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# Intermediate trophoblastic tumor: the clinical analysis of 62 cases and prognostic factors

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## Abstract

**Purpose** The aim is to analyze the clinical characteristics of intermediate trophoblastic tumor (ITT).

**Methods** 12 cases diagnosed at Qilu Hospital of Shandong University from January 2005 to December 2016 were investigated. Additionally, 50 cases were selected from MEDLINE and CBM databases between January 2010 and December 2016. The clinical data extracted from those aforementioned 62 cases were analyzed.

**Results** There were 42 cases with placental site trophoblastic tumor (PSTT), 19 cases with epithelioid trophoblastic tumor (ETT), and 1 case with mixed type (PSTT and ETT). No significant differences were found between PSTT and ETT in terms of age, type of antecedent pregnancy, main complaints, serum β-hCG peak, FIGO stage or prognosis. However, the interval between antecedent pregnancy and the onset was longer in ETT than in PSTT ($P=0.01$). FIGO stage was irrelevant to serum β-hCG ($P=0.263$). All 62 cases underwent surgeries and seven cases preserved fertility. Fifteen cases with high risk factors were not treated with adjuvant chemotherapy. Univariate analysis results showed that age ≧40 years, serum β-hCG peak ≧1000 IU/L and nonstandard treatment were associated with poor survival, but only age remained significant on multivariate analysis for ITT ($P=0.018$).

**Conclusion** PSTT and ETT have similar clinical characteristics generally. Serum β-hCG can not reflect the progress of ITT. Age ≧40 years is the independent high risk factor for ITT.

**Keywords** Intermediate trophoblastic tumor · Placental site trophoblastic tumor · Epithelioid trophoblastic tumor · Clinical characteristics

## Introduction

Intermediate trophoblastic tumor (ITT) is a malignant disease that consists of placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT), which is originated from abnormal proliferation of placental site and epithelioid intermediate trophoblast, respectively. As a member of gestational trophoblastic neoplasia (GTN), ITT is rare and resistant to chemotherapy, which is different from other types of GTN, such as invasive mole or choriocarcinoma. As a result, surgery is vital and the first choice for the treatment of ITT. Chemotherapy is only applicable for patients who cannot be operated on or have high risk factors as postoperative adjuvant treatment [1].

PSTT was first identified as a malignant tumor by Scully in 1981, then accepted by World Health Organization (WHO) in 1983 [2, 3]. ETT was first found from lung metastasis by Michael in 1989, then WHO put it into GTN category in 2003 [4, 5]. The morbidity of ITT is fairly very low, accounting for about 0.7–2% in gestational trophoblastic disease (GTD). It was estimated that the incidence of PSTT was approximately equivalent to 1/10 million pregnancies [6]. However, ETT is rarer than PSTT in general [7, 8].

The optimal treatment and prognostic factors are limited due to low incidence and information about clinical features. There are many reports concentrating on PSTT, and it is generally believed that ETT and PSTT have the same therapeutic principles. Therefore, we aimed to distinguish the clinical differences between PSTT and ETT and to identify indicators of recurrence.

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## Materials and methods

### Patients

The study was approved by the medical ethics committee of Jining First People's Hospital. Because it was retrospective and based on anonymous patient records, informed consent was not necessary. There were two methods to gather cases in our study.

The first one was to search for case reports published from January 2010 to December 2016 from MEDLINE and CBM databases. The key phases included "trophoblastic pseudotumor," "placental site trophoblastic tumor," "epithelioid trophoblastic tumor," and "intermediate trophoblastic tumor." Both English and Chinese literature must meet the inclusion and exclusion criteria. The inclusion criteria were as follows: (1) the patient was pathologically confirmed with PSTT, ETT or ITT and had undergone immunohistochemical test. (2) The patient had complete clinical data. The exclusion criteria were displayed below: (1) patients had other types of pregnancy simultaneously, such as hydatidiform mole, abortion, ectopic pregnancy, and term pregnancy. (2) patients had other types of GTN simultaneously, such as invasive mole or choriocarcinoma. Because other types of GTN or pregnancy would interfere with serum β-hCG levels, we must exclude these cases in our study. The screening process is shown in Fig. 1.

Another one was to collect data from patients who were registered between January 2005 and December 2016 in Qilu Hospital of Shandong University. A total of 589 patients were diagnosed with GTD at this hospital. Thereinto, nine patients with PSTT and three patients with ETT were identified by professional pathologists. All patients were followed up until March 2017, except one patient with ETT was lost.

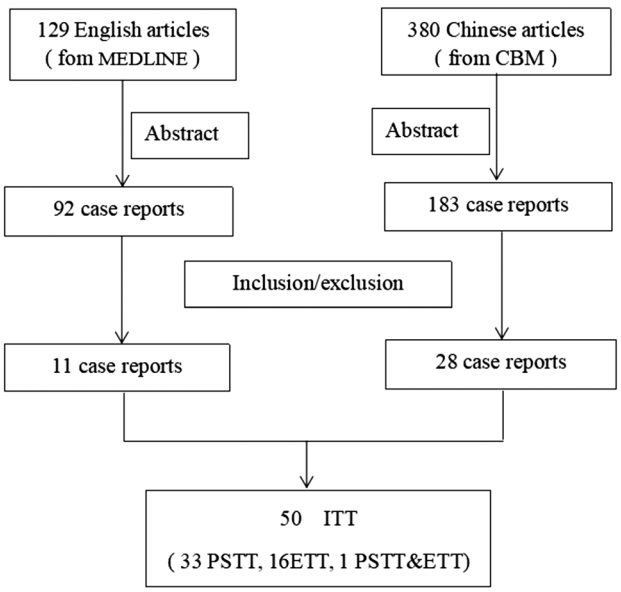


**Fig. 1** Literatures selection process

### Study design

The basic information such as age, complaint, tumor type, the interval since antecedent pregnancy (ISAP) and the outcome of antecedent pregnancy, serum β-hCG peak, International Federation of Gynecology and Obstetrics (FIGO) stage, surgical procedure and postoperative chemotherapy, pathological results and follow-up status were gathered from each patient. All patients in our studies were operated on first. Pathology specimens were partly stained by Ki67. The mitotic count per 10 high-power field and serum hPL were unavailable in most articles. The peak concentration of serum β-hCG during treatment was recorded. ISAP is the time from the end of antecedent pregnancy to the beginning of the diagnosis.

