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Diagnostic Challenges and Treatment Conflicts for Pure Primary Non Gestational Choriocarcinoma Ovary

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Abstract

Pure primary NGCO (non-gestational choriocarcinoma of ovary) is a type of ovarian germ cell tumor with elevated human chorionic gonadotrophin (hCG), posing diagnostic challenges in the patients of reproductive age group. Clinically and histopathologically, NGCO is indistinguishable from GCO. The both are differentiated on the basis of DNA polymorphism analysis and presence of mRNA for BMG (β2-microglobulin) in NGCO. Diagnostic criteria set by Saito et al helps to make a diagnosis of NGCO. It is possible to cure NGCO while preserving fertility, which is an important consideration as most are young age group patients. As these are rare tumors, recommendations for treatment of primary nongestational choriocarcinomas are not available. The principles of surgical management of NGCO are similar to the ovarian epithelial tumors. GCO is treated by methotrexate based chemotherapy, but some studies reported that NGCO is resistant to this chemotherapy, and it requires more aggressive combination chemotherapy as later has bad prognosis as compared to GCO. Various chemotherapy regimens are BEP, EMA/CO, EMA/EP, VAC etc. The serial quantitative measurement of urinary or serum β-hCG is essential for diagnosis, monitoring efficacy of the treatment, and follow-up of the patients. Role of radiation therapy is limited as a palliative setting in metastatic NGCO. In this article, we have tried to conclude the diagnostic methods and best possible treatment protocol.

Keywords: nongestational, choriocarcinoma, chemotherapy.

1. Introduction

Ovarian germ cell tumors include neoplasms derived from the primordial germ cells of the embryonal gonad. Five percent of these germ cell tumors are malignant which represent only three to five percent of all the ovarian carcinomas. Pure primary NGCO (non-gestational choriocarcinoma of ovary) accounts for less than one percent of all ovarian tumors (Gon et al., 2010; Scully, 1979). Because of elevated human chorionic gonadotrophin (hCG), these tumors pose diagnostic challenges in the patients of reproductive age group Primary ovarian choriocarcinoma could be gestational or nongestational in origin (Gon et al., 2010). Gestational choriocarcinoma is a variety of Gestational trophoblastic neoplasms (GTNs) which comprise conditions arising from

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abnormal fertilization, and consist of five different entities: PHM (partial hydatidiform mole), CHM (complete hydatidiform mole), IM (invasive mole), CCA (choriocarcinoma), and PSTT (placental site trophoblastic tumors) (Goldstein et al., 2015). GCO (gestational choriocarcinoma of ovary) occur following pregnancy and it is characterized by uterine cavity presentation (Choi et al., 2013; Park et al., 2009). These tumors represent less than 1 % of the gynecologic malignancies, and they are curable with reproductive potential preservation if treated at early stage and according to established guidelines (Goldstein et al., 2015). NGCO most of the time arises from the ovarian germ cell tumors but they can originate from any epithelial cancer, including cancer of the stomach, bowel and lung (Oladipo et al., 2007). NGCO differentiates in the direction of trophoblastic structures along the extraembryonic chorionic tissue and it is usually mixed with other types of neoplastic germ cell elements (Radotra, 2001; Jacobs et al., 1982; Russell, Farnsworth, 1997; Scully et al., 1998). It is possible to cure NGCO while preserving fertility, which is an important consideration as most are young age group patients (Cannistra et al., 2015). NGCO is indistinguishable from GCO morphologically and immunohistochemically as both has similar histopathological features. The both are differentiated on the basis of DNA (deoxy ribonucleic acid) polymorphism analysis and presence of mRNA (messenger ribonucleic acid) for BMG (β2-microglobulin) in NGCO (Tsujioka et al., 2003; Tanaka et al., 1981). GCO is managed by single agent chemotherapy in low risk disease and by multiagent chemotherapy in high risk disease, while NGCO is treated by polychemotherapy as later has bad prognosis as compared to GCO. Role of radiation therapy is limited as a palliative setting in metastatic NGCO. The aim of this study is the in depth review of the case reports documented so far to conclude the optimal treatment strategy for NGCO.

