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An update on the management of the rare gestational trobhoblastic tumor namely –placental site trophoblastic tumor: A systematic review

Kulvinder Kochar Kaur[1*], Gautam Allahbadia[2], Mandeep Singh[3]
[1] Scientific Director, Reproductive Endocrinologist and Infertilily specialist, Dr Kulvinder Kaur Centre For Human Reproduction, GTB Nagar, Jalandhar, Punjab, India
[2] Scientific Director, Reproductive Endocrinologist and Infertilily specialist, Ex-Rotunda-A Centre for Human reproduction, Kalpak Garden, Perry Cross Road, Near Otter's Club, Bandra, Mumbai, India
[3] Consultant Neurologist, Swami Satyanand Hospital, Near Nawi Kachehri, Baradri Ladowali road, Jalandhar, Punjab, India

Abstract
A rare kind of Gestational trophoblastic Disease (GTD) that is Placental site trophoblastic tumor (PSTT) represents a rare kind of tumor originating from placental area intermediate trophoblasts. In contrast to hydatiform mole, invasive hydatiform mole as well as choriocarcinoma to diagnose PSTT is more complex in view of the absence of particular tumor markers that are specific as well as sensitive. Since most PSTT women show a malignant tendency the best way of treating PSTT primarily is hysterectomy. But most of PSTT cases are young women hence fertility preservation becomes essential to be kept in mind. Since rarely metastases takes place that might even result in death in low percentage PSTT patients, hence it is important to treat them with adequate chemotherapy as per individualization of the case and better to use chemotherapy in FIGO stage II-IV. The biggest hurdle in improving prognosis of PSTT cases is chemotherapy resistance. Thus importance of finding adequate tumor biomarkers in view of various targeting factors like VEGF, TGF-β3 signaling as well as prokineticin signalling so that adequate targeted therapy can get initiated. Other important aspect is utilization of immunotherapy on the basis of programmed death -1 (PD1) antibody like nivolumab might be important. Still need of the hour is to carry on multicentric studies to understand the pathogenesis of this very rare kind of GTD for improving its prognosis.

Keywords: PSTT, GTD, fertility preservation, hysterectomy, VEGF, TGF-β3 signaling, prokineticin signalling, nivolumab

1. Introduction

Gestational trophoblastic neoplasia (GTN) is a type of rare malignant gynecological tumors that are invasive mole, choriocarcinoma, as well as intermediate trophoblastic tumor (ITT). Particularly, ITT includes placental site trophoblastic tumor (PSTT) and Epitheloid trophoblastic tumor (ETT) [1]. PSTT takes its origin from the placental implantation site. Initially it was labelled as ''trophoblastic pseudotumor'' by Kurman & Scully in 1976 [2]. With >insight of this disease, this term PSTT is accepted slowly to include both benign as well as malignant potentials of this particular kind of tumor. WHO included PSTT as the 4th trophoblastic disease in 1944, in addition to hydatiform mole, invasive hydatiform mole as well as choriocarcinoma. of these tumors partial /complete hydatiform mole is believed to be benign hyperplasia of the villi, while choriocarcinoma as well as PSTT are thought to be tumor tissues [3]. Disease particular mortality of PSTT was demonstrated to be > as compared to other GTN subtypes 16.1% for PSTT,6.5% for hydatiform mole,13.4% for choriocarcinoma was revealed by a global survey [4]. The properties of PSTT is present in its non-predicted biological presentation, poorer prognosis in contrast to other GTN subkinds, with <responsivity to chemotherapy. It represents 0.2 % of GTD, having a morbidity of approx 1/10,000/delivery. As per earlier literature in recent yrs there are minimal variations in incidence in all various areas throughout world [5, 6]. Clinical presentation is mostly benign, although some might relapse as well as metastasize showing the malignant biological properties. Early diagnosis of PSTT, doesn't get confirmed, with problems in differential diagnoses from benign as well as malignant forms of PSTT in the initial stages [7]. Current difficulties in PSTT management are anticipating malignancy, fertility preservation, recurrence as well as chemotherapy. This review is subgrouped into I-Mechanism, II Clinical Features, III Treatment as well as prognosis.

2. Methods

Thus we conducted a systematic review utilizing the pubmed search engine utilizing the Me SH terms like Gestational trophoblastic neoplasia; placental site trophoblastic tumor (PSTT) and Epitheloid trophoblastic tumor (ETT); Mechanism of occurrence; Clinical presentation; Treatment including surgery, imaging; chemotherapy; targeted therapy. immunotherapy as well as fertility preservation and prognosis.

3. Results

We found a total of 595 articles from 1975 to 2020 till date, out of which we used 98 articles for a review. No meta-analysis was

done.

4.Mechanism

4.1 Pathogenesis

GTN includes hydatiform mole, choriocarcinoma, PSTT as well as ETT. PSTT gets its origin through; placental area intermediate trophoblasts, that is cells at the distant villus which anchors to the endometrium and gets dispersed and have independent cell lines, and then assume the properties of; proliferation as well as migration(fig1A).