### Statistical analysis

SPSS19.0 software was used to assess the clinical differences between PSTT and ETT. The median combined with inter-quartile range showed skewness distribution data, while the means with the standard deviations indicated normal distribution data. Two groups of independent samples were assessed by Rank-Sum test, while three groups were calculated by Kruskal–Wallis test. The univariate Kaplan–Meier analysis and multivariate COX regression analysis were performed to identify the potential risk factors of recurrence. All $P$ values were significant at $\alpha < 0.05$.

## Results

There were 50 patients retrieved from the literature reviews ("Appendix 1"). Added to 12 patients from Qilu hospital of Shandong University ("Appendix 2"), a total of 62 patients were included for the final analysis, which contained 42 patients with PSTT, 19 patients with ETT and 1 patient with PSTT AND ETT.

12 patients with ITT were selected from 589 patients with GTD in Qilu hospital of Shandong University, which showed a morbidity of about 2%, concretely 1.5% with PSTT and 0.5% with ETT. We acquired the universality and individuality of PSTT and ETT.

The common features of PSTT and ETT are showed as follows: the mean age at diagnosis was 36 years (range, 20–60 years). Approximately 71% patients were less than 40 years, and 29% patients were older than 40 years, yet four patients were diagnosed after menopause. The mean gravida

**Table 1** The influential factors of FIGO stage

| FIGO stage | I | II–III | *P* |
|---|---|---|---|
| Number | 48 | 14 | |
| Age | 35.4 ± 8.4 | 37.8 ± 8.4 | 0.186 |
| ISAP | 22 (12, 81) | 20 (5.8, 51) | 0.296 |
| β-hCG | 208.6 (36.8, 720.35) | 416.3 (82.3, 1209.6) | 0.263 |

FIGO, international federation of gynecology and obstetrics; β-hCG, beta-human chorionic gonadotropin; ISAP, the interval since antecedent pregnancy

**Table 2** Partial comparisons between PSTT and ETT

| | PSTT | ETT | *P* |
|---|---|---|---|
| Number | 42 | 19 | |
| Age (years) | 34.5 ± 8.0 | 38.7 ± 8.2 | 0.143 |
| β-hCG (IU/L) | 207.2 (54.8, 521.6) | 464.5 (26, 1950) | 0.183 |
| ISAP (months) | 72 (22, 150) | 17 (11, 60) | 0.01 |
| Recurrence (number) | 3 | 3 | 0.168 |

PSTT, placental site trophoblastic tumor; ETT, epithelioid trophoblastic tumor; β-hCG, beta-human chorionic gonadotropin; ISAP, the interval since antecedent pregnancy

was 2.7 (range, 0–7), and the mean para was 1.4 (range, 0–3). Molar pregnancy has not been counted in gravida. The antecedent pregnancies included term labor (56.5%), abortion (21%), molar pregnancy (14.5%), premature labor (1.6%) and unknown (6.4%). Additionally, 71% patients presented with irregular vaginal bleeding, 13% with amenorrhea, 5% with bellyache, 3% with elevated serum hCG during follow-up of hydatidiform mole, as well as 2% with abnormal vaginal fluid. Serum β-hCG peak ranged from zero to 20,196 IU/L, with an average of 1119.9 IU/L, and 77.4% patients had levels less than 1000 IU/L. Besides, primary lesions were mostly located in uterine body (70.6%), in addition to cervix, vagina, broad ligament and lung [9]. Furthermore, 78.5% patients with PSTT and 73.7% patients with ETT belonged to FIGO I stage. FIGO stage was irrelevant to age, hCG or ISAP. (Table 1).

Table 2 compares some clinical characteristics between PSTT and ETT. We found a significant difference between them in the aspect of ISAP. The average ISAP of ITT was 63.5 months (range, 2–444 months), and the ISAP of ETT was relatively longer than PSTT [72 (22, 150) vs. 17 (11, 60), $P = 0.01$]. Another obvious diversities between PSTT and ETT were also found as follow: 5% patients presented with renal edema, existed only in PSTT but not in ETT [10]. And edema symptom would disappear after focal resection.

However, the level of serum β-hCG and the type of antecedent pregnancy was not correlated with ISAP ($P = 0.564$; $P = 0.083$). 77.4% of patients had lesions confined to the uterus, 22.6% of patients manifested metastases, which mainly occurred in pelvis (12.9%) and lung (9.7%). One patient with ETT had lesion in lung not in pelvic, presented with isolated nodule. Then we relegated it to FIGO III [9].

All the patients received surgical treatment, seven cases of PSTT and three cases of ETT have been resected lesion only then preserved fertility. The remaining patients underwent hysterectomy or/and adnexectomy or/and pelvic lymphadenectomy. We have set three high risk factors of recurrence, including ISAP ≧ 2 years and extrauterine metastasis and fertility-sparing surgery. Patients met with one of these aforementioned three risk factors must undergo adjuvant chemotherapy soon after surgery until serum hCG is negative for consecutive 3 weeks [1]. And then we defined it as the standard treatment. As a result, 36 patients received standard treatment, including 17 patients without postoperative therapy and 19 patients with timely enough chemotherapy. However, 16 patients with high risk factors had nonstandard treatment, including 14 patients without chemotherapy, 1 patient who started chemotherapy 35 days after surgery with the appearance of lung metastasis, and 1 patient without enough chemotherapy. Postoperative chemotherapy status was unknown in 10 patients. EMA-CO was the most common regimen (11/36), followed by BEP (5/36) and EMA-PE (3/36).

Except for one patient with ETT from Qilu hospital of Shandong University lost to follow, all the rest 61 patients were followed up. The median follow-up period was 22 months (range, 1–102 months). Fifty patients had no recurrent disease (90%), but four patients died of ITT, and two patients had local recurrence or distant metastases. In the present study, five cases with PSTT and two cases with ETT have merely resected local lesion then with their uterine preserved. The mean follow-up time was 36 months (range, 6–96 months) and no patient has recurred. The longest follow-up time of ETT was 28 months, which was shorter than that of PSTT of 96 months. The latter has borne children twice.

