

## Gestational Trophoblastic Neoplasm; Case Series and Literature Review

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### Abstract

**Objective:** Appropriated management of patients with advanced of Gestational Trophoblastic Neoplasm (GTN) appear to be a great deal. This study was conducted to evaluate the value of the imaging method of fluorine-18-fluorodeoxyglucose positron emission/Computed tomography scanning (PET/CT) in treatment planning and outcome in patients with GTN and localizing of metastatic site.

**Methods:** A retrospective study on four patients with persistent GTN who had been studied with whole body PET/CT to detected the extension of tumor. Based on these data all our patients underwent surgery, therefor clinical impact strength of PET/CT had been analysis.

**Results:** In 3 of 4 cases the PET/CT had positive accordance with other anatomical and clinical impact. In one case the PET/CT not enable detected the source of viable neoplasm.

**Conclusion:** The additional value of the PET/CT with respect to other imaging modality; mainly is in differentiating between residual viable tumor tissue and necrosis, in discloser of chemo resistant lesion in GTN. Due to the expensive equipment despite of its value, unfortunately PET/CT, its use is limited in certain cases to detected the source of viable neoplasm.

**Keywords:** Chemo resistance, Gestational trophoblastic tumor, FDG PET/CT Scan.

### 1. INTRODUCTION

GTN It is derived from abnormal proliferation of placenta and includes: the malignant transformation of hydatidiform mole, invasive mole, choriocarcinoma (CC), placental site trophoblastic tumor (PSTT). Serum human

chorionic gonadotropin ( $\beta$ HCG) is a sensitive tumor marker in diagnosis and evaluating treatment response of GTN (1). The diagnosis of GTN is based on plateau, rise of serial  $\beta$ HCG level or unexplained persistence of  $\beta$ HCG level during 6 months after molar pregnancy

evacuation, histopathological diagnosis of CC or PSTT; and presence of metastatic disease on imaging (2). GTN are a reproductive age malignancy that consider curable. The goal of GTN management is timely diagnosis and accurate treatment planning based on FIGO staging and prognostic scoring (3). However combination chemotherapy is indicated in high risk GTN. A key issue in the management of GTN is chemo resistance cases which is likelihood mortality. The important issue is finding metastasis sites with the unclear location (4). Another recommendation have been proposed is to repeat imaging methods again for evaluation of localize metastatic site as follows: abdominal CT- scan, pelvic MRI, chest- XR and pulmonary CT- scan (5, 6). The efficacy of PET/CT as a noninvasive method for detection the active neoplastic tissue is yet has not been adequately investigated (7). A systematic review of the relevant literature from 1996 until 2018 was performed in PubMed and MEDLINE. For the first time Hebart et al reported on the diagnostic capacity of whole body PET/CT in C. C cases in 1996 ( 8) in study of Shaw et al, sensitivity and specificity of PET/CT in detect of malignant focuses in PSTT cases was 90% & 80% (9). Indeed PET/CT is combining of the detailed anatomical information obtained by CT scans with the metabolic localization of PET scans The important thing is we must keep in mind that confounding factor that interfere with interpretation of PET/CT finding, most of the time lead to false positive report than false negative. The reason of false positive result interpreted can be because inflammatory and granulomatous lesion makes abnormal FDG tagged isotope uptake (10). The factors that cause it are surgical inflammation, vascular compromise on the site of surgical retraction, surgical transposition. All of these causes could decrease the accuracy of method PET/CT. Based on this phenomenon it is often recommended that excluding other site of tumor deposit prior to removing metastasis. (11, 12).

There are few case reports that addressed the efficacy of PET/CT in detecting metastatic site in patients with GTN that was missed or misinterpreted on other investigational radiological modality (13)

The aim of the present study is to evaluated accuracy of PET/CT scan in chemo resistance GTN, case series and literature review