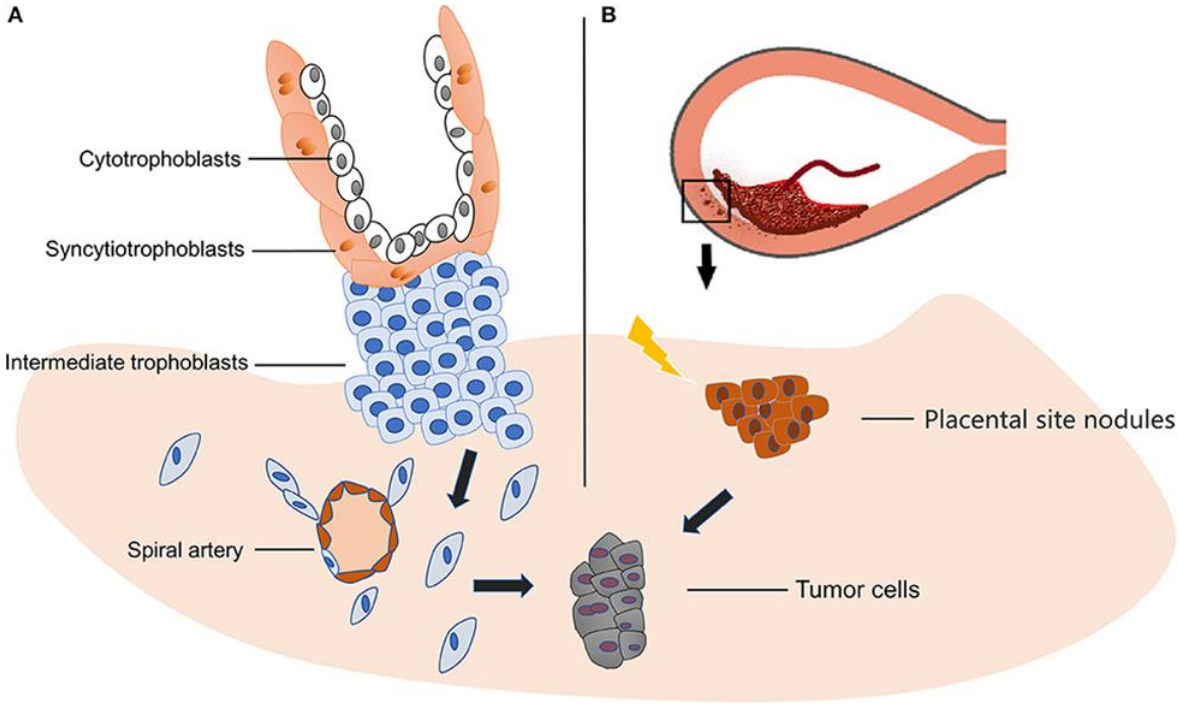

Fig 1: Legend for.

Courtesy ref no-54- Origin of PSTT. **(A)** PSTT originates from extravillous trophoblasts, and then acquires the abilities of proliferation and migration. Afterwards, those cells migrate away from placenta and invade the decidual artery and uterine spiral artery to remodel the blood vessels which in turn provide nutrition for the embryo. The disruption of this well-regulated invasion process may lead to PSTT. **(B)** During delivery, placenta detaches from decidual, leaving small nodules and form placental site nodules in the myometrium. In the process of reabsorbing, some adverse trigger or stimuli may cause atypical mitosis and result in neoplasm. During normal pregnancy, these cells migrate distant from placenta and thus invasion of the decidual artery uterine spiral artery for refashioning the blood vessels, that in turn give nutrition to the embryo.These properties of Extra Villous Trophoblast(EVT) are just like that of tumor cells,and help in proper placental implantation. This mechanism has very stringent temporal as well as spatial control during normal placentaion [8]. It is believed that PSTT originates through hyperplasia of intermediate trophoblast,whereas hydatiform mole as well as choriocarcinoma, occur secondary to abnormal or malignant proliferation of syncytiotrophoblasts as well as cytotrophoblast. Other theories are that PSTT originates at the time of placenta detaching from the uterus and the small nodules of the placental tissue persisting in myometrium, and getting resorbed over time. At the time of this complicated mechanism, mitosis escalates and becomes atypical placental nodules or PSTT(Fig 1B).Development of PSTT has close association to the alterations of the invasive capacity of trophoblasts, a process which involves a lot of cytokines, Extra cellular matrix(ECM)components as well as enzymes.

4.2 Molecular Mode

The changes in intracellular signalling paths,intercellular information propagation, as well as ECM aid in the development of the tumor. Various studies have pointed that ERK, m TOR signalling pathway, transcription factor NFκB,Kiss-1 as well as GATA 3 might be having crucial in the invasiveness as well as metastasis of PSTT (Fig2) [9].

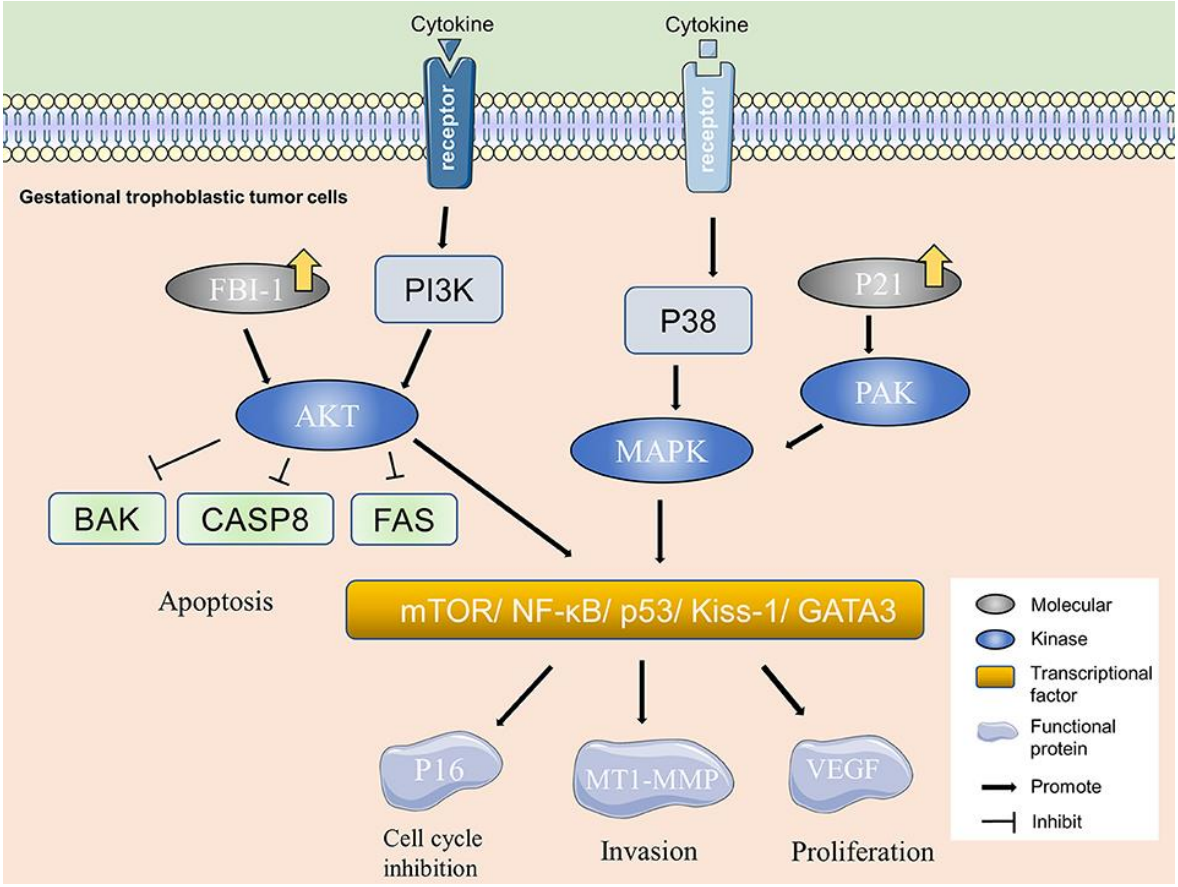

Fig 2: Legend for.

Courtesy ref no-54- Molecular mechanism of PSTT. PI3K/AKT and MAPK are important molecular pathways in PSTT. Over-expression of molecules, such as FBI-1 and P21 can activate kinases, such as PAK and AKT in gestational trophoblastic tumor cells and consequently cause changes in the adhesion-associated and cell cycle regulation proteins, resulting in alterations of biological behaviors including invasion and proliferation of PSTT.