Univariate prognostic analysis showed that antecedent gravidity, ISAP, Ki67 positive rate, chemotherapy or FIGO stage could not predict survival of ITT. Fertility-preserving surgery was feasible for young patients with ITT ($P = 0.342$). However, age, serum β-hCG peak and standard treatment were related with poor prognosis of ITT (Table 3). Only age remained significant through multivariate analysis (Table 4). Furthermore, patients with an age over 40 years presented a rapid decline of survival rate in the short term compared to those who aged less than 40 years (Fig. 2).

## Discussion

Moutte et al. [8] has counted a total of 2989 cases with GTD in France from 2000 to 2011, and then found the morbidity of PSTT was 0.5% and ETT was 0.2%. Although the

**Table 3** Univariate prognostic analysis of ITT

| Outcome | No-recurrence | Recurrence or death | *P* |
|---|---|---|---|
| *Age* | | | |
| < 40 | 42 | 1 | |
| ≧40 | 13 | 5 | 0.004 |
| *B-hCG (IU/l)* | | | |
| < 1000 | 44 | 3 | |
| ≧1000 | 11 | 3 | 0.045 |
| *ISAP (year)* | | | |
| < 2 | 30 | 1 | |
| 2 | 25 | 5 | 0.141 |
| *Antecedent gravidity* | | | |
| Term | 31 | 3 | |
| Molar pregnancy | 8 | 1 | |
| Abortion | 12 | 1 | |
| Premature birth | 1 | 0 | |
| Unknown | 3 | 1 | 0.807 |
| *Ki67 rate (%)* | | | |
| < 20 | 16 | 2 | |
| ≧20 | 25 | 3 | |
| Unknown | 14 | 1 | 0.949 |
| *Chemotherapy* | | | |
| Yes[a] | 24 | 3 | |
| No | 24 | 1 | |
| Unknown | 7 | 2 | 0.558 |
| *FIGO stage* | | | |
| I | 43 | 4 | |
| II–III | 12 | 2 | 0.366 |
| *Tumor type* | | | |
| PSTT | 39 | 3 | |
| ETT | 15 | 3 | |
| Mixed type | 1 | 0 | 0.168 |
| *Fertility preserve* | | | |
| No | 48 | 6 | |
| Yes | 7 | 0 | 0.342 |
| *Treatment* | | | |
| Standard[b] | 36 | 0 | |
| Nonstandard | 12 | 3 | |
| Unknown | 7 | 3 | 0.013 |

β-hCG, beta-human chorionic gonadotropin; ISAP, the interval since antecedent pregnancy; FIGO, international federation of gynecology and obstetrics; PSTT, placental site trophoblastic tumor; ETT, epithelioid trophoblastic tumor

[a]Patients who received post-op chemotherapy regardless of standard treatment or not

[b]Patients who have preserved fertility or had risk factors, either ISAG ≧2 years or extrauterine metastasis, then received post-op chemotherapy soon after surgery until serum hCG was negative for consecutive 3 weeks

incidence of disease varies from region to region, but ITT is generally rare, and PSTT is twice or thrice the morbidity of ETT.

**Table 4** Multivariate prognostic analysis of ITT

| Factors | HR (95% CI) | *P* |
|---|---|---|
| Age | 0.03 (0.002–0.544) | 0.018 |
| β-hCG | 0.128 (0.011–1.458) | 0.098 |
| ISAP | 1.335 (0.078–22.927) | 0.842 |
| FIGO stage | 1.885 (0.119–29.859) | 0.653 |
| Chemotherapy | | 0.3 |
| Chemotherapy (1) | 0.746 (0.023–23.725) | 0.868 |
| Chemotherapy (2) | 0.096 (0.004–2.381) | 0.096 |

β-hCG, beta-human chorionic gonadotropin; ISAP, the interval since antecedent pregnancy; FIGO, international federation of gynecology and obstetrics

ITT often occurs in reproductive age, occasionally in postmenopausal women. There were reported, demonstrating that a patient with PSTT has been menopausal for 6 years, while a patient with ETT has been menopausal for 11 years [11, 12]. Brett et al. [13] reported that ETT in a 32-year-old woman with systemic metastasis was unrelated with antecedent pregnancy through microsatellite genotyping of liver metastatic tumor. This implied that ITT can occur in menopausal women, perhaps originated from the mutation of self gene. However, most patients with ITT are related to the abnormal differentiation of intermediate trophoblast from the antecedent pregnancy [14]. ITT can be secondary to various types of pregnancy, of which term labor is the majority. However, ITT is able to coexist with pregnancy, molar pregnancy or choriocarcinoma. Monclair et al. [15] reported a full-term pregnant women and her fetus were invaded by PSTT simultaneously, resulting in death of the newborn.

Significant differences have been found in ISAP among different patients. In our study, the longest ISAP was 444 months of ETT and 288 months of PSTT [16, 17]. Through rank-sum test, we found the ISAP of ETT was longer than PSTT ($P = 0.01$). Although there is no relevant report yet, ISAP is the obvious difference between PSTT and ETT.

Our study confirmed many common features between PSTT and ETT. Though these clinical manifestations were nonspecific, fortunately, most patients can be diagnosed at an early stage by abnormal vaginal bleeding. Notably, some patients with PSTT presented with edema, proteinuria and hypoalbuminemia, while the specific mechanism remains unknown. It is believed that PSTT is able to activate the coagulation system and produce immune complexes deposited in the glomeruli. The hypothesis was verified by renal biopsy and immunofluorescence techniques [10]. The symptoms subsided quickly after the tumor resection and patients do not have to delay chemotherapy. It should be highlighted that edema could be found only in PSTT but not in ETT,