## 2. MATERIAL AND METHODS

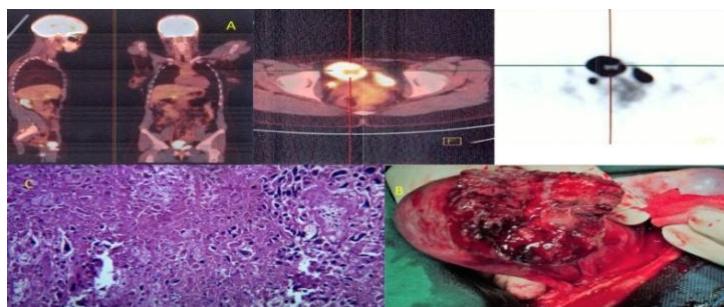
This retrospective study was conducted on four chemo resistant GTN patients were referred to the Oncology Department Gynecology at academic hospital, Mashhad, Iran from April 2014 to Feb. Based on conventional evaluations method our department for all particular persistent GTN cases TVS, chest- XR, chest and abdominal CT scan, brain and pelvic MRI was happening as needed. Based on multidisciplinary consultation in the cases of isolated metastatic lesion that these methods were not effective we requested modality of PET/CT. Finally accuracy of PET/CT scan in chemo resistance GTN cases evaluated.

It should be noted that all patients received inform consent conscientious written

## 3. CASES REPORT

### 3.1.1. Case 1

A 27-year-old woman MG<sub>2</sub> post-molar refractory GTN, despite second line chemotherapy (EMA-EP) with persistently elevated hCG serum levels is introduced .all our conventional evaluations method above mention could not be effective. Therefor PET/CT requisite revealed a hyper metabolic lesion in about 35 mm in the anterolateral of the uterus that seems to invade to myometer. The patient underwent surgery and a necrotic rupture mass in the fondues of uterine was detected. Based on fertility sparing surgery, wedge resection with free margin of the lesion was obtained. Histological examination confirmed pathology of choriocarcinoma (Figure1).



**Figure1.** A) PET scan detected a hyper metabolic area in the uterine, B) Intra operation, a rupture mass found in uterine fondues, C) Pathologic study revealed choriocarcinoma.

### 3.1.2. Case 2

A 25 year-old NG, GTN patient who was treated with (EMA-CO) chemotherapy regimen she had history 7 courses of chemotherapy but after that due to low level quiescent GTN (hCG 120 mIU/ml) was investigated and discussed at the tumor board meeting. Based on all our conventional evaluations method were not effective, therefore PET/CT scan recommended. But because of this modality nothing was found any evidence of occult metastasis, the patient

observed with monthly  $\beta$ HCG measurement. After 2 months the  $\beta$ HCG re-elevated to 6000 mIU/ml abdominal CT scan showed a 1.5 cm mass with irregular border foci in left adnexa. In Laparotomy we observed a 3×3 cm mass in right cornea of the uterus. Pathologic examination of frozen section showed metastases of choriocarcinoma. Therefore due to fertility sparing surgery wedge resection of cornea of uterine with free margin was performed (Figure2).

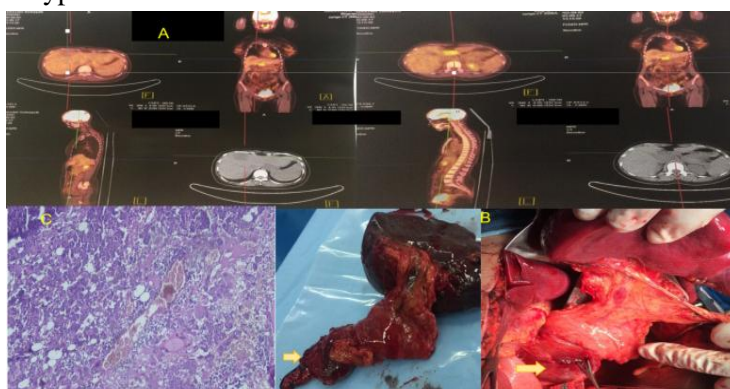


**Figure2.** A) PET scan couldn't detect any pathology, B) Pelvic CT scan detected pathology in adnexa, C) Fertility sparing surgery was performed, D) Pathologic examination revealed metastases of choriocarcinoma.

### 3.1.3. Case 3

A 35 year-old MG woman with diagnosis of PSTT in abdominal hysterectomy specimen and chemo resistant combined chemotherapy with EMA-CO and EMA-EP regimen was reported. Regarding to evaluation of increased of  $\beta$ HCG level after all investigation; PET/CT scan was requested. Only one hyper metabolic lesion in

about 4 cm in lesser sac in favor of metastasis was detected. Laparotomy showed pancreas head mass adjacent to spleen so, partial pancreatectomy with splenectomy was obtained. The pathology confirmed the PSTT metastasis in all of them (Figure3).