[9]. The adhesion molecules which bring about cell-cell as well as cell-matrix interaction can result in metastasis as well local inflammation. Like integrin α5β1, that expresses on the cell surface and is from the adhesion molecule family can act with ECM parts and has the ability to fix the cytoskeleton. It has been found that P-Selectin as well as integrin α5β1, have an association with the formation, invasion as well as metastases of PSTT [10]. Other molecules like p65, CD44vs6 CD146.P21,FBI-1 as well as F-Cadherin are needed for performing the same action [9, 11]. Additionally, the breakdown of ECM parts aids in cancer cell invasion as well as metastases. Tumor metastases can further be facilitated by Heparanase (HPA) by destroying heparinase sulphate proteoglycan (HSPG) in ECM. Routinely the HPA expression gets limited till placenta as well as immune organs.In case of invasive malignant tumors HPA expression has been documented to be escalated, like in breast cancer, esophageal cancer, rectal cancer, as well as bladder cancer [14]. and is found to be expressed in EVT [12]. It has been posited that HPA is associated with invasion of PSTT. Moreover implication is that matrix metalloproteinase (MMP), tissue inhibitor of metalloproteinase (TIMP) as well as other molecules of the matrix might aid in PSTT metastases [13].

4.3 Genetic Mode

Various kinds of GTN have been described by different genetic mechanisms. Different theories regarding the underlying genetic mode of PSTT are present. In the evaluation of X Chromosome inactivation of PSTT patients it was revealed that PSTT needs a special genetic mechanism needing the paternal X (X_p) and PSTT form through the extra embryonic tissue of an antecedent female conception. Once X_p Chromosome duplication occurs it is thought to lead to anomalous genetic overloading and has an essential part in trophoblastic proliferation [14]. Proof is there X Chromosome-associated genetically imprinted diseases control extra embryonic tissues [15]. X Chromosome inactivation is key for the formation of normal extra embryonic tissues [16]. It is thought that uniparental gene expression might cause cancer development risk. It is posited that X_p) carries a dominant oncogene or tumor development takes place secondary to anomalous dose of functional X Chromosomes. Probable oncogenes are Esx1, Pem, MYCL2, as well as IAP [15, 16]. Utilizing short sequence evaluation of X Chromosome, Zhao *et al*. corroborated the importance of maternal X Chromosome in the development of PSTT.

Platelet –leukocyte C kinase substrate analog family A2(PHLDA2) represents a paternally imprinted gene whereas expressed maternally and is present at 11p15.5 that is from a known tumor suppressor gene area. The PHLDA2 protein gets

expressed only in EVT. PHLDA2 enhanced apoptosis –related proteins as well as reduced manufacture of cyclin as well as cyclin dependent kinases, hence stimulating apoptosis of trophoblasts and decreasing the trophoblastic proliferation capacity. With the use of Genomic Hybridization studies it has been seen that regional chromosomes gains which involve 21q in PSTT patients, pointing that chromosomes gains related to 21q might be correlated with PSTT pathogenesis. More studies are required to further find the genes relation in PSTT development.

4.4 Immunological modes

Immunological surveillance might be dodged by tumor cells, thus fight and avoid removal via Immunological system and in some cases result in Immune tolerance. A lot of emphasis has been given to Immunological system in recurrence of GTD. On the maternal f *et al* interface immune response abnormality might be associated with anomalous reproductive disease. HLA-G represents a non-classical class 1 histocompatibility complex that is expressed in EVT, that can confer protection to cells from getting murdered by NK cells as well as CD40T cells as well as maintaining maternal as well as f *et al* Immunological tolerance. Trophoblasts have the ability of upregulaing the expression of HLA-G that aids in abnormal proliferation, infiltration as well as metastases of trophoblasts [28] .Th1 /Th2 as well as Th17/Treg balance have a close association to placental development as well as pregnancy maintainance. Changes in Th1 /Th2 as well as Th17/Treg balance in PSTT have not been documented, and needs to be evaluated deeply.

5. Clinical Course

PSTT usually present in women of childbearing age, at an average age of 32yrs.It might develop after a term pregnancy, preterm delivery, hydatiform mole as well as choriocarcinoma, with a time period between the development as well as prior pregnancy varying from mths to various yrs. Most cases of PSTT form within a year of the preceding pregnancy. Tumors that are in early stage remain localized within the uterus with growing at small pace. Main symptomatology is colporrhagia as well as amenorrhea [3, 17]. As compared to rest of trophoblastic tumor, the HCG serum amounts is minimally escalated in most PSTT patients. Rarely, HCG serum amounts might reach 100,000IU/L, that might occur secondary to tumors mixing with choriocarcinoma tissues. Though the metastases; potential of PSTT is < as compared to choriocarcinoma, it takes place rarely. Main areas of metastases are lung as well as CNS [18].Other clinical symptomatology like haemoptysis, nephrotic symptoms as well as abdominal mass occur once the progression of tumor occurs or it metastasizes. Very rare cases correlate with nephropathjy like protein urea as well as microangiopathy [19]. As per one study a PSTT patient had coexistence with para neoplastic nodular regenerative hyperplasia of the liver. Some researchers think that these symptomatology's etiology might be precancerous syndrome that might get induced by the immune response to cancer cells or humoral factors. These para neoplastic abnormalities mostly revert following hysterectomy and/or chemotherapy.

5.1 Histopathological Changes and Differential Diagnosis

Various trophoblastic disease have separate origins as well as pathological presentations. In case of PSTT, the disease remains usually limited at the placental implantation area, and is huge or polypoidal. Protruding uterine cavity. Haemorrhagic focus might be observed in PSTT. Under microscopic examination hardly any normal villous structure is seen [20]. PSTT tumor cells invade into the uterine myometrium. Additionally there are multiple intermediate trophoblasts, but no syncytiotrophoblasts as well as cytotrophoblast [20]. Invasion of PSTT tumor cells into the uterine myometrium occurs in a strip like fashion, showing that the invasive capacity of intsermediate trophoblasts at the implantation area. PSTT Invasion occurs deep in the myometrium and goes further to serosa in certain patients [35]. Mitotic figures differ in PSTT cases. Nuclei might be seen in variable stages of mitosis. Monomorphic population of large polyhedral cells are presented by tumor cells that possess irregular nuclei that are hyperchromatic. On the other hand there is eosinophilic or transparent substance in the cytoplasm which might be huge amount of fibrin [18]. Ṭhough apparent infiltration is there the artery walls are mostly intact, with a few bleeding areas as well as mild inflammation or necrosis (fig3).

