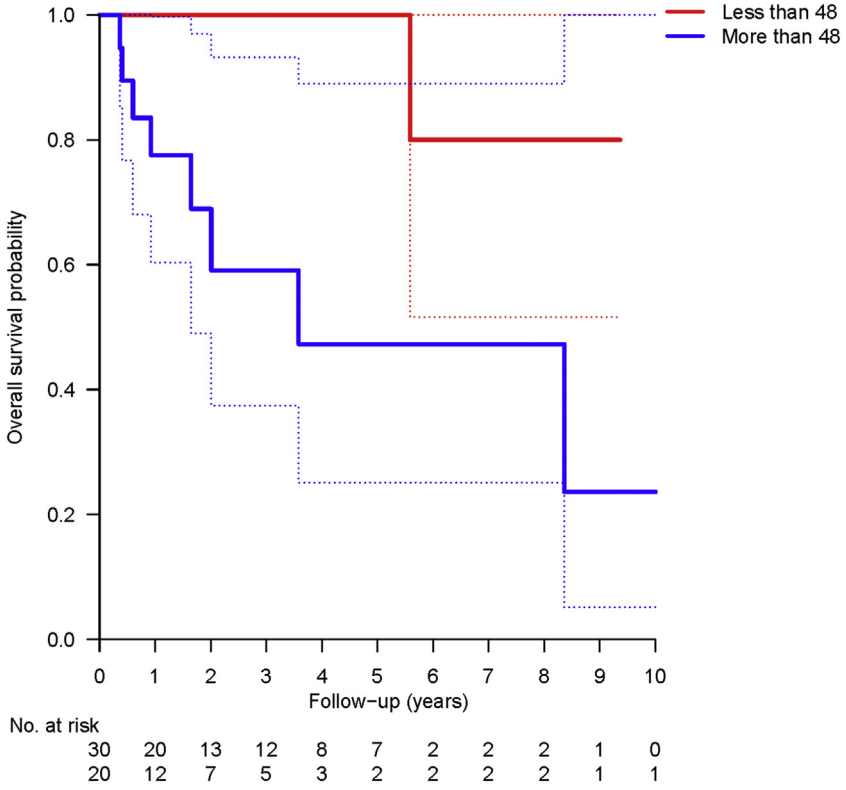

Fig. 2. Kaplan Meier estimate of overall survival by time since antecedent pregnancy (≤48 months vs >48 months, $p = 0.002$, log-rank test). Colored dotted lines are the corresponding 95% Confidence Intervals.

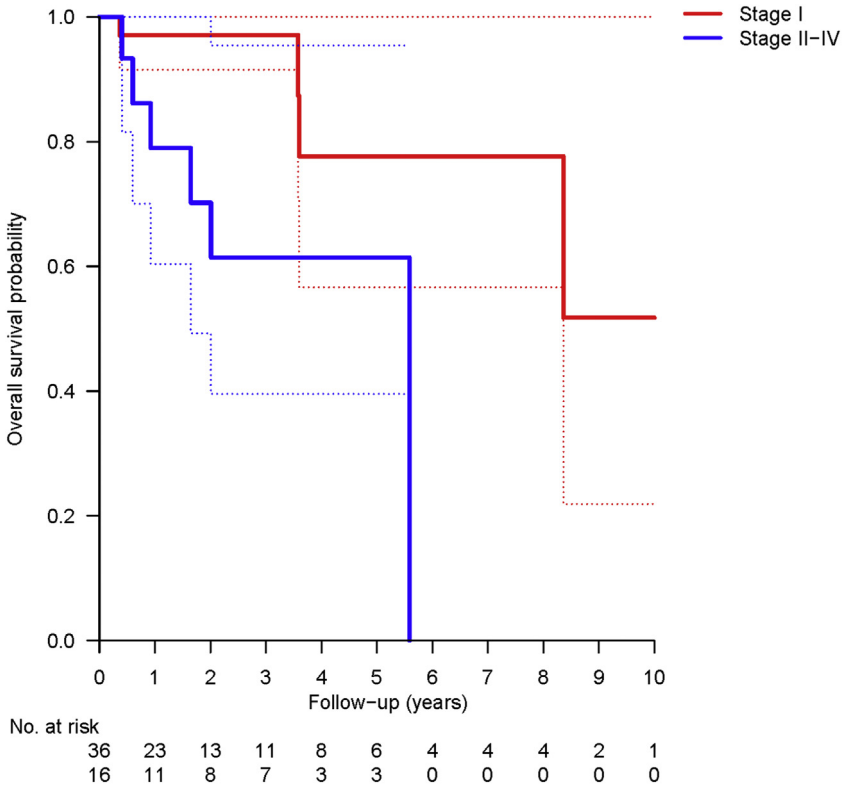

Fig. 3. Kaplan Meier estimate of overall survival by FIGO stage (stage I vs stages II–IV), $p = 0.012$, log-rank test). Colored dotted lines are the corresponding 95% Confidence Intervals.

Table 3
Cox regression analysis of overall survival in 54 ETT patients.