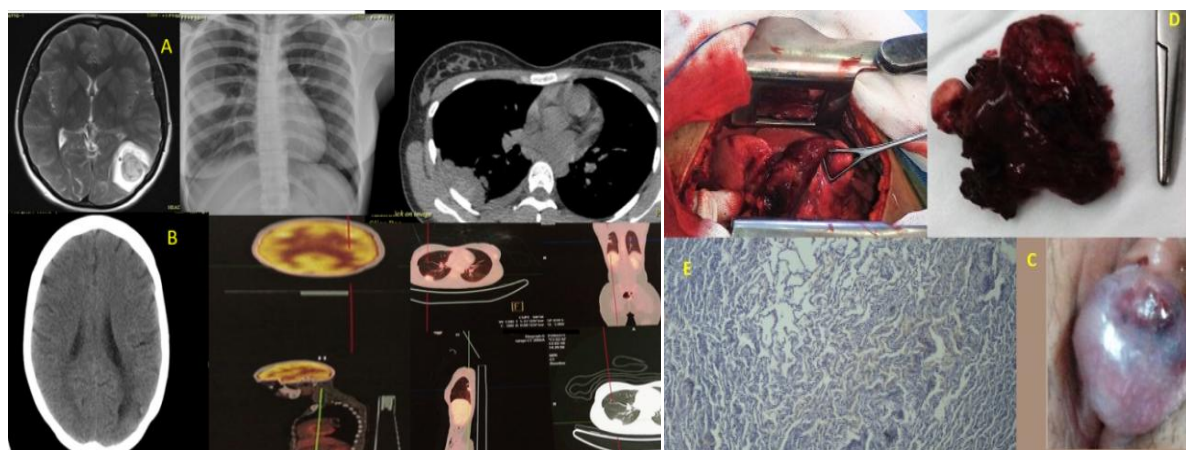
**Figure3.** A) PET scan showed FDG uptake by a 3×3cm mass in lesser sac. The intrahepatic and pancreatic mass was seen only in CT scan. B) Intra laparotomy a pancreatic mass was detected which omitted radically. C) Histologic finding was suggestive of PSTT.

### 3.1.4. Case 4

A 20 year-old MG woman with diagnosis of stage IV of GTN (lung, brain) metastasis was referred. Despite cranial radiotherapy and 5 cycle of chemotherapy (EMA-CO) regimen,  $\beta$ HCG titer did not reach to normal level. EMA-EP regimen chemotherapy did not respond, therefor traditional our center imaging diagnostic modality were used. However they

were able to show lung lesion and smaller size brain lesion, but these findings were not exactly distinguish. So PET/CT was demanded. This modality shown that lung lesion; abnormal hyper metabolic foci (SUV max 2.9), thoracotomy and wedge resection of this lesion was performed. Report of histology confirm metastasis choriocarcinoma (Figure4).





**Figure4.** A) The initial imaging (CT scan) revealed tumoral lesion in brain & chest, B) The masses in the last evaluation persisted but regressed in size; which PET scan distinguished viable mass in lung from fibrotic tissue in brain, C) The purple metastatic mass in labia minor, D) wedge resection of pulmonary metastasis was performed via thoracotomy, E) pathologic study confirmed the diagnosis of choriocarcinoma metastasis.

Detailed clinical information, imaging studies, histopathological reports and outcomes are shown in table1.

**Table1.** Patient characteristics, disease statues, imaging finding, treatment and outcomes. G: gravidity, C\*: choriocarcinoma, L: live child, A: abortion history, M: molar pregnancy. BEP: Bleomycin, Etoposide, Cisplatin-TE/TC: Taxol, Etoposide, Cisplatin

Case	Age	histology	Indication of imaging	CT/MR I finding	PET SCAN finding on resistance	HCG(mi U/ML) before the surgery	The selected surgical approach	HCG(mi U/ML) after surgery (one week)	management change after surgery	outcome
1	27 G2M1	PSTT/C*	Chemoresistant	Leiomyoma of uterine	Active site of tumor in uterine fundus	4800	Uterine wedge resection	66	Chemotherapy: dose dense TC	Initial relative response, but poor prognosis.
2	25 G1A1	C*	Chemoresistant	Nothing in initial imaging but the active foci discovered by CT less than 2 months later	2months before obtaining pelvic CT, the PET didn't detect the pathology	6000	Uterine wedge resection	100	Chemotherapy: BEP	Cure, no recurrences after 1 year.
3	32G3 L2A1	PSTT	Chemoresistant	Multiple mass in liver & pancreases	Single active mass in lesser sac	403	Partial splenectomy +pancreatectomy	15	Chemotherapy: TE/TC	Cure, No recurrences after 5 months.
4	20 G1A1	C*	Chemoresistant	Mass in lung & brain	Single active mass in lung	2300	Metastatectomy by thoracotomy.	300	Chemotherapy: TE/TC	Under treatment now