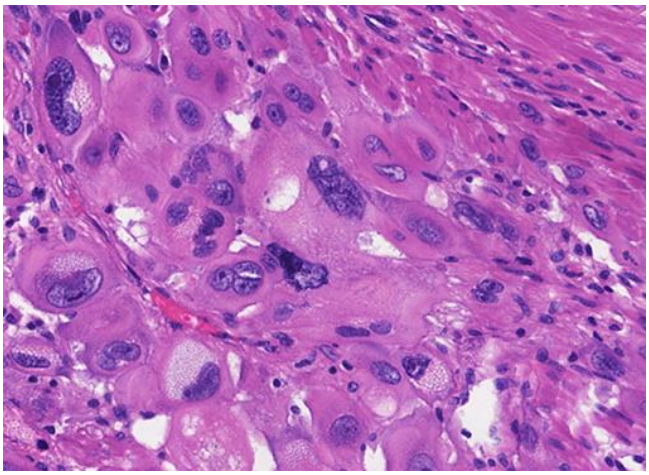

Fig 3: Legend for.

Courtesy ref no-54- Histopathological features of PSTT. Tumor cells present monomorphic population of large polyhedral cells with irregular hyperchromatic nuclei, which are at different stages of mitosis. Besides, there is eosinophilic or transparent substance in the cytoplasm that could be large amount of fibrin. Tumor cells grow like nest or bands into myometrium, with a handful of bleeding foci and mild inflammation or necrosis.

.Immunohistochemistry evaluation have displayed the expression of prolactin (HPL), cytokeratin(CK),melanoma adhesion molecule (Mel-CAM),Cyclin E as well as CD 146 is diffuse positive in the cytoplasm of PSTT tumor cells, whereas HCG expression is locally positive and vimentin is negative. Demonstration has been done that inhibiting, epithelial membrane antigen (EMA) as well as placental alkaline phosphatise (PLAP) are focally positive. In PSTT Ki 67-positive cells, whose expression positively associates with the proliferation capacity of tumor tissue might reach 15%,although in choriocarcinoma it might rise as large as 60-70%.In comparison ETT takes origin from chorionic type intermediate trophoblast cells. In ETT, the lesions are present at deciduas that is beyond the implantation area, and might be visualized in the

uterine body, fundus as well as cervical canal. Generally these ETT lesions are mostly solid or cystic, with few areas having haemorrhage as well as necrosis. A nested/bulk pattern type of growth is revealed by tumor cells. just like the biological presentation of smooth chorion under microscopic evaluation. Typical geographic alterations, that is necrosis as well as eosinophilic vitreous matrix around the tumor cells[3]..CK18 as well as P63 show diffuse positive immunoreactivity whereas HPL is negative or present focally within cytoplasm.CD146 is negative or locally positive within cytoplasm. CD 146 is negative or present locally, although PLAP, E-Cadherin as well as EGFR are present on the membranes. Differential Diagnosis of ETT from PSTT can be made by the expression of HPL as well as P63. Earlier studies had contrasted the expression of P40 as well as P63 in PSTT as well as ETT, and pointed that P40 is an equal marker of ETT.

Initiation of choriocarcinoma takes place from chorio trophoblasts, with the lesions presenting within the myometrium of uterus. It might also extend into the uterine cavity or invade the serosa. Significant necrosis as well as plenty of blood supply is present within choriocarcinoma areas[.On microscopic evaluation typical cytotrophoblast as well as syncytiotrophoblasts having mitotic figures more than 10/10 HP. It has marked vascular infiltrations associated with marked haemorrhage as well as necrosis. Strong positive immunoreactivity is shown by HCG in choriocarcinoma with presence of lots of cytotrophoblast that alternate with syncytiotrophoblasts, with focal positive HPL or negative [21]. Differential Diagnosis of choriocarcinoma from PSTT are Ki 67-positive cells being >50% as well as escalated serum β- HCG amounts [21]. Few studies also explored the probable markers, like pregnancy –associated major basic protein (PMBP) that has been demonstrated to stain positively in huge escalated placental sites as well as PSTT cells. Due to chemoresistance of PSTT, it is essential to find biomarkers for helping in diagnosis as well as stratifying it. Glypican -3(GPC3), carcinoembryonic antigen related cellular adhesion molecule 1(CEACAM 1).GATA binding protein 3(GATA3) as well as HLA-G were demonstrated to be positively expressed in PSTT [22], whereas bcl -2 as well as spalt like transcription factor 4(SALL 4), were negatively expressed in PSTT [22]. SALL 4 as well as bcl -2 are moderately present within choriocarcinomaand HLA-G is only present in intermediate trophoblasts,.

Overall, various trophoblastic diseases get separate origins as well as pathological presentations. Though the Immunohistochemistry markers along with β HCG amounts add to the Differential Diagnosis of GTN,it continues to be ambiguous in some cases. Thus > non-invasive Diagnosis markers will help in correct diagnosis.

5.3 Liquid Biopsy

Recently, Liquid Biopsy that includes circulating tumor cells (CTC's), circulating tumor DNA (ctDNA), circulating tumor (ctRNA) as well as extracellular vesicles (EV's), has assumed a useful position in cancer diagnosis. It has been demonstrated that solid tumors liberate ctDNA into blood that is sufficient to get picked up. Evaluation of ctDNA might aid in molecular genotyping, mutational evaluation, cancer diagnosis as well as follow up following therapy. Earlier studies have demonstrated that it is possible to extract cell free DNA(cf DNA) to use in the form of Liquid Biopsy in cases without HPE for diagnosis. Lot of usefulness of Liquid Biopsy is there in case of PSTT.1stly Liquid Biopsy is utilized for diagnosis as well as Differential Diagnosis. Along with molecular technology, like short tandem repeats(STR),SNP, as well as amplification refractory mutation system –PCR(ACMR-PCR), Liquid Biopsy can pick up paternal or maternal alleles to help the diagnosis of GTN. Knowing that in GTN tumors there is non-maternal DNA, properties of these tumors might get easily picked up. Hence the quantity of ctDNA might point the tumor burden and has been shown to be correlated with HCG in invasive molar disease. Other than that Liquid Biopsy might be utilized for post-operative tracking for recurrence as well as metastases. If histology is not present or minimal metastases takes place that can't be tracked by imaging ctDNA might be utilized in helping in early diagnosis with benefit of it being painless, low risk as well as costing less [23]. Further ctDNA might add specific genetic knowledge which can aid in formatting individualized therapy.Moreover,the amount of ctDNA might get influenced by chemotherapy, hence ctDNA might be utilized for checking drug resistance mutations[23].Further Zhang *et al*. showed that early growth response 1(EGR1) was markedly expressed in the carcinoma –associated fibroblasts(CAF's) of PSTT tissues. More data revealed that miR 363 downregulated EGR1 expression while long noncoding RNA NONHSAT003875(lnc003875) up regulated EGR1 expression in PSTT produced CAF's. lnc003875 had no influence on miR 363 expression but it recovered the reduction of EGR1 produced by miR 363 mimic. Conditioned media from PSTT CAF's that received treatment with miR 363 mimic ameliorated the tube formation ability of human umbilical vein endothelial cells(HUVECs),that gets partially replaced by lnc003875 over expression. Further over expression of EGR1 facilitated the liberation of Angiopoietin-1(Ang1) in PSTT produced CAF's and improved the tube formation of HUVECs, that could be efficiently ameliorated by Ang1 siRNAs. *In vivo* vasculogenesis assay showed that lnc003875/ EGR1 in PSTT produced CAF's facilitated the vasculogenesis of HUVECs in C57BL/6 mice. Together these observations pointed that lnc003875/ miR 363/ EGR1/ Ang1 in CAF's might be key for the angiogenesis of PSTT [24].