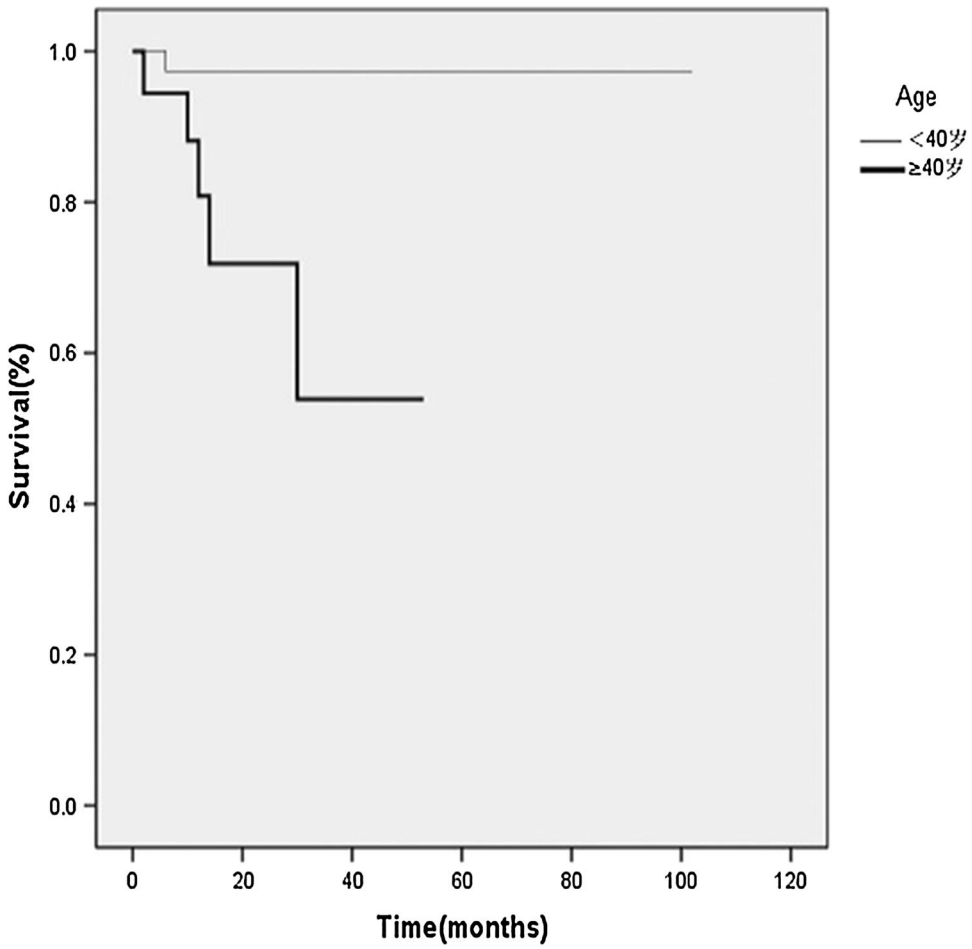


**Fig. 2** Kaplan–Meier estimate of survival by age (≧40 years vs. <40 years)

which is another significant difference between PSTT and ETT.

Unlike other types of GTN such as choriocarcinoma, serum β-hCG levels were not significantly increased in patients with ITT. The levels of most patients are less than 1000 IU/l, or even negative. However, there existed exceptions with levels exceed 100,000 IU/L [18]. In our study, no marked relationship was found between the level of serum β-hCG and FIGO stage in patients with ITT ($P=0.186$), which demonstrated that β-hCG fails to reflect the progress of the tumor. Therefore, serum β-hCG is not the only indicator of chemotherapy withdrawal and follow-up monitoring. Imaging examination is more important for ITT.

Lan C et al. reported that 5.9% PSTT can metastasize via lymphatics, which were confirmed by immunohistochemistry [19]. In our study, pelvic lymphadenectomy was performed in three cases with ETT and four cases with PSTT, and all the seven patients proved without metastasis. Therefore, we could speculate that direct spread or hematogenous metastasis may be the main pathway of ITT. Based on which, the systemic imaging examination is necessary due to the distant metastases via blood. Sumi et al. [20] have divided PSTT into two kinds according to blood signal in ultrasound, namely hypervascular type and relatively hypovascular type. A literature has once made an analysis on the ultrasound images of 12 cases with ETT, and then found abundant peripheral blood flow around the tumor, but less blood flow in the tumor [21]. Whatever blood signal is, abnormal echo light mass should be vigilant.

The first choice of ITT is surgical treatment, which in principle removes all lesions, including hysterectomy, bilateral adnexectomy and metastasectomy [1]. Pelvic lymphadenectomy is controversial. We suggest that the enlarged lymph nodes should be excised and pelvic lymphadenectomy should not be performed routinely. Fertility-preserving surgery can be used in young patients, which has been proven to be feasible through prognostic survival analysis in our study ($P=0.342$), as well as in a literature of 23 cases with PSTT [22]. Nevertheless, there is a lack of related reports on ETT.

ITT is not sensitive to chemotherapy, but chemotherapy should be considered when there are high risk factors. There is no clear conclusion on the risk factors, which may consist of mitotic figures > 5/10 HPF, extensive coagulative necrosis, ISAP≧2 years, deep myometrial infiltration, extrauterine metastasis, etc. [1]. In our study, we have defined ISAP≧2 years, extrauterine metastasis as well as fertility-sparing surgery as high risk factors. Generally, distant metastases with multiple lesions cannot be resected

thoroughly. If the patient has one of aforementioned three high risk factors, adjuvant chemotherapy should be given soon after surgery until serum hCG is negative for consecutive 3 weeks. But the regimen is inconsistent. FIGO in 2015 has recommended EMA-PE for both PSTT and ETT [23]. DGGG, OEGGG and SGGG have jointly recommended EMA-CO or EMA-PE, but BEP when neither was valid [1]. We are unable to judge which one is more effective due to small sample size and very different regimens in our study. Therefore, more researches are needed to further elucidate our results.

Schmid et al. have analyzed 62 cases with PSTT and concluded that the 10-year survival time was 90% of stage I, 52% of stage II, and 49% of stage III. But only ISAP ≥ 2 years made sense in the multivariate analysis [6]. Several literatures showed that FIGO stage was the independent prognostic risk factor for both PSTT and ETT [18, 22]. However, we have found that there were no prognostic difference in terms of FIGO stage, Ki67 positive rate, ISAP or other factors between PSTT and ETT. Univariate analysis indicated that age, serum hCG peak and nonstandard treatment had a great influence on the prognosis of patients with ITT, but only age still remained significant on the multivariate analysis. Age ≧ 40 years predicted poor prognosis. All the enrolled patients were operated on first and there was low proportion of advanced patients, so we thought that FIGO stage had little effect on patients with ITT in the study. Schmid et al. did not mention the mechanism of ISAP functioned on the prognosis, but ISAP ≧ 2 years is a widely accepted risk factor for patients with ITT. Though we did not reach the same conclusion, the standard treatment which included the acknowledged risk factor predicted poor survival in the univariate analysis. Serum hCG peak ≧ 1000 IU/L was relatively rare in ITT, but which suggested poor prognosis through our analysis. The author conjectures a prognosis scoring system may be needed for ITT for the reason that the risk factor is not always unique. In the current study, the follow-up time was short, with only 4 patients having a long-term survival of more than 60 months; meanwhile, 80% of patients were followed up less than 36 months. Therefore, more cases and longer follow-up time are needed to further study the clinical outcomes.