Univariable Cox regression				Multivariable Cox regression		
	Hazard ratio	95% CI	*P* Value	Hazard ratio	95% CI	P Value
Age ≤ vs >40 years	1.219	0.35–4.24	0.755			
Interval since antecedent pregnancy ≤48 months vs >48 months	13.343	1.66–107.31	**0.015**	16.19	1.85–141.93	**0.012**
Tumor size 1–3 cm vs >3 cm	34.111	0.02–70,400.42	0.365			
Pre-treatment hCG $<10^3$ vs $\geq 10^3$ IU/L	2.070	0.51–8.35	0.307			
FIGO stage Stage 1 vs Stages II–IV	4.575	1.12–18.74	**0.035**	8.711	1.34–56.55	**0.023**
Histology ETT vs ETT/PSTT	0.553	0.11–2.70	0.464			

ETT, epithelioid trophoblastic tumor; FIGO, International Federation of Gynecology and Obstetrics; PSTT, placental site trophoblastic tumor. Bold indicates a p-value < 0.05.

4. Discussion

The present study describes the largest case series of ETT so far in literature known to us. Common patient and tumor characteristics were analyzed and prognostic factors were identified. Both FIGO stage and interval of >48 months were shown to have a HR for poor outcome in multivariate analysis (HR 8.7, $p = 0.023$ and HR 16.2, $p = 0.012$, respectively).

As ETT and PSTT both originate from intermediate trophoblast, there are many overlapping clinical and pathological features including slow growth rates, relatively low hCG concentrations, and a poorer response to chemotherapy in contrast to other types of GTN [4,9,14]. Mixed histology's are also frequently seen. (Table 2).

The uterus is most often the primary site (40%) of ETT, followed by the cervix (31%). However, 25–35% of ETT patients present with metastases, most frequently in the lung. [1–3,5] Indeed, 33% of the patients in this series had metastatic disease at the time of presentation and 6 out of 18 patients had evidence of metastases in the lungs. Similar to previous reports, most of the patients in this series presented with vaginal bleeding at reproductive age. [3,4,8,15,16] However, many other initial presenting features occurred, which emphasizes the difficulty in diagnosing ETT. Therefore, Gestational Trophoblastic Disease (GTD) and GTN should always be considered in the differential diagnosis of patients with unusual presentations after antecedent pregnancy, in particular in case of ongoing abnormal uterine bleeding.

HCG concentrations are often only mildly elevated in ETT patients (<2500 IU/L) [1,3,5], unlike classic choriocarcinoma where very high hCG values are often found (>10,000 IU/L). In our series, pre-treatment hCG concentrations ranged from normal values up to 500,000 IU/L, with a median of 15 IU/L. One patient had a very high pre-treatment hCG concentration and was thought to be treated for disseminated choriocarcinoma. However, final pathology after chemotherapy and hysterectomy demonstrated ETT. Davis et al. hypothesized that an explanation of the very high hCG concentrations (>100,000 IU/L) may be a result of mixed pathology of ETT with a molar or choriocarcinoma component [8]. Such patients are being treated apparently effectively with chemotherapy and demonstrating only the persistence of ETT on the final pathology [8]. Another explanation of high pre-treatment hCG concentrations may be tumor burden, which is higher in advanced staged disease. Indeed, pre-treatment hCG concentrations were <15 IU/L for all our patients with early-stage disease and above 2500 lU/L for 14 of 18 patients (78%) with advanced stage disease. In 8 of our patients the hCG concentration at presentation was normal. This makes hCG a less reliable tumor marker for diagnosis and follow-up of especially early-stage and/or low-volume disease.

In general, GTN is very sensitive to chemotherapy. In contrast, ETT is relatively resistant to chemotherapy. Therefore surgical resection remains the recommended primary treatment modality. [2,3,5,8,15,16] Indeed, 89% of our patients underwent surgical treatment with 80% undergoing hysterectomy. Lymphadenectomy did not improve survival, although numbers of patients undergoing this procedure are limited. The best clinical outcome was seen in patients with FIGO stage I disease who underwent surgery (Fig. 1). In our series, 11 patients underwent resection of metastases. Because ETT is less chemotherapy sensitive surgical resection of residual or recurrent disease may be necessary. The majority of patients treated with multi-agent chemotherapy regimens had a poor clinical outcome. However, some patients may achieve long-term remission with multi-agent chemotherapy. In this series, seven patients with FIGO stages II–IV, treated with multi-agent chemotherapy (with or without surgery), were alive with no evidence of disease at time of follow-up (Fig. 1). Median follow up time of these patients was 39 months (range 6–63 months). Therefore, chemotherapy should be given in advanced stage ETT if surgical treatment is not possible or has been unsuccessful.