2. Materials and methods

EPIDEMIOLOGY

Ovarian germ cell tumors are less common than ovarian epithelial tumors, accounting for only 2% to 3 % of all ovarian cancers in Western countries. NGCO usually occur in younger women, with peak incidence in early 20s. An increased incidence of NGCO is found in blacks and Asian societies, where they represent about 15% of all ovarian cancers (Cannistra et al., 2015).

PATHOLOGY

Choriocarcinoma of the ovary can develop in association with gestational ovarian choriocarcinoma; or as a part of metastatic choriocarcinoma from non-ovarian (chiefly uterus) gestational choriocarcinoma; or as a germ cell tumor with trophoblastic differentiation which is known as non-gestational choriocarcinoma (Park et al., 2009). Table 1 shows WHO classification of ovarian tumor (Park et al., 2009). The germ cell tumors of the ovary are usually divided into dysgerminoma and nondysgerminoma (Cannistra et al., 2015). Choriocarcinoma is usually characterized by the presence of two types of cell lines: cytotrophoblast, which lie in sheets to form villus like structures, and syncytiotrophoblast, which secretes human placental lactogen and beta-human chorionic gonadotrophin; and is usually seen at advancing edge of the tumor (Rao et al., 2015; Kidd et al., 1998). Pure ovarian choriocarcinoma is defined as a tumor occurring in the absence of other germ cell tumors (Russell, Farnsworth, 1997; Scully et al., 1998).

CLINICAL FEATURES AND SPREAD

NGCO mainly occurs in young females, and approximate 50% of cases are diagnosed at an early stage (Hayashi et al., 2015). Abdominal distension, lower abdominal pain, urinary symptoms and pelvic fullness are chiefly encountered symptoms. Severe abdominal pain may be present in minority of patients, which is usually the result of rupture, hemorrhage, or ovarian torsion. The rapid growth of NGCO cause moderate to severe pain as a result of ovarian capsule stretching, and prompts the patient to seek medical attention (Cannistra et al., 2015). Approximate 60% to 70% of ovarian germ cell tumors are diagnosed at stage I, stages II and IV disease are not common, and 25% to 30% of tumors are diagnosed at stage III. Bilateral involvement of ovary is uncommon in most germ cell tumors, although mature cystic teratoma and dysgerminoma may be bilateral in 10% to 15% of cases (Cannistra et al., 2015).

Clinical diagnosis of NGCO is usually difficult, not solely owing to rarity of the tumor but also due to similar presentation as that of GCO. Pure NGCO is histopathologically not distinguishable

from GCO, except in the patients who have never had sexual intercourse or who are not able to conceive (Kong et al., 2009). Most NGCO cases occur in adolescence and children (Radotra, 2001; Jacobs et al., 1982). The primary extra uterine choriocarcinoma is difficult to diagnose because the clinical features are usually nonspecific and they can mimic other common conditions occurring in the young women, such as tubo-ovarian abscess, hemorrhagic ovarian cyst, ectopic pregnancy and ovarian torsion (Gerson et al., 2007). The symptoms of pelvic pain, vaginal bleeding, an adnexal mass and elevated hCG level, usually lead to incorrect diagnosis of cervical polyp, threatened or incomplete abortion, ectopic pregnancy, or other types of malignancy (Imai et al., 2001).

NGCO most commonly metastasizes to multiple peritoneal surfaces and retroperitoneal lymph nodes, although ascites is uncommon (Cannistra et al., 2015). The metastasis is usually hemorrhagic because of innate capacity of the trophoblastic cells to invade and erode vessel walls (Kidd et al., 1998). NGCO usually spread to the lungs (80%), vagina (30%), pelvis (20%), and kidney, brain, liver, gastrointestinal tract and spleen (10%) (Cannistra et al., 2015; Kidd et al., 1998). The central nervous system involvement is seldom in the absence of lung metastases (Kidd et al., 1998). Around 10% of NGCO metastasize to brain while on treatment or as a relapse after partial remission. Brain metastasis is a poor prognostic indicator and is a leading cause of death (Choi et al., 2013; Dadlani et al., 2010).