**Author contributions** YZ, data management, data analysis and manuscript writing; SZ, project development and manuscript editing; WH, data collection; TC, data collection; HY, data collection; YZ, data collection.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Human and animal rights** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Because of the retrospective study based on anonymous patient records, informed consent was not required.

## Appendix 1

See Table 5.

**Table 5** 50 patients retrieved from literature review

| No. | Author | Year | ISSN | doi | Age | Complaint | Antecedent pregnancy | Gender of antecedent pregnancy |
|---|---|---|---|---|---|---|---|---|
| 1 | 李雪峰 | 2016 | 1671-8348 | 10.3969/j.issn.1671-8348.2016.32.049 | 34 | Irregular vaginal bleeding | Term labor | – |
| 2 | 曾友玲 | 2010 | 1002-3429 | 10.3969/j.issn.1002-3429.2010.02.005 | 27 | Irregular vaginal bleeding | Term labor | – |
| 3 | 肖长纪 | 2015 | 0529-567X | 10.3760/cma.j.issn.0529-567x.2015.08.012 | 20 | Renal edema | Abortion | – |
| 4 | 张敏 | 2010 | 1671-7368 | 10.3969/j.issn.1002-3429.2010.02.011 | 39 | Irregular vaginal bleeding | Term labor | Boy |
| 5 | 陶红艳 | 2014 | 1008-1372 | 10.3760/j.issn.1008-1372.2014.z2.198 | 37 | Amenorrhea | Hydatidiform mole | – |
| 6 | 毛雪梅 | 2011 | 1671-170X | – | 39 | Irregular vaginal bleeding | Abortion | – |
| 7 | 郑建琼 | 2011 | 1671-0800 | 10.3969/j.issn.1671-0800.2011.06.064 | 28 | Irregular vaginal bleeding | Abortion | – |
| 8 | 王登凤 | 2016 | 0529-567X | 10.3760/cma.j.issn.0529-567x.2016.10.013 | 60 | Irregular vaginal bleeding | – | – |

**Table 5** (continued)

| No. | Author | Year | ISSN | doi | Age | Complaint | Antecedent pregnancy | Gender of antecedent pregnancy |
|---|---|---|---|---|---|---|---|---|
| 9 | 张晚鱼 | 2010 | 1671-6450 | 10.3969/j.issn.1671-6450.2010.03.018 | 46 | Lower abdominal pain | Term labor | Girl |
| 10 | 岑立微 | 2012 | 1004-7379 | 10.13283/j.cnki.xdfckjz.2012.05.016 | 31 | Irregular vaginal bleeding | Premature labor | – |
| 11 | 褚丹霞 | 2015 | 1672-1861 | 10.13390/j.issn.1672-1861.2015.06.028 | 24 | Irregular vaginal bleeding | Term labor | Girl |
| 12 | 陶红艳 | 2014 | 1008-1372 | 10.3760/j.issn.1008-1372.2014.z2.198 | 26 | Amenorrhea | Term labor | – |
| 13 | 王宝 | 2012 | 1672-0369 | 10.3969/j.issn.1672-0369.2012.08.015 | 40 | Irregular vaginal bleeding | Hydatidiform mole | – |
| 14 | 邹亮 | 2012 | 1001-7399 | 10.3969/j.issn.1001-7399.2012.10.025 | 42 | Irregular vaginal bleeding | Abortion | – |
| 15 | 李菁 | 2013 | 0529-567X | 10.3760/cma.j.issn.0529-567x.2013.12.020 | 33 | Renal edema | Term labor | Girl |
| 16 | 汤桂英 | 2010 | 1672-3511 | 10.3969/j.issn.1672-3511.2010.09.095 | 43 | Amenorrhea | Abortion | – |
| 17 | 朱燕 | 2015 | 1009-5519 | 10.3969/j.issn.1009-5519.2015.18.068 | 33 | Irregular vaginal bleeding | Abortion | – |
| 18 | 刘素晓 | 2011 | 1671-0800 | 10.3969/j.issn.1671-0800.2011.02.059 | 27 | Irregular vaginal bleeding | Term labor | – |
| 19 | 曾宪玲 | 2016 | 1673-5293 | 10.3969/j.issn.1673-5293.2016.03.040 | 36 | Abnormal vaginal fluid | Term labor | Girl |
| 20 | 王磊 | 2014 | 1007-8096 | 10.3969/j.issn.1007-8096.2014.03.014 | 41 | Irregular vaginal bleeding | – | – |
| 21 | 蔡兆根 | 2010 | 1000-2200 | 10.3969/j.issn.1000-2200.20https://doi.org/10.https://doi.org/10.008 | 30 | Irregular vaginal bleeding | Term labor | – |
| 22 | 姜旭平 | 2012 | 1672-9455 | 10.3969/j.issn.1672-9455.2012.04.066 | 54 | Irregular vaginal bleeding | – | – |
| 23 | 屈云飞 | 2013 | 1673-5250 | 10.3877/cma.j.issn.1673-5250.2013.04.037 | 47 | Irregular vaginal bleeding | Term labor | Girl |
| 24 | 朱晓静 | 2014 | 0253-3685 | – | 42 | Irregular vaginal bleeding | Hydatidiform mole | – |
| 25 | 时萍 | 2012 | 1673-5552 | 10.3969/j.issn.1673-5552.2012.17.036 | 41 | Irregular vaginal bleeding | Term labor | – |
| 26 | 王宝 | 2012 | 1672-0369 | 10.3969/j.issn.1672-0369.2012.08.015 | 34 | Irregular vaginal bleeding | Term labor | – |
| 27 | 肖长纪 | 2015 | 0529-567X | 10.3760/cma.j.issn.0529-567x.2015.08.012 | 31 | Renal edema | Term labor | Boy |
| 28 | 肖萍 | 2012 | 1002-0179 | – | 27 | Irregular vaginal bleeding | Abortion | – |
| 29 | 时萍 | 2012 | 1673-5552 | 10.3969/j.issn.1673-5552.2012.17.036 | 39 | Irregular vaginal bleeding | Hydatidiform mole | – |
| 30 | 张薇珊 | 2014 | 0529-5807 | 10.3760/cma.j.issn.0529-5807.2014.12.013 | 56 | Irregular vaginal bleeding | Term labor | – |
| 31 | 时萍 | 2012 | 1673-5552 | 10.3969/j.issn.1673-5552.2012.17.036 | 35 | Irregular vaginal bleeding | Term labor | – |
| 32 | 王宝 | 2012 | 1672-0369 | 10.3969/j.issn.1672-0369.2012.08.015 | 30 | Irregular vaginal bleeding | Hydatidiform mole | – |
| 33 | 时萍 | 2012 | 1673-5552 | 10.3969/j.issn.1673-5552.2012.17.036 | 39 | Irregular vaginal bleeding | Hydatidiform mole | – |
| 34 | 王宝 | 2012 | 1672-0369 | 10.3969/j.issn.1672-0369.2012.08.015 | 33 | Irregular vaginal bleeding | Term labor | – |
| 35 | 马晨涵 | 2014 | 1673-5293 | 10.3969/j.issn.1673-5293.2014.06.065 | 33 | Irregular vaginal bleeding | Term labor | – |
| 36 | 马晨涵 | 2014 | 1673-5293 | 10.3969/j.issn.1673-5293.2014.06.065 | 36 | Amenorrhea | Abortion | – |
| 37 | 马晨涵 | 2014 | 1673-5293 | 10.3969/j.issn.1673-5293.2014.06.065 | 27 | Irregular vaginal bleeding | Term labor | – |
| 38 | 马晨涵 | 2014 | 1673-5293 | 10.3969/j.issn.1673-5293.2014.06.065 | 26 | Irregular vaginal bleeding | Term labor | – |
| 39 | Abrão FC | 2011 | 1556-0864 | 10.1097/JTO.0b013e318215a214 | 31 | Irregular vaginal bleeding | Term labor | – |