It is still impossible to draw a conclusion about the preferred regimen to treat ETT as in our series 18 different chemotherapy regimens were given. In the literature, EMA/EP is suggested to treat ETT or PSTT [9,10]. In our series 9 out of 12 patients who were treated with EMA/EP survived with no evidence of disease. Factors significantly associated with unfavorable outcome in PSTT include advanced stage disease and interval ≥ 48 months from the antecedent pregnancy. [10,17,18]. In the study of Schmid et al. all 13 PSTT patients presenting with an interval ≥ 48 months after antecedent pregnancy died, in contrast to 1 out of 49 patients with an interval < 48 months [10]. A cutoff point of 48 months since antecedent pregnancy could differentiate between patients' probability of survival (<48 months) or death (≥48 months) with 93% specificity and 100% sensitivity, and with a PPV of 100% and a NPV of 98% [10]. Forty-eight months or more since antecedent pregnancy was also a good predictor of poor prognosis of disease in our study, although the sensitivity, specificity, PPV and NPV of this cut-off point were lower than reported by Schmid et al. [10] We identified the optimal cutoff point in our series, and found that 38.8 months could differentiate between patients' probability of OS with 97% sensitivity, 69% specificity and a PPV of 46%. However, the False Positive Rate was higher in patients with an interval ≥ 38.8 months (31%) compared to those with an interval ≥ 48 months (24%) and lead to greater risk of overtreatment with risk-adapted management. These results with wide confidence intervals indicate that more (follow-up) data is needed to realize an exact reliable cut-off point in PSTT and ETT patients. Until that time, the use of 4-years interval since antecedent pregnancy as a prognostic indicator besides FIGO stage could help to select high-risk ETT patients for risk–adapted management. Surgery with adjuvant chemotherapy could be considered in these high-risk patients. Zhang et al. failed to demonstrate interval since antecedent gestation as a prognostic factor for ETT in an outcome-based literature review [9]. However, they used a different cut-off point with an interval of 24 months since antecedent pregnancy and inherent reporting bias in the limited data set from multiple case reports could have influenced their analysis.

There are several limitations to the present study which have to be noted besides its retrospective data collection. Although this is to our knowledge the largest case series of ETT patients reported in literature, it is still a relatively small number of patients. For this reason, the results of our study are exploratory and should be interpreted with caution. Unfortunately, prognostic value of specific pathological features, such as mitotic rate and molecular markers, could not be analyzed due to lack of data. It is unknown if the definitions of tumor response (e.g. partial response) were defined similarly for all patients. In the absence of clear definitions of tumor response in GTN, treating physicians may have interpreted tumor response slightly differently regarding rise, plateau or fall of hCG values after primary treatment. It was unknown how many cases were genetically confirmed to be gestational and to originate from the last pregnancy. Hypothetically, the interval from an earlier pregnancy to treatment of some patients could be longer than reported. Furthermore, the information regarding long term follow-up care (i.e. 5- or 10-year survival) is still limited. Because the exact dates of the recurrence are lacking, it is impossible to advice on the optimal duration of follow-up of patients. Because of the absence of a reliable biomarker, we cannot be absolutely sure that patients are indeed disease free. Therefore, some patients may have developed a recurrence which has not been discovered yet. Finally, there is inevitably overlap in patients of our dataset with previously reported cases. Despite these limitations, we have provided more insight into the characteristics and treatment outcome of ETT and identified important prognostic factors that should guide optimal management of treatment and follow-up of this rare disease.

In conclusion, ETT is a rare potentially high-risk GTN. A surgical approach is recommended for early-stage disease. Surgery and multichemotherapy is the preferred treatment modality in metastatic disease. Like PSTT, ETT patients with advanced-stage disease and an interval of 48 months or more since antecedent pregnancy have a poor prognostic outcome. Since an interval of 48 months or more from the antecedent pregnancy to first presentation is an independent poor prognostic factor, this suggests that patients with any stage disease should be considered for combination agent chemotherapy. However, there is insufficient data within the current data-set to know if this is really going to be beneficial in patients with stage I disease with a long interval since antecedent pregnancy. Expertise in ETT treatment is required, and therefore these patients should be treated in a trophoblastic disease center to provide optimal management. Future cases should be reported to the International Society for the Study of Trophoblastic Diseases PSTT and ETT database to increase our knowledge in ETT management and treatment (http://stdc.group.shef.ac.uk/psttuhr/).

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CRediT authorship contribution statement

M.M. Frijstein: Conceptualization, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **C.A.R. Lok:** Conceptualization, Resources, Writing - review & editing. **N.E. van Trommel:** Conceptualization, Resources, Supervision, Writing - review & editing. **M.J. ten Kate-Booij:** Conceptualization, Resources, Writing - review & editing. **L.F.A.G. Massuger:** Conceptualization, Resources, Writing - review & editing. **E. van Werkhoven:** Formal analysis, Visualization. **B. Kaur:** Writing - review & editing. **J.A. Tidy:** Writing - review & editing. **N. Sarwar:** Writing - review & editing. **F. Golfier:** Writing - review & editing. **M.C. Winter:** Writing - review & editing. **B.W. Hancock:** Conceptualization, Data curation, Writing - review & editing. **M.J. Seckl:** Supervision, Writing - review & editing.

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Conflict of interest statement

The authors have declared no conflicts of interest.

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