DIAGNOSIS

Patients mostly have a palpable adnexal mass which is usually evaluated by transvaginal ultrasonography (TVU), demonstrating a complex cyst comprised of cystic and solid regions. Serum levels of AFP (α-fetoprotein) and β-HCG (β-human chorionic gonadotrophin) often helps to diagnose embryonal carcinoma (both β-HCG and AFP elevation), endodermal sinus tumor (AFP elevation only), or choriocarcinoma (β-HCG elevation only). Patients with pure immature teratoma of ovary mostly have normal levels of β-HCG and AFP, although AFP may get elevated in 30% of the patients. Patients with dermoid cyst (mature cystic teratoma), a benign germ cell tumor, usually have normal levels of β-HCG and AFP. Measurement of β-HCG and AFP levels is also useful to measure the effectiveness of postoperative therapy and in monitoring for recurrence of the disease. Patients with choriocarcinoma, occasionally, may have extreme β-HCG elevation resulting in hyperthyroidism due to homology between TSH (thyroid-stimulating hormone) and β-HCG. Hyperthyroidism may also be seen in patients with mature cystic teratoma, which is related to the tumor-derived thyroxine secretion, (struma ovarii) (Cannistra et al., 2015).

Saito *et al* in 1963 first described the diagnostic criteria for nongestational choriocarcinoma which include exclusion of molar pregnancy, absence of disease in the uterine cavity, pathological confirmation of disease and exclusion of coexistence of intrauterine pregnancy (Saito et al., 1963). Distinction of gestational choriocarcinoma from non-gestational choriocarcinoma is not possible on histopathology unless other germ cell neoplasms are encountered or there is an evidence of pregnancy. The distinction between the two entities is not easy, but it is necessary, as the non-gestational type has got bad prognosis (Lv Lin et al., 2011). However, no distinctive immunohistochemical or ultra structural differences have been reported between gestational and nongestational choriocarcinomas (Yamamoto et al., 2007). Tsujioka et al showed that DNA polymorphism analysis using two or three appropriate variable number of tandem repeats (VNTR) loci from the tumor, and the patient for paternal sequences identification, establishes the diagnosis of non-gestational or gestational choriocarcinoma (Tsujioka et al., 2003; Yamamoto et al., 2007). Tanaka *et al* reported a lack of effective mRNA (messenger ribonucleic acid) for BMG (β2-microglobulin) in cell lines of human choriocarcinoma of gestational origin, as well as the presence of mRNA for BMG in nongestational choriocarcinoma (Tanaka et al., 1981). Kato *et al* investigated choriocarcinoma cells that produced moderate amounts of surface and secreted BMG (Kato et al., 1991). Norman *et al* demonstrated that in choriocarcinoma, serum BMG level was elevated (Norman et al., 1983). These studies showed that BMG may be clinically used as a serum marker for NGCO in the future. However, the cause for BMG expression in NGCO remains unclear (Hayashi et al., 2015).

Speculum examination helps to rule out metastases to vagina. Ultrasound of the pelvis rules out pelvic spread and retained trophoblastic tissue, if any. Chest imaging rule out metastases to lungs, as most common site for metastases is lung. CT scan (computed tomography scan) detects lung metastases in upto 40% of the patients with negative chest imaging (Muller, Cole, 2009).

Brain and liver metastases are rare when there are no metastases to lung and vagina, brain imaging is omitted usually. Contrast enhanced magnetic resonance imaging (MRI) of brain is mandatory in metastatic disease and in all patients with biopsy proven choriocarcinoma. As the tumor is highly vascular, histopathological examination may be skipped. Positron emission tomography (PET) scan identify active disease sites (Goldstein et al., 2015; Berkowitz et al., 1983). NGCO is staged as per FIGO staging in table 2 (Prat, 2015).