5.4 Imaging findings and Differential Diagnosis

Imaging modalities like ultrasonography (USG), Computer radiography (CR) as well as PET-CT might aid in the diagnosis of PSTT. Gynaecologic USG is utilized for USG helped dilatation and curettage (D&C) or hysteroscopically guided biopsy in helping in diagnosis as well as preoperative staging[25].Along with clinical history as well as HCG serum amts, USG is the 1st line imaging technique for GTN Diagnosis in view of ease and cheap [26].Transabdominal as well as transvaginal (TVS) USG can be done.On USG alterations in size,morphology, echo, surrounding lymph nodes as well as association within uterus as well as surrounding organs. Essential is to know the degree of lesion along with choice of therapy. Classification of PSTT can be made on the basis of Imaging findings on the basis of placement of tumor. On TVS 3 kinds are type I-most of tumors bulging out in the uterine cavity, Type II-Location of the lesion is within uterine cavity as well as part of

the myometrium, Type III-whole lesion is within the myometrium. Most lesions are present in the body of uterus, with rare cases documented in cervix/pelvic wall[reviewed in [27]]. As per published series size varies from 7 to 62mm.Lesions are solid or cystic or mixed with solid capsules. Roughly 50%present as hypoechoic or echogenic lesions [26]. No definite boundary is visualised among the lesion and the tissue around. One can misdiagnose these cystic as well as mixed cystic lesions in the form of hydatiform mole as well as choriocarcinoma. Blood flow signal of PSTT is low as well as low blood flow resistance index [25, 26, 28]. The haemodynamic features of PSTT tumor vessels display that the Doppler signal is present throughout the lesion with high blood flow signal that might be secondary to vasodilation ordevelopment of arteriovenous fistula [29]. (figure4a,b).

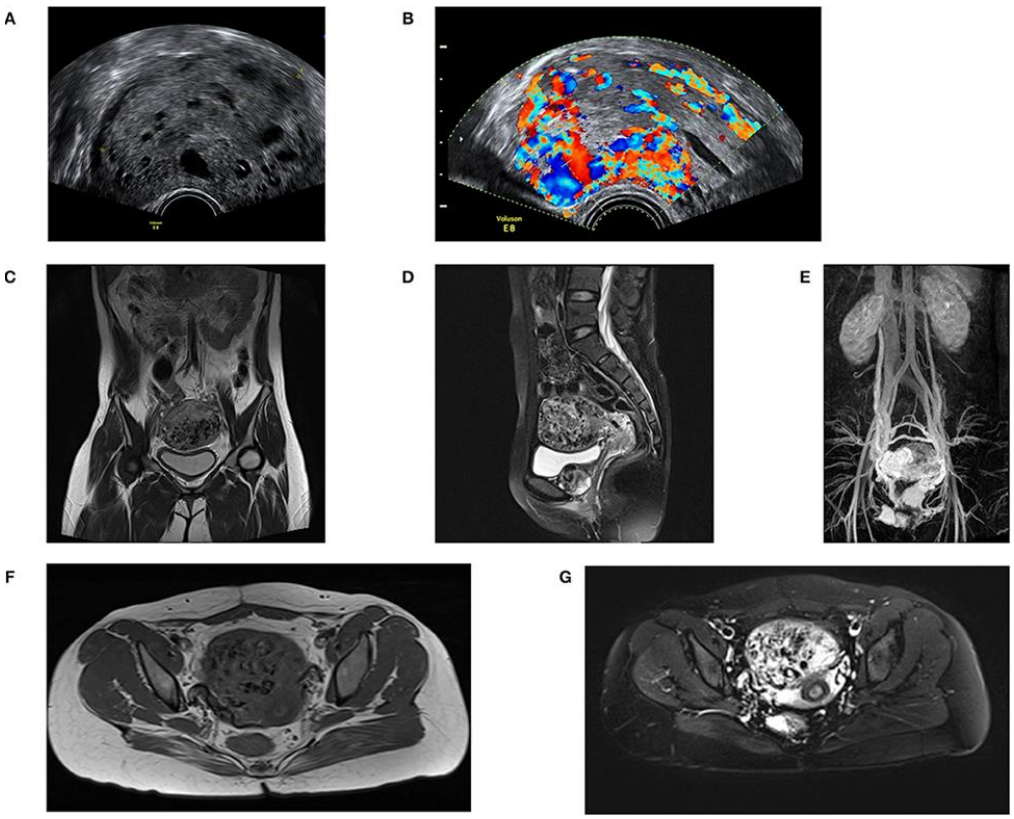

Fig 4: Legend for.

Courtesy ref no-54- Imaging features of PSTT. **(A)** Ultrasound feature of PSTT: the mass shows as a mixed mass with intact capsule and presents as echogenic bulk. **(B)** Ultrasound feature of PSTT: formation of arteriovenous fistula can be observed. **(C, D)** MRI imaging of sagittal position: PSTT presents as uterine dilatation with short T1 and long T2 signals. **(E, F)** MRI imaging of axial position. **(G)** Enhancement imaging: the parauterine artery can be observed.

One can divide PSTT into the one having lot of vessels or ii) relatively lesser bv types as picked up by Doppler signal. In the former D&C should not be attempted. In contrast to PSTT, USG of ETT shows typical echogenic lump present within myometrium, having lot of blood flow signals [28]. In case of ETT necrosis throughout tumor is visualized.

Though USG is not thought to be a diagnostic method for PSTT as per the International Federation of Gynaecology and Obstetrics (FIGO), it is thought that solid lesions along with low blood flow signals as well as lesser β HCG amounts in serum are the diagnostic features of PSTT [30]. Besides its use in diagnosis, USG has important role in later post treatment follow up. Certain workers have pointed that the uterine artery pulsation index (UAPI)<1 might be utilized to anticipate chemoresistance risk. Further color Doppler USG is a very sensitive process for watching the residual lesions.