**Table 5** (continued)

| No. | Author | Year | ISSN | doi | Age | Complaint | Antecedent pregnancy | Gender of antecedent pregnancy |
|---|---|---|---|---|---|---|---|---|
| 40 | Ahmet | 2011 | 1028-4559 | 10.1016/j.tjog.2011.01.026 | 34 | Irregular vaginal bleeding | Abortion | – |
| 41 | Ahmet | 2011 | 1028-4559 | 10.1016/j.tjog.2011.01.026 | 38 | Amenorrhea | Term labor | – |
| 42 | BJ Chen | 2013 | 1746-1596 | 10.1186/1746-110.1186/1746-1596-8-856-8-85 | 41 | Irregular vaginal bleeding | Term labor | – |
| 43 | FY Huang | 2013 | 0959-9673 | PMID: 23826431 | 36 | Irregular vaginal bleeding | Term labor | – |
| 44 | HY Zhang | 2015 | 1936-2625 | PMID: 25932270 | 40 | Irregular vaginal bleeding | Hydatidiform mole | – |
| 45 | John W | 2013 | 2211-338X | 10.1016/j.gynor.2013.11.001 | 53 | Irregular vaginal bleeding | Unknown | – |
| 46 | L Rauw | 2013 | 2211-338X | 10.1016/j.gynor.2013.05.006 | 46 | Lower abdominal pain | Term labor | – |
| 47 | R Lucas | 2015 | 0144-3615 | 10.3941/jrcr.v9i4.2146 | 34 | Amenorrhea | Term labor | – |
| 48 | Stănculescu RV | 2016 | 1220-0522 | PMID: 28174805 | 35 | Amenorrhea | Abortion | – |
| 49 | Xiao Tang | 2013 | 0377-4929 | 10.4103/0377-4929.120405 | 29 | Irregular vaginal bleeding | Abortion | – |
| 50 | Xf Zhang | 2014 | 1936-2625 | PMID: 25550880 | 44 | Irregular vaginal bleeding | Abortion | – |

| No. | ISAP (month) | G–P | Serum hCG peak(IU/l) | Hysterectomy | Fertility preserve | Type | Ki67(%) |
|---|---|---|---|---|---|---|---|
| 1 | 72 | 3–1 | 1388.1 | Yes | – | ETT | 20 |
| 2 | 14 | – | 2046 | Yes | – | ETT | |
| 3 | 9 | 1–0 | 6773 | Yes | – | PSTT | 30 |
| 4 | 11 | 2–2 | 284 | Yes + BSO | – | PSTT | 0 |
| 5 | 14 | 3–2 | 498 | Yes | – | PSTT | |
| 6 | 12 | – | 22 | Subtotal hysterectomy | – | ETT | 20 |
| 7 | 30 | – | 300 | Yes | – | ETT | |
| 8 | 444 | – | 802 | Yes + BSO + PL | – | ETT | 90 |
| 9 | 228 | 2–2 | 0 | Subtotal hysterectomy | – | PSTT | |
| 10 | 20 | – | 0 | Yes | – | ETT | 10 |
| 11 | 12 | – | 55 | Yes | – | PSTT | 40 |
| 12 | 12 | 2–1 | 70 | Yes | – | PSTT | 30 |
| 13 | 144 | – | 240 | Yes | – | PSTT | 10 |
| 14 | 4 | 3–2 | 357.6 | Yes + BSO | – | ETT | 20 |
| 15 | 13 | 1–1 | 1028 | Yes + left SO | – | PSTT | |
| 16 | 204 | 7–2 | 2081 | Yes + BSO | – | ETT | 25 |
| 17 | 4 | 4–1 | 20,196 | Lesion resection | Yes | PSTT | 80 |
| 18 | 18 | – | 31 | Yes | – | PSTT | |
| 19 | 10 | 2–1 | 66.14 | Yes | – | PSTT | 10 |
| 20 | 168 | – | 1038.8 | Yes + vaginal lesion | – | ETT | 35 |
| 21 | 48 | – | 5240 | Yes + BSO + PL | – | ETT | 45 |
| 22 | 336 | 2–1 | 11.58 | Yes + BSO | – | ETT | |
| 23 | 216 | 3–2 | 227.2 | Yes + BSO | – | PSTT | 50 |
| 24 | 36 | – | 96 | Lesion resection | Yes | ETT | 50 |
| 25 | 84 | – | 228 | Yes | – | PSTT | 11 |
| 26 | 60 | – | 99 | Yes | – | PSTT | 20 |
| 27 | 18 | 1–1 | 96 | Yes + BSO | – | PSTT | 10 |
| 28 | 13 | 3–1 | 2047 | Yes | – | PSTT | 30 |
| 29 | 120 | – | 190 | Yes | – | PSTT | 22 |
| 30 | 324 | 3 | 464.5 | Yes + BSO + PL | – | ETT | 10 |
| 31 | 60 | | 105 | Yes | – | PSTT | 22 |
| 32 | 60 | | 460 | Yes | – | PSTT | 20 |
| 33 | 72 | | 410 | Yes | – | PSTT | 11 |
| 34 | 96 | | 230 | Yes | – | PSTT | 10 |
| 35 | 20 | 1 | 8.5 | Yes | – | PSTT | |
| 36 | 13 | 3 | 18.5 | Yes | – | PSTT | |