MEASUREMENT OF β-hCG

Any woman in the reproductive age group who presents with abnormal bleeding or evidence of metastatic disease should undergo β-hCG screening to rule out choriocarcinoma (Goldstein et al., 2015; Berkowitz, Goldstein, 2009). The serial quantitative measurement of urinary or serum β-hCG is essential for diagnosis, monitoring efficacy of the treatment, and follow-up of the patients. hCG is a glycoprotein consisting of two subunits, an alpha subunit (common to other glycoproteins), and hormone specific beta subunit. So, hCG measurement should be performed by beta subunit measuring assays only (Hancock, 2006). hCG is produced by the choriocarcinoma itself (Cole, Butler, 2008). Persistence of β-hCG levels represent either local or metastatic disease, which allows for early detection and intervention. During the treatment, response of beta-hCG is used as a tool to decide whether to continue the treatment with the agent or switch to some other agent. Monitoring of beta-hCG levels after the treatment allows for identification of the relapsed disease that requires additional treatment measure (Goldstein et al., 2015). A false-positive β-hCG result must be suspected if the laboratory results and the clinical features are discordant, or if the patients with persistent low β-hCG levels do not respond appropriately. False-positive findings on the β-hCG tests occur with the presence of heterophile antibodies that usually interfere with the immunoassay. False-positive tests led to inappropriate treatment protocol, in the form of chemotherapy, surgery or both. In rare situations, especially in women of menopausal group, pituitary gland is β-hCG source (Khanlian, Cole, 2006). A urinary assay must be performed when a false-positive β-hCG test is suspected, because renal tubules are not crossed by heterophile antibodies (Goldstein et al., 2015). Once elevated and/or rising β-hCG level is determined, a thorough evaluation is required to determine the disease extent, including blood tests to assess hepatic and renal function, peripheral blood counts, and baseline serum β-hCG levels (Goldstein et al., 2015; Berkowitz et al., 1983).

TREATMENT

Non-gestational choriocarcinomas are resistant to single agent chemotherapy, have a poor prognosis, and so require aggressive combination chemotherapy in comparison to GCO (Lv Lin et al., 2011). Pure primary NGCO is an extremely rare tumor and is a diagnostic challenge to the oncologists. However, differentiation between non-gestational and gestational choriocarcinoma is necessary in view of the prognostic value and the management (Dadlani et al., 2010). As the tumor is rare, published literature on clinical features and treatment options is less. Methotrexate based chemotherapy is used to treat GCO, but NGCO is chemotherapy resistant, and aggressive combination chemotherapy is needed for it (Balat et al., 2004). Weiss et al suggested either to treat this tumor as GCO and decide single-agent or combination chemotherapy; or to treat as a germ cell tumor protocol, such as BEP (bleomycin/etoposide/ cisplatinum) or VAC (vincristine/actinomycin-D/cyclophosphamide) (Park et al., 2009; Weiss et al., 2001).

SURGERY

The principles of surgical management of NGCO are similar to the ovarian epithelial tumors, with the important caveat that fertility can be preserved in most of the patients by sparing uterus, fallopian tube and contralateral ovary (Cannistra et al., 2015). If the contralateral ovary is grossly abnormal, biopsy or cystectomy can be performed. In case of a dysgenetic gonad, bilateral salpingo-oophorectomy may be undertaken. After opening the peritoneal cavity, peritoneal washings are collected, and all the fluids are sent for histopathological examination. In case of pelvic confined disease, random biopsies are taken as in the early stage of ovarian epithelial carcinomas. Particular attention is paid to pelvic and para-aortic lymph node enlargement, because these are the sites which are frequently involved in advanced NGCO (Cannistra et al., 2015). Although sentinel lymph node sampling is usually done for staging, no evidence suggests any benefits of lymphadenectomy. Billmire et al found that the less comprehensive surgical staging did

not compromise the survival (Billmire et al., 2004). Further studies for the extent of the surgical staging are warranted. Cytoreductive surgery for NGCO is recommended as in ovarian epithelial tumors. As extensive disease of NGCO is usually more chemosensitive than ovarian epithelial tumors, so, whether such an aggressive approach for surgery is necessary in the selected patients with extensive NGCO remains unresolved. There is no established role of routine second-look operations in NGCO patients who are declared clinically free of the disease after chemotherapy. Especially, if primary tumor is completely resected and no teratomatous components are seen, then second-look operations after the chemotherapy are of no proven benefit. If teratomatous components are seen, then the second-look operations may be beneficial. Such type of patients may have residual mature teratoma, which is insensitive to chemotherapy, therefore, a second-look operation may be considered if technically possible. The rationale for this is based on the experience with the testicular germ cell cancer, in which residual teratoma are known to enlarge and cause local complications or rarely may transform to an undifferentiated sarcoma or carcinoma. However, extent to which the residual teratoma may transform to a more aggressive histology in NGCO patients is not well studied (Cannistra et al., 2015).