MRI is another imaging way to examine the situation of PSTT. Abnormal heterogenous signal alterations can be visualised in the uterine wall in the T2 weighted image. In cases that have been documented, MRI mostly shows uterine dilatation having short T1 as well as long T2 signals (fig4cdfg),with enhanced vascular empty effect in myometrium as well as bilateral para uterine tissue. Following contrast material injection highlighted heterogenous tumor as well as para uterine tissue might be seen (fig4e). Where tumors can't be; picked up by USG, MRI can be utilized for detection [26, 31]. PET is not believed to be a routine imaging way to examine the situation of PSTT. Wide application not done for checking PSTT as well as other kinds of GTN Diagnosis But it is revealed that PET correlates a lot with USG, chest X Ray as well as CT, in staging of GTN, that is not better than traditionally utilized imaging ways, but still it has its part in the diagnosis and examination of high risk cases. Hence there is lot of scope for evaluation of a variety of lesions along with metastases [32, 33]. Additionally >sensitivity is there in picking up

metastatic lesions. F-FDG PET can survey active tumor lesions and can be utilized in watching the recurrence of PSTT as well as chemoresistance. Using MRI in head a as well as pelvis as well as CT in chest as well as abdominal and Doppler USG in the pelvis has been implemented in USA in a study [26]. The pointing of site as well as size of lesion will have >comprehensiveness as well as precision once data from CT, USG, as well as MRI are integrated. Role of F-FDG PET is not clear and is just kept for cases where doctors are unsure of the lesions or to find the resection area [34]. With the β HCG amounts not having reliability, better results are anticipated utilizing imaging methods for prognostic follow up.

6. Therapy as well as Prognosis

6.1 Surgery

Mostly 2 kinds of treatment plans are decided as per the patient analysis, simple hysterectomy and systemic therapy. It is agreed upon that FIGO Stage1 gets cured by simple hysterectomy with or without pelvic lymoh node biopsy [17]. In a trial run over 17yrs,clinical trial of PSTT, of total patients who had surgery 5/13 patients had a relapse with a recurrence rate of 50%. The > recurrence rate shows that managing metastatic lesions is key for surgery. Lymphatic metastasis occurs more in PSTT, as compared to choriocarcinoma has been recognized. Retroperitoneal lymph nodes particularly the para aortic lymph nodes, are the commonest areas where metastasis occurs. Cartain workers thought that para aortic lymph nodes had an important role in Lymphatic connection as well as metastasis among pelvic lymphoid tissue. They noted that lymph nodes metastasis was present in 39.1% of the 24 subjects in the study[36]. Hence for Stage II to IV PSTT, lymph nodes biopsy is needed for examining for Lymphatic metastasis so that idea is there if lymphadenectomy is required. Multidisciplinary management is needed as well as for treating PSTT. Regarding ovarian removal it is controversial. Some study documented metastatic lesions in the ovary, that points ovarian metastasis may take place and hence need for oophorectomy. But individualized evaluation taking into account age, staging metastasis, general condition, need for fertility should be done prior to doing oophorectomy. Further workers point leaving ovary behind should also consider family history of ovarian diseases and bilateral oophorectomy needs to be considered seriously for decreasing risk of ovarian metastasis.

6.2 Chemotherapy

As per risk conditions that are prevalent following surgery systemic therapy is decided. Variable guidelines of PSTT are present [29, 70] table1.Importantly WHO prognostic index score for GTN is not applicable to PSTT. Different workers, have documented various criteria that correlate with poor prognosis, that are time period among antecedent pregnancy >2 yrs, deep invasion, necrosis, mitotic index >5/10 under microscope. Those who are at high risk need to use multidrug chemotherapy. Those in FIGO stage II-IV, hysterectomy followed by adjuvant chemotherapy is a reasonable choice [18]. For those with metastasis, it is thought that targeted surgery as well as high dose –platinum-containing chemotherapy having platinum or etoposide are the ones recommended therapies. Chemotherapies that are advantageous are EMA/EP (etoposide, methotrexate, actinomycin –D/ etoposide, cislatin), EMA/CO (etoposide, methotrexate, actinomycin –D/ vincristine, cyclophosphamide), and TE/TP (taxol, etoposide./Taxol/cisplatin [37]. It has been demonstrated that best remission rates are obtained with EMA/EP,but also is accompanied with high toxicity and probable later haematological adverse effects like neutropenia ATP as well as TE regimens get used within the clinic as well. Greater chemosensitivity is displayed by EMA/EP as well as TP for relapsed cases. Hence it is the 1st line therapy choice mainly for refractory or relapsed PSTT cases. Additional salvage Chemotherapies are BEP(bleomycin/etoposide/cislatin),and ICE(ifosfamide/cislatin/etoposide)are utilized in chemotherapy resistant patients.

High dose chemotherapy regimen that has platinum significantly enhanced overall survival in cases with high risk GTD, with 5/11 high risk PSTT patients getting therapy with remission 8-12 Wks EP /EMA regimen on the basis of patient tolerance is utilized in UK, following which stem cell mobilization is started, then various courses of high dose chemotherapy are used. After this above method, autologous stem cell transplant support sequential chemotherapy is used.Fang *et al*.[27] proposed that early starting of high dose chemotherapy with peripheral blood stem cell support treatment in high risk PSTT patients having time period among antecedent pregnancy >2 yrs as well as in young patient having low HCG amts have >efficacy. Disadvantages of high dose chemotherapy being toxic adverse effects along with induced POF that influences future fertility. Thus chemotherapy causes reduction in follicular cells and hence reduced ovarian reserve as well as premature ovarian failure (POF). Antimullerian hormone (AMH) is utilized for checking female ovarian reserve and regulating menopausal process. Serum AMH amt get reduced markedly following use of etoposide (VP16) in cases of GTN and thus checking AMH throughout chemotherapy has advantages of ovarian protection [38].

As a rule PSTT patients have tendency to acquire chemotherapy resistance and thus need to be treated with proper surgical therapy in proper time. Additionally chemotherapy response for every individual needs to be found out to prevent low reaction. For those with metastasis, comprehensive plans of treatment, like high dose multidrug combination chemotherapy, surgery imaging examination along with utilization of colony stimulating factor (G-CSF) are used. Right now no literature on how examining chemotherapeutic reactivity of trophoblastic tumors exists. Experiences by treating other kinds of tumors have revealed that measuring chemotherapy effectiveness can decide the clinical benefit response(CBR),that is tumor associated symptoms following chemotherapy improvement, drug susceptibility examination, imaging examination that is CT, MRI, radionuclide scanning as well as angiography, tumor measurements, blood supply of tumor as well as tumor density alterations. Further no checking of drug resistant genes in PSTT patients that could also be a direction of further work that needs evaluation.