**Table 5** (continued)

| No. | ISAP (month) | G–P | Serum hCG peak(IU/l) | Hysterectomy | Fertility preserve | Type | Ki67(%) |
|---|---|---|---|---|---|---|---|
| 37 | 11 | 3 | 118.5 | Yes | – | PSTT | |
| 38 | 7 | 2 | 162.3 | Yes | – | PSTT | |
| 39 | 96 | 2–2 | 700 | Pulmonary lesion resection | Yes | ETT | |
| 40 | 2 | | 763 | Yes | – | PSTT | |
| 41 | 12 | | 337 | Yes + BSO + PL + omentectomy | – | PSTT | |
| 42 | 12 | 3–2 | 1 | Yes | – | Mixed | < 20 |
| 43 | 31 | 4–2 | 7.79 | Yes | – | PSTT | |
| 44 | 36 | 3–2 | 0 | Vaginal lesion | Yes | PSTT | 5% |
| 45 | 12 | | 1517.7 | Yes + BSO + PL + omentectomy | – | PSTT | < 20 |
| 46 | 96 | 4–3 | 41 | BSO + vaginal lesion + PL | – | PSTT | 60–70 |
| 47 | 11 | 1–1 | 68.4 | Yes + BS + PL | – | PSTT | 9% |
| 48 | 120 | 4–2 | 0 | Yes | – | ETT | 25% |
| 49 | 24 | 4–0 | 1722 | Lesion resection | Yes | PSTT | 80% |
| 50 | 132 | 4–1 | 6587 | Yes + left ovary + BS | – | ETT | 77% |

| No. | FIGO stage | Chemotherapy | Follow-up time (month) | Outcome | Label | Standard treatment |
|---|---|---|---|---|---|---|
| 1 | I | – | 1 | Fine | | No |
| 2 | I | TP 3 cycles | 3 | Fine | | Yes |
| 3 | I | – | 4 | Fine | Renal edema, disappeared 1 month after operation | Yes |
| 4 | I | KSM + VCR 1 cycle | 6 | Fine | Renal edema, disappeared 5 days after operation | Yes |
| 5 | I | Refuse | 6 | Fine | | No |
| 6 | I | Refuse | 7 | Fine | | No |
| 7 | I | EMA-CO | 7 | Fine | | Yes |
| 8 | I | TBL 4 cycles + radiotherapy | 7 | Fine | Postmenopause, combined with cervical adenocarcinoma | Yes |
| 9 | I | ACM 2 cycles | 10 | Dead | Start chemo after the occurrence of pelvic and pulmonary metastases; dead from systemic metastasis | No |
| 10 | I | EMA-CO 3 cycles | 12 | Fine | The antecedent pregnancy had pregnancy—induced hypertension syndrome and premature labor | Yes |
| 11 | I | EMA-CO 2 cycles | 12 | Fine | | Yes |
| 12 | I | – | 12 | Fine | | Yes |
| 13 | I | Unknown | 12 | Dead | Dead of pulmonary metastasis 1 year after operation | Unknown |
| 14 | II | – | 12 | Fine | | No |
| 15 | III | EMA-CO 5 cycles, then hCG normal, additional 3 cycles | 12 | Fine | Renal edema, pulmonary and left adnexal metastases | Yes |
| 16 | I | Refuse | 12 | Fine | | No |
| 17 | III | BEP 3 cycles | 12 | Fine | Pulmonary metastasis, disappear in follow-up | Yes |
| 18 | I | EMA 2 cycles | 13 | Fine | | Yes |
| 19 | I | 5-FU, MTX, VP-16 1 cycle, EMA-CO | 14 | Fine | | Yes |
| 20 | II | Yes, unknown | 14 | Dead | Relapse in vagina 5 months after operation, in whole pelvis 12 months; died 14 months | Unknown |
| 21 | I | FA | 22 | Fine | | Yes |

**Table 5** (continued)

| No. | FIGO stage | Chemotherapy | Follow-up time (month) | Outcome | Label | Standard treatment |
|---|---|---|---|---|---|---|
| 22 | I | Unknown | 24 | Fine | | Unknown |
| 23 | I | Refuse | 26 | Fine | | No |
| 24 | II | – | 28 | Fine | | No |
| 25 | I | Unknown | 30 | Relapse | Relapse in kidney 30 months | Unknown |
| 26 | I | Unknown | 31 | Fine | | Unknown |
| 27 | I | – | 32 | Fine | Renal edema, disappeared 1 month after operation | Yes |
| 28 | I | EMA-PE 3 cycles | 36 | Fine | | Yes |
| 29 | I | Unknown | 39 | Fine | | Unknown |
| 30 | I | Refuse | 39 | Fine | Postmenopause | No |
| 31 | I | Unknown | 42 | Fine | | Unknown |
| 32 | I | Unknown | 42 | Fine | | Unknown |
| 33 | I | Unknown | 50 | Fine | | Unknown |
| 34 | I | Unknown | 60 | Fine | | Unknown |
| 35 | I | – | 22 | Fine | | Yes |
| 36 | I | – | 22 | Fine | | Yes |
| 37 | I | EMA-CO 1 cycles | 22 | Fine | | Yes |
| 38 | I | – | 22 | Fine | | Yes |
| 39 | III | – | 12 | Fine | | No |
| 40 | I | EMA-CO 6 cycles | 6 | Fine | Combined with right ovarian cyst | Yes |
| 41 | II | EMA-CO 6 cycles | 6 | Fine | | Yes |
| 42 | I | – | 30 | Fine | | Yes |
| 43 | I | EMA-CO 4 cycles | 40 | Fine | | Yes |
| 44 | II | EMA-PE 2 cycles | 6 | Fine | | Yes |
| 45 | I | – | 10 | Fine | | Yes |
| 46 | II | – | 10 | Fine | Hysterectomy 4 years ago for cervical high grade intraepithelial neoplasia and poor healing of scar in cesarean section which lead to abnormal bleeding | No |
| 47 | I | – | 9 | Fine | | Yes |
| 48 | I | – | 6 | Fine | | No |
| 49 | II | EMA-CO 6 cycles | 18 | Fine | Acute massive vaginal bleeding | Yes |
| 50 | I | EMA-PE4 cycles | 2 | Relapse | hCG became normal after 3 cycles, but author referred to 5 cycles should be given | No |