LAPAROSCOPIC AND FERTILITY-PRESERVING APPROACH IN NGCO

The use of laparoscopy and thus, fertility-preserving procedures in the non-epithelial ovarian malignancies is extremely controversial. Xin et al reported that a 23-year-old woman underwent emergency laparoscopy and left oophoroplasty was performed, and primary NGCO was diagnosed. Approximately after 3 weeks, laparoscopic staging surgery was performed, including left adnexectomy, retroperitoneal lymphadenectomy, peritoneal biopsies and omentectomy. Patient received ovarian suppression with goserelin followed by adjuvant chemotherapy of bleomycin, etoposide, and cisplatin. No sign of recurrence was seen post 9 months and she reassumed normal menstrual cycles with normal levels of tumor markers and gonadotrophin. This study brings new insights into the possibility of using the minimally invasive surgery and fertility-preserving methods for NGCO treatment (Xin et al., 2015).

CHEMOTHERAPY

Treatment for NGCO is surgery followed by combination chemotherapy, as early stage NGCO patients have a significant risk of the relapse and that can be reduced by postoperative adjuvant chemotherapy (Cannistra et al., 2015). The treatment consists usually of polychemotherapy, including regimens that have generally shown to be beneficial with acceptable high cure rates and low recurrences (Axe et al., 1985; Berkowitz, Goldstein, 1996). Mostly used chemotherapy regimen is BEP. The Gynecologic Oncology Group (GOG) reported that those patients were remained free of disease after 3 cycles of adjuvant chemotherapy with BEP whose tumors were completely resected (Boyd, Rubin, 1997). Toxicities of BEP include the risk of etoposide-induced leukemia; bleomycin induced pulmonary damage, and platinum-induced nephropathy and neuropathy. Most of the patients receiving BEP regimen regain fertility after treatment completion. Several studies have reported that at least 80% of the patients with ovarian germ cell tumors who were treated with the fertility-sparing surgery and postoperative adjuvant chemotherapy regained normal menstrual cycle, and normal pregnancies (Tonin et al., 1996). However, patients are at increased risk for the development of the premature menopause following chemotherapy (Cannistra et al., 2015).

The primary treatment for all patients is multiagent chemotherapy. Table 3 summarizes the regimens which are most commonly used like EMA/CO, which includes etoposide, methotrexate, actinomycin-D, and cyclophosphamide and vincristine having 70-90% cure rates (Cagayan, 2012). Another regimen EMA/EP having cisplatin (in place of vincristine) is used if resistance is found against EMA/CO (Xiang et al., 2004). Dose-intensive treatment is done at an interval of 2 to 3 weeks, toxicity permitting. The treatment is continued till β-hCG level becomes undetectable for a period of 3 continuous weeks. It is recommended that three cycles of remission regimen should be administered after achieving remission. Death can occur due to advanced disease, drug resistance, inadequate treatment, life-threatening complications like central nervous system hemorrhage and respiratory failure (Xiang et al., 2004).

Extreme rarity of NGCO hinders therapeutic considerations (Ozaki et al., 2001; Ramarajapalli et al., 2012). Beta-HCG is a good predictive indicator of prognosis and recurrence (Rao et al., 2015). Adjuvant polychemotherapy with EMA (etoposide 100mg/m2, methotrexate

100mg/m2, actinomycin-D 0.5mg) regimen may be given, for six to nine courses at seven days interval (Choi et al., 2013).

RECURRENT OR PROGRESSIVE DISEASE

Serum β-hCG levels should be monitored weekly during the treatment, then every 2 weekly for next 3 months, then monthly for the next 3 months, and then every 2 months for the next 6 months. If the treatment fails to demonstrate a continuous fall in the β-hCG titers, or if disease recurs after chemotherapy cessation, then reevaluation of the patient is performed, and therapy different from the one that previously employed should be initiated. Alternatively, if β-hCG level becomes undetectable, then chemotherapy should be continued for two more cycles in case of GCO, but more extended chemotherapy should be considered in case of NGCO (Park et al., 2009; Hammond et al., 1978).

ROLE OF RADIATION THERAPY

Radiation therapy has limited role in patients with NGCO except in the selected patients with brain metastases. The use of whole or localized brain radiotherapy in combination with chemotherapy may prevent a debilitating or life-threatening, so it should be initiated promptly (Brace, 1968). Alternatively, intrathecal methotrexate may be given in combination with polychemotherapy, particularly in the presence of meningeal involvement (Newlands et al., 2002).

ROLE OF BONE MARROW TRANSPLANTATION

Metastatic NGCO is curable with the cisplatin-based multiagent chemotherapy with or without surgery. Second-line chemotherapy with cisplatin and ifosfamide combination is given to the patients who fail or relapse after first-line therapy and have only 15–25% salvage rate. Initial experience with high-dose multiagent chemotherapy using carboplatin and etoposide containing regimens showed that 10–15% of heavily pretreated (two or more cycles) patients could achieve long-term remissions (Mandanas et al., 1998).

Patients with the relapsed or refractory NGCO may be treated with high-dose chemotherapy and marrow transplantation (HDC/BMT). The patients had received at least two prior chemotherapy regimens or had cisplatin-refractory disease (defined as progression within 4 weeks of a cycle of cisplatin-based chemotherapy). HDC regimens used are mostly combinations of cyclophosphamide with etoposide and cisplatin or carboplatin. Other combinations are carboplatin plus thiotepa plus cyclophosphamide, carboplatin plus etoposide plus ifosfamide. Times to engraftment of granulocytes and platelets were reasonable with only the patients receiving growth factors. HDC/BMT provides significant long-term disease-free survival as salvage therapy for relapsed germ cell tumor patients who are not refractory to cisplatin (Mandanas et al., 1998).

A comparison of case reports of ovarian choriocarcinoma is presented in Table 4. The summarized cases show limitations in that they are not all fully staged and the chemotherapy protocols are diverse. Analysis of the cases documented thus far suggests that the disease responds well to the combination of surgery and postoperative adjuvant chemotherapy. However, long term effects of such therapy should be further studied with more cases.

3. Conclusions

Because of the small number of patients with pure NGCO, a consensus on the treatment regimen including surgery and chemotherapy is lacking. Despite aggressive management of primary disease, prognosis is poor. Complete excision of the primary tumor, followed by combination chemotherapy may prolong the survival. Radiotherapy is useful in metastatic presentation. A long follow-up with regular beta HCG level estimation is advised to deal with the risk of delayed metastases even when the primary has been well controlled.

4. Conflict of interest

We have no conflict of interest to declare.

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Table 1. World Health Organization classification of malignant ovarian tumors (Park et al., 2009)

COMMON EPITHELIAL TUMORS

Malignant Serous Tumor
Adenocarcinoma
Papillary adenocarcinoma
Papillary cystadenocarcinoma
Surface papillary carcinoma
Malignant adenofibroma, cystadenofibroma
Malignant Mucinous Tumor
Adenocarcinoma, cystadenocarcinoma
Malignant adenofibroma, cystadenofibroma
Malignant Endometrioid Tumor
Carcinoma
Adenocarcinoma
Adenoacanthoma
Malignant adenofibroma, cystadenofibroma
Endometrioid stromal sarcoma
Mesodermal (mullerian) mixed tumor:
homologous and
Heterologous
Other
Clear cell (mesonephroid) tumor, malignant
Carcinoma and adenocarcinoma
Brenner tumor, malignant
Mixed epithelial tumor, malignant

Undifferentiated carcinoma
Unclassified

SEX CORD-STROMAL TUMORS
Granulosa-Stromal Cell Tumor

Androblastoma: Sertoli-Leydig Cell Tumor
Well differentiated
Tubular androblastoma
Sertoli cell tumor
Tubular androblastoma with lipid storage
Sertoli cell tumor with lipid storage
Sertoli-Leydig cell tumor
Leydig cell tumor, hilus cell tumor
Of intermediate differentiation
Poorly differentiated (sarcomatoid)
With heterologous elements
Gynandroblastoma
Lipid (lipoid) cell tumors
Unclassified

GERM CELL TUMOR
Dysgerminoma
Endodermal sinus tumor

Embryonal carcinoma
Polyembryoma
Choriocarcinoma
Immature teratoma
Mature dermoid cyst with malignant transformation
Monodermal and highly specialized
Struma ovarii
Carcinoid

Struma ovarii and carcinoid
Others

Granulosa cell tumor	Mixed forms
Tumor in the thecoma-fibroma group	**GONADOBLASTOMA**
Fibroma	Pure
Unclassified	Mixed with dysgerminoma or other form

Table 2. International Federation of Gynecology and Obstetrics Staging System for Ovarian Cancer (Prat, 2015)

Stage I	*Tumor limited to ovary or ovariesa*
IA	One ovary, without malignant ascites, positive peritoneal washings, surface involvement, or rupture
IB	Both ovaries, without malignant ascites, positive peritoneal washings, surface involvement, or rupture
IC	Malignant ascites, positive peritoneal washings, surface involvement, or rupture present IC1: Surgical spill IC2: Capsule rupture before surgery or tumor on ovarian or fallopian tube surface IC3: Malignant cells in ascites or peritoneal washings
Stage II	*Ovarian tumor with pelvic extensiona*
IIA	Involvement of the uterus or fallopian tubes
IIB	Involvement of other pelvic organs (e.g., bladder, rectum, or pelvic sidewall)
Stage III	*Tumor involving the upper abdomen or lymph nodes*
IIIA	Positive retroperitoneal nodes only or microscopic peritoneal disease outside of the pelvis. IIIA1: Positive retroperitoneal nodes as the only site of extrapelvic spread IIIA1(i): Metastases up to 10 mm in greatest dimension IIIA1(ii): Metastases >10 mm in greatest dimension IIIA2: Microscopic extrapelvic peritoneal involvement (with or without nodal involvement)
IIIB	Macroscopic peritoneal metastases ≤2 cm in diameter (with or without nodal involvement)*b*
IIIC	Macroscopic peritoneal metastases >2 cm in diameter (with or without nodal involvement)*b*
Stage IV	*Distant organ involvement, including pleural spacec or hepatic/splenic parenchyma* IVA: Pleural effusion with positive cytology IVB: Parenchymal metastases (e.g., hematogenous spread to liver) or metastases to extra-abdominal sites such as inguinal lymph nodes

a Patients with disease that appears to be confined to the ovaries or pelvis require nodal biopsy for complete staging, in order to exclude the possibility of occult nodal involvement

b Disease measurements for staging purposes are made before debulking has been attempted.

c Pleural effusion must be cytologically proven to be malignant if used to define stage IV disease.

Table 3. Protocol for various chemotherapy regimens (Cagayan, 2012)

S.No.	Day	Drug	Dose
FIRST LINE CHEMOTHERAPY			
1.			**Protocol for BEP 46**
	1-5	Cisplatin	20 mg/m2 IV
	1-5	Etoposide	100 mg/m2 IV
	1,8,15	Bleomycin	30 mg IV
			3 weekly for 3-4 cycles
2.			**Protocol for EMA/CO Regimen**
	1	Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
		Actinomycin D	0.5 mg IV push
		Methotrexate	100 mg/m2 IV push
			200 mg/m2 by infusion over 12 h
	2	Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
		Actinomycin D	0.5 mg IV push
		Folinic acid	15 mg q 12 h × four doses IM or PO beginning 24 h after starting MTX
	8	Cyclophosphamide	600 mg/m2 by infusion in saline over 30 min
		Vincristine	1.0 mg/m2 IV push
3.			**Protocol for EMA/EP Regimen**
	1	Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
		Actinomycin D	0.5 mg IV push
		Methotrexate	100 mg/m2 IV push
			200 mg/m2 by infusion over 12 h
	2	Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
		Actinomycin D	0.5 mg IV push
		Folinic acid	15 mg q 12 h × four doses IM or PO beginning 24 h after starting MTX
	8	Cisplatin	60 mg/m2 with prehydration
		Etoposide	100 mg/m2 by infusion in 200 ml saline over 30 min
4.			**Protocol for EMA**
		Etoposide	100 mg/m2 IV
		Methotrexate	100 mg/m2 IV
		Actinomycin-D	0.5 mg IV
			Weekly 6 to 9 courses
SECOND LINE CHEMOTHERAPY			
1.	1	Vincristine	2 mg/m2 IV
	1	Actinomycin-D	1.5 mg/m2 IV
	1	Cyclophosphamide	1 gm/m2 IV
2.	1	Cisplatin	100 mg/m2 IV
	1	Ifosfamide	1200 mg/m2 IV
3.	1-5	Cisplatin	20