6.3 Fertility Preservation

In view of PSTT involving young women, it is very important to consider preservation of fertility during chemotherapy. Currently for conservation surgical as well as chemotherapeutic modifications are required. Surgical procedure used can be

abdominal removal, laparoscopic remloval as well as hysteroscopic [6, 38] Utilization of modified Stausmamnn procedure(MSP)has been documented in proper patients suitable for that. By arterial administration of chemotherapeutic drugs certain workers found significantly enhanced uterine preservation.

Success of Fertility Preservation therapy has been found to be high in relative terms in young women. But, small amt of patients undergoing Fertility Preservation ultimately required hysterectomy in view of incomplete resection of residual lesions. Zhao *et al*. carried out a single hospital study revealed that roughly 21% of patients whose uterus was preserved during surgery successfully preserved fertility [6]. In another study it was documented that on attempting preservation of uterus by performing local resection of tumors 5/6 had total hysterectomy in light of hidden lesions not removed. Problem with Fertility Preservation therapy is the absence of any criteria decided to pick the patients suitable for Fertility Preservation therapy. Proposals given are in Stage I,<35 yrs age, strong need for fertility, acceptable chemotherapy responsiveness, no prospective malignant conditions like deep myometrial invasion [38]. Still > data is needed for confirmation of these.

6.4 Targeted treatment

Recently newer ways like use of targeting vascular growth factors as well as immunological checkpoints, as well as mifepristone application has been highlighted [40]. This Targeted treatment might enhance effectiveness and at same time reduce adverse effects as they only target particular selected paths. Mostly chemotherapy in usual regimens inhibit proliferating cells as compared to Targeted treatment is meant to inhibit molecular mechanisms like phosphatidyl inositol-3-kinase(PI3K),mitogen associated protein kinase (MAPK), signalling paths which are a must for tumor cell growth as well as surviving. Escalated expression of VEGF as well as TGF-β3 in PSTT tissues has been observed by various workers [41]. Both vascular endothelial growth factor (VEGF) as well as transforming growth factor -β(TGF-β3) are growth factors having crucial role in angiogenesis, embryo implantation as well as placenta development. TGF-β3 controls trophoblasts, by inhibition of proliferation as well as invasiveness. Essentially the time point of TGF-β3 expression corroborates the part played by TGF-β3 in control of trophoblast invasion throughout pregnancy. Overexpression of VEGF as well as TGF-β3 might escalate the invasiveness of trophoblastic tumors is what is thought and correlates with poor prognosis [42]. Another vascular growth factor endocrine derived –VEGF(EG-VEGF) or prokineticin gets expressed exclusively in endocrine tissues (ovary,testis, adrenal cortex and placenta),without having anti action on endothelial cells of other tissues [reviewed by [43]. EG-VEGF can stimulate phosphorylation of p42/p44 MAP kinases as well as Akt path via receptors PKR1 as well as PKR2. Variations in expression of EG-VEGF as well as prokineticin receptor1(PKR1) as well as prokineticin receptor 2 (PKR2) among normal villous tissues and choriocarcinoma cell lines with PKR1 mainly expressed in EVT as well as syncytiotrophoblasts. Inhibition of PKR2 expression by small interfering RNA showed that EG-VEGF can inhibit EVT invasion by controlling matrix m *et al.* loproteinase (MMP2) as well as MMP9 pointing that EG-VEGF might be essential in the formation of trophoblastic tumors. Future studies are required to evaluate if targeted treatment of VEGF, TGF-β3, as well as EG-VEGF can aid in PSTT diagnosis as well as therapy.

6.5 Immunotherapy

Immunotherapy has been seen to be of use in therapy of various kinds of cancer patients following 1st line chemotherapy [44, 45, 46]. That Immunotherapy is of use in PSTT therapy has been posited [47] Immunological check points have been in limelight. Programmed death 1(PD1)is a transmembrane receptor expressed on the surfaced of Tcells as well as B cells, NK cells along with antigen processing cells (APC's).Following binding with the ligand (PD-L1), PD1/ PD-L1 can inhibit the synthesis of activated Tcells, that controls the immunosuppressive action along with immune tolerance. Inhibitors against this particular membrane surface protein might block the binding of PD1/ PD-L1,and preventing the immunosuppressive action and facilitating the killing action of T cells on tumor cells [47]. PD-L1 has been demonstrated to be widely expressed on all trophoblasts besides cytotrophoblasts, whereas PD-L1, B7-H3, as well as VISTA were positively expressed on PSTT tissue, pointing that PD-L1 blocker might be a potential therapy in PSTT. PD1 blockers (nivolumab, Pembrolizumab) as well as PD-L1 blockers (Atezo lizumab, Avelumab, Durvalumab) have been utilized in therapy of cancer [44, 45, 46]. In a recent study it was demonstrated that Pembrolizumab is very efficacious in patients possessing chemotherapy resistant GTN [47]. Also intra venous Pembrolizumab has good tolerance having an acceptable toxicity profile, that makes it a good therapy of choice [47]. As predominantly PSTT patients are young ladies who want Fertility Preservation therapy, that means a local removal only, enhanced risk of recurrence as well as metastasis is there. Maximum PSTT patients attain chemotherapy resistance in platinum based regimen, with PD1 blockers(nivolumab, Pembrolizumab having been utilized for therapy of platinum- resistant ovarian cancer patients and enhancing the prognosis of PSTT. Additionally, utilization of PD1 antibody might turn out to be a therapy that saves the life for chemotherapy resistance patients and better the prognosis of PSTT. Moreover PD1/ PD-L1 might be utilized in combination with a CTLA4 inhibitor or an antiangiogenic targeted drug to escalate the therapeutic efficacy. In view of the memory function of the immune system, on PD1 blockers working patients can get an opportunity to get long term cure, that has already been seen in malignant tumors, like malignant melanoma. Anticipation of responsiveness to Immunotherapy might have basis on human leukocyte antigen class -1(HLA-G),microsatellite instability high (MSI-H0,deficient mismatch repair (DMMR), microsatellite detection(MSI),tumor mutation burden(TMB),and tumor infiltrating lymphocytes [45,47]. But this application of Immunotherapy in PSTT patients needs more evaluation.

immune checkpoints Inhibitors are anticipated to enhance the therapy success rate, although right now no research is there regarding pregnancy outcomes following use of immune checkpoints Inhibitors in cases of GTD. Whatever literrature is there, documents various immune associated adverse effects caused by them like endocrine system disorders, sexual dysfunction, as well as damage to the reproductive

system[48].Other theory is that inhibition of PD1 path might decrease immune tolerance of the maternal-f *et al.* interface in pregnancy[49]. If and how these adverse effects will cause long term reproductive function influence has to be examined see fig 5 for an outline of therapy.