**4. DISCUSSION**

In our study in 3 of 4 chemo resistant GTN cases PET/CT had positive accordance with other anatomical, histological finding. Generally GTN cases are curable even in the presence of disseminated metastasis. However some of the GTN patients become persistent or recurrence especially in pathology of; which is a critical problem. Most studies believe that emphasis on usefulness of mapping metastatic site to detect the source of viable-resistance tumor and requisiteness of surgery in patient with persistent or rise  $\beta$ HCG titer after chemotherapy (14, 15). Serum  $\beta$ HCG titer is an excellent tumor marker for GTN but it couldn't suggest the location of tumor. Diagnose of localization metastatic site is a crucial point in treatment of GTN cases. There are limited data on the best management in chemo refractory patients (16). It is important to note the limitation of the traditional imaging study in differentiation neoplastic lesions from necrotic tissue due to chemo-radiotherapy effect (17). Although there are some problems with PET/CT. According to recommendations that have been made in cases where the method PET/CT is intended it should be at least 3 & 8 weeks later of chemotherapy and radiotherapy this modality is to be used (18 ). However in study of Chang et al., 7 days is sufficient for this interval for cases under chemotherapy (19). There are some confounding factor that interfere with interpretation of PET/CT: inflammatory and granulomatous lesion lead to false positive report however radiotherapy and chemotherapy could lead to abnormal FDG uptake( 20). Bone marrow suppression as the chemotherapy side effect might be treated with GCSF, which lead to disseminated FDG uptake in bone marrow and spleen (21). In the other hand in an article

about PET scan pitfall recommended 10-20 days interval between traditional and long acting GCSF administration and PET scan (22).The PET/CT is not much used in malignancy with slow growth malignant cell, which is one of the main reason for false negative reports. Small size tumor (less than 5-7 mm in diameter) couldn't identified by the PET scan (23). But conversely, Grisaru et al., in their study on 55 patients showed that accuracy this method for detecting < 1cm lymph node (24). By the way this study could be useful in GTN which has high potency of prompt progression and it is expected that explain the false negative reports in PSTT cases. One of the preparation criteria before administration of intravenous FDG is patient blood sugar, which must be less than 140 mg/dl. The hyperglycemia statues is a confounding factor that could easily resolved by consumption 24 hours low carbohydrate diet which followed with 4-6 hour of complete fasting (except water) the day before the imaging evaluation (25). In articles of Pawar et al., on 56 cases of gynecologic cancer including GTN there is a strong emphasis on using this method for treatment decisions is (26). The Studies that focus solely on chemoresistant GTN cases are very limited and most are retrospective (table2). In general, in all oncology cases sensitivity and specificity of PET/CT in comparing with either conventional imaging modality for detecting malignant tumor location is 90% & 80% (27). In our study this rate was 75%.

In fact the appropriate treatment and close monitoring in GTN patients is corner stone of treatment. In addition accurate assessment occult viable tumor is crucial. Based on this study PET/ CT is very value in detection of active tumor in metastatic site.

**Table2.** Article review

	article	N (cases)	age	$\beta$ HCG (miU/ml) at referring time	Indication for PET SCAN	The accuracy of PET/CT	Management	pathology	The outcome
1	Sironi s (2003)	3	38	200, 3400, >10000	HCG elevation	PET scan was correct in all but CT scan report was correct only in one case	Lobectomy +chemo	choriocarcinoma	cure
2	Mapelli P(2013)	7	34	22, 330, 1900, 20, 5300, 66000,10000	Hcg elevation & chemo resistance	The finding were disconcordant in 2 metastatic site detection	Surgery or chemo regimen change in others with uterus involvement	choriocarcinoma	cure