BSO, bilateral salpingo-oophorectomy; PL, pelvic lymphadenectomy; BS, bilateral salpingotomy; SO, salpingo-oophorectomy; KSM, dactinomycin; VCR, vincristine; T, taxel; P, platinum; EMA-CO, etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine; EMA-PE, etoposide, methotrexate, actinomycin D, cisplatinum, etoposide; BEP, bleomycin, etoposide, platinum; VP-16, etoposide; EMA, etoposide, methotrexate, actinomycin D; MTX, methotrexate; 5-FU, 5-fluorouracil; L, lobaplatin

## Appendix 2

See Table 6.

**Table 6** 12 patients from Qilu Hospital of Shandong University

| No. | Type | Age | Complaints | Serum hCG peak(IU/l) | Antecedent pregnancy |
|---|---|---|---|---|---|
| 1 | ETT | 34 | Lower abdominal pain 3 days | 26.19 | Term labor |
| 2 | ETT | 31 | Irregular vaginal bleeding 1 month | 1950 | Term labor |
| 3 | ETT | 37 | Irregular vaginal bleeding 3 months | 393.3 | Term labor |
| 4 | PSTT | 38 | Irregular vaginal bleeding 9 days | 14.65 | Term labor |
| 5 | PSTT | 24 | Irregular vaginal bleeding 1 month | 54 | Term labor |
| 6 | PSTT | 28 | Irregular vaginal bleeding 1 month | 61.34 | Term labor |
| 7 | PSTT | 51 | Elevated serum hCG during follow-up of hydatidiform mole | 224.32 | Hydatidiform mole |
| 8 | PSTT | 35 | Irregular vaginal bleeding 1 month | 475 | Term labor |
| 9 | PSTT | 30 | Irregular vaginal bleeding 3 months | 592.4 | Term labor |
| 10 | PSTT | 31 | Amenorrhea, 4 months | 798.5 | Term labor |
| 11 | PSTT | 22 | Elevated serum hCG during follow-up of hydatidiform mole | 5611 | Hydatidiform mole |
| 12 | PSTT | 43 | Irregular vaginal bleeding 1 year | 0 | Abortion |

| No. | ISAP (month) | Stage | Hysterectomy | Complication | Chemotherapy | Follow-up time (month) |
|---|---|---|---|---|---|---|
| 1 | 24 | I | Yes | | No | – |
| 2 | 5 | III | Yes | Pulmonary metastasis | PE 1 cycles, refuse | 6 |
| 3 | 72 | I | Yes | | PE 4 cycles | 3 |
| 4 | 16 | II | Yes | Right ovarian metastasis | BEP 4 cycles | 5 |
| 5 | 11 | I | No | | BEP 4 cycles | 80 |
| 6 | 7 | I | Yes | | No | 16 |
| 7 | 24 | III | Yes | Pulmonary metastasis | PE 2 cycles | 15 |
| 8 | 6 | III | Yes | Pulmonary metastasis | BEP 5 cycles | 102 |
| 9 | 6 | I | Yes | | No | 22 |
| 10 | 48 | I | Yes | | No | 12 |
| 11 | 29 | I | No | | BEP 2 cycles | 96 |
| 12 | 18 | I | Yes | | No | 53 |

| No. | Outcome | Label | Standard treatment | Immunohistochemical results |
|---|---|---|---|---|
| 1 | – | Lost | No | HPL (++), HCG (+), E-cad (++), α-inhibin (++), Ki67 (−) |
| 2 | Dead | Brain metastasis | No | HPL focal (+), HCG partial (+), P63 (−), E-cad diffuse (+), α-inhibin (+), CK18diffuse (+), CK19 (+), Ki67 < 20% |
| 3 | Fine | | Yes | HPL few (+), HCG most (+), P63 (+), α-inhibin few (+), CK (+), CK7 (+), CK5/6 (−), P53 (+, 40%), Ki67 60–70% |
| 4 | Fine | | Yes | HPL (+), HCG focal (+), P63 (−), α-inhibin (+), CK (+), Ki67 20% |
| 5 | Fine | | Yes | HPL (+), HCG focal (+), E-cad (+), Ki67 20–25% |
| 6 | Fine | | Yes | HPL (+), HCG focal (+), P63 (−), α-inhibin (+), PLAP (−), Ki67 8% |
| 7 | Fine | No progression in the chest X-ray | Yes | HPL diffuse (+), hCG partial (+), P63 (−), α-inhibin week (+), DOG-1diffuse (+), PLAP partial (+), Ki67 15–20% |
| 8 | Fine | No progression in the chest X-ray | Yes | HPL (+), HCG few (+), P63 (−), α-inhibin (−), CK (+), PLAP few (+), CD99 week (+), Ki67 60% |
| 9 | Fine | | Yes | HCG (+), CK (+), Ki67 30% |
| 10 | Fine | | No | HPL focal (+), HCG focal (+), P63 (+), α-inhibin focal (+), CK (+), Ki67 10–15% |
| 11 | Fine | Give birth twice | Yes | HPL partial (+), HCG partial (+), P63 (−), Ki67 < 10% |
| 12 | Fine | | Yes | HPL partial (+), HCG (−), α-inhibin (+), CK18 (+), P63 (−), Ki67 15% |

G, gravida; P, para; A, abortus; L, living children; B, bleomycin; E, etoposide; P, platinum

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