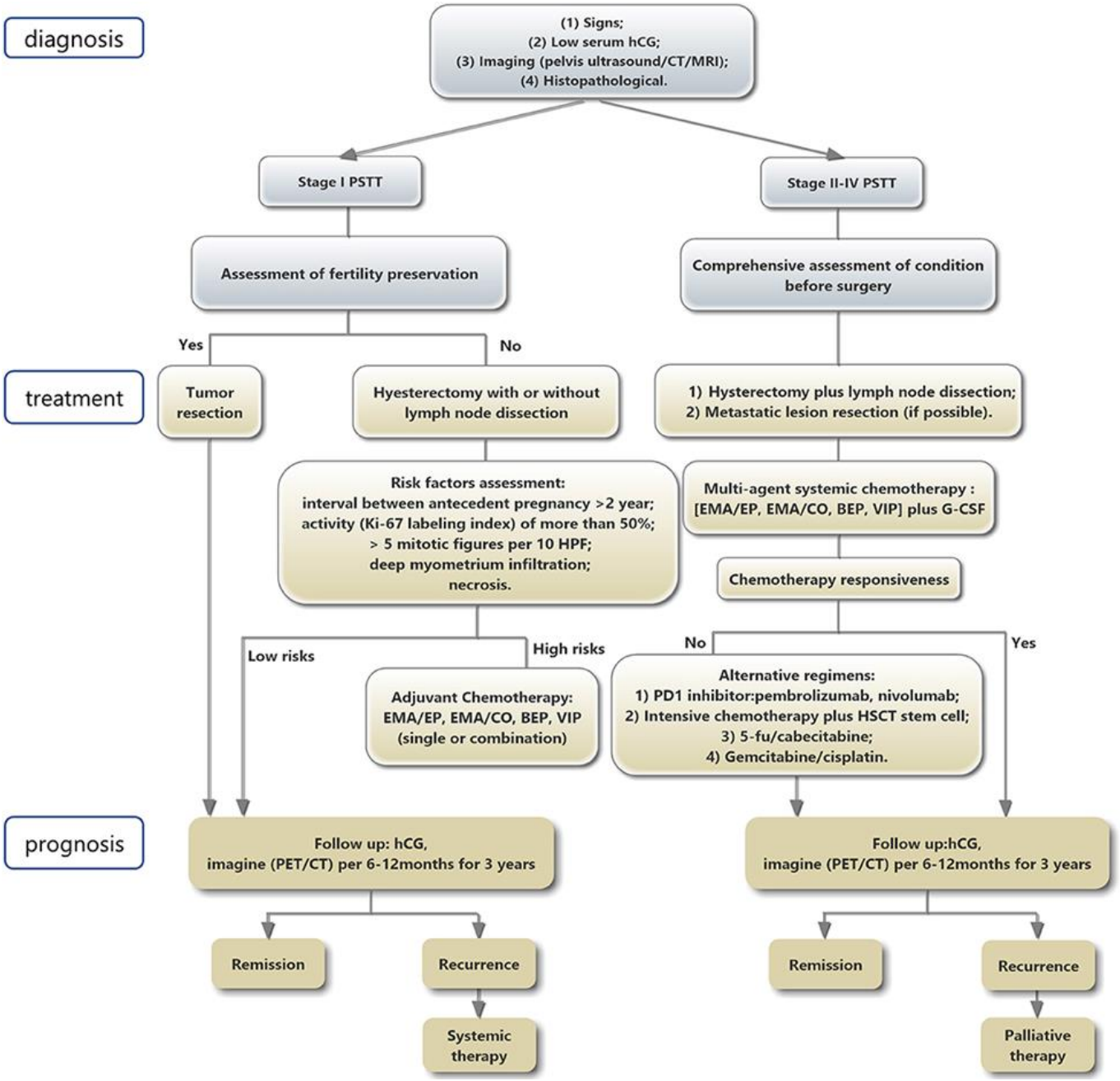

Fig 5: Legend for.

6.6 Courtesy ref 54-Schematic flow diagram of PSTT diagnosis, treatment and prognosis

6.6.1 Prognosis

Mostly prognosis is good in PSTT, though metastasis or recurrence also occurs. Gaducci *et al*. has already reviewed the prognosis in details [17]. FIGO staging remains the biggest condition modulating prognosis [6]. Brandt *et al*. in a retrospective study that included 62 PSTT patients documented a 10yrs survival of 90% for stage I patients 52% for stage II patients, 49% for stage III as well as IV patients stage I patients generally have a good prognosis following TAH, with 10yr survival rate high upto 100%.But those PSTT patients become infertile subsequent to TAH and might get future psychological as well as social stress. Stage II-IV PSTT cases usually have a relatively poor prognosis. Though the propagation is slow, it has slight malignant risk. As per statistics from UK, 10yr survival rate of Stage II- IV PSTT cases was roughly 49% in time period 1976-2006. Those having recurrent refractory disease has even worse prognosis with 5yr survival rate of 22% [45]. In another review of evaluation of survival rate of stage III as well as IV patients was just 30%

[50].

Biggest hurdle is chemotherapy resistance in prognosis of PSTT. Of 108 PSTT cases in Beijing only 7 deaths were seen, pointing that early diagnosis with proper chemotherapy helped with these deaths just due to poor response to chemotherapy as well as recurrence [6]. Hence urgently prognostic as well as predicting biomarkers are required to stratify patients. Immunoreactivity of VEGF as well as EGFR points towards targeted therapy being effective [68]. In another study p53 could find out with success the those PSTT cases that were confined as well as metastatic [44]. Other markers like MMP as well as TIMP could anticipate biological outcomes that included invasive as well as metastatic properties of PSTT [28]. Currently very little studies are there that are trying to study the mode of PSTT chemotherapy resistance. It is key to understand molecular basis of chemotherapy resistance for getting innovative methods of treating PSTT.

7. Conclusions

PSTT represents a kind of trophoblastic neoplasia having quiet low incidence along with benign properties. Just like many other kinds of tumors, PSTT might occur secondary to a comprehensive interaction among genetic, immunological as well as environmental factors. Mostly it has a good prognosis but metastasis or recurrence does take place in certain cases. With most patients being young women fertility preservation consideration becomes essential. Biggest hurdle is chemotherapy resistance and studying molecular mechanism is a priority. In view of it being rare a method of central registration and well preserved data will aid in future research. Properly done multicentric studies having good sample size are needed to watch how pathological progression occurs. Greater studies are required for knowing proper mode of PSTT to format preventive as well as early pickup methods as well as innovative methods of treating to improve prognosis for PSTT patients.

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