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		38	34		Primary GTN diagnosis	The findings were concordant (accuracy: 81%) The findings were discordant(false negative :18%)	Chemotherapy -multi agent		
		12	34	Undetectable HCG ;complete response	Evaluation of treatment response	25% both revealed complete response, in 75% the CT scan detected metastatic site yet but with lesser size	Follow up		
3	Chang chang T(2006)	14	35 (21-53)	370, <3, 230, 12000, 18000,670, 470, 21000, <3, 5500,26000, 30, 32000, 180	BHCG re elevation after molar pregnancy evacuation and for all cases of PSTT Or high risk choriocarcinoma, when suspected lesion for metastasis detected on staging imaging method and for chemo resistant patient.	Benefit for 44% of cases; disc ordinance with CT scan, which PET scan was the correct one 2 false negative PET Scan finding	treated with chemotherapy lonely if there were discrepancy between PET and CT, or when the site of viable tumor was uterine only OR when there were multiple metastasis , BRAIN RT for one brain metastasis that dint show neither with PET nor CT.	3 cases was PSTT The other high risk choriocarcinoma	No recurrence s after 6-27 months of follow up
4	Dose j(2000)	1	37	31 increase to 8000 during 4 years; persistent elevated hcg	Normal curettage, laparoscopy and other imaging; unknown source of hcg secretion	TVS showed subserosal leiomyoma(myometrial mass with high fellow): PET show uptake on it	The tumor showed chemo refractory; so hysterectomy was performed +chemo	choriocarcinoma	cure
5	.2005	1	22	200	Elevated hcg for more than 6 months after term pregnancy & vaginal bleeding. History of metastatic GTN with complete response 3years before.	Only PET scan in regard of normal CT /MRI showed a metabolic active focus in broad ligament	Hysterectomy and oophorectomy +chemo	choriocarcinoma	cure

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6	Shaw (2005)	1	38 multiparity	380	11 months after an abortion with irregular bleeding and sudden onset oliguria, leg edema, elevated serum creatinine and a heterogeneous hypervascular nodule in the uterine and multiple nodule in lung. Hcg test: positive	Nodular lung lesion only in CXR. chest CT but not in PET	HYSTRECTOMY+ chemo	PSTT	No recurrences after 15 months of complete response
7	Nieves L(2008)	1	35 multiparity	2200	Elevated hcg in regard of hysterectomy +chemo	Persistent Lung nodule in PET; which was showed before by CT scan	Wedge resection of lung	PSTT	cure
8	Zaheer S(2009)	1	51 multiparity with past medical history of hysterectomy; oophorectomy; under HRT.	30000( checked first time after surgery)	Dyspnea and fever that didn't respond to antibiotic therapy, Intraluminal filling defect in distal pulmonary artery CT scan of thorax, due to non-regression of nodule on anticoagulant therapy PET scan was performed.	An intra pulmonary artery nodules on CT scan which was hypermetabolic on PET scan	Wedge resection of lung lobe + chemotherapy	choriocarcinoma	cure
9	Kelly (2009)	1	47y multiparity and she had tubal ligation 10years ago	190	Amenorrhea and chronic cough , the antecedent pregnancy as 12 years earlier, multiple nodule on CXR & CT.	Innumerable pulmonary nodule on CT, negative PET	Wedge resection and endometrial curettage	PSTT	

10	Espillat (2007)	1	18	After term pregnancy. non metastatic .persistent low level hcg	Chemoresistance with low level BHCG	Increased uptake in an area of the uterus which had shown with MRI too	Wedge resection of the uterus+ MAC chemotherapy		
11	Dhillon(2006)	7			Chemoresistance or recurrence GTN	2 false negative and 1 false positive PET due to sarcoidosis.			
12	Sureyya ceci(2016)	1	37 multi parity	2.7	Intra operation(cesarean section for term pregnancy), a mass on the site of hysterectomy, with BX showed PSTT	A mass in the uterine corpus on TVS, confirmed on PET. Increased breast and endometrial uptake	Hysterectomy. Oophorectomy and LND	PSTT	

**5. CONCLUSION**

With PET/CT there is a lot of diagnostic accuracy in detecting of metastatic disease in chemo resistant GTN cases. The additional benefit of the PET/CT with respect to other imaging modality is differentiating between residual viable tumor tissue and necrosis. However PET/CT has a valuable ability for PSTT patient who are relatively insensitive to chemotherapy and might have distant metastasis that need radical surgery as the mainstay of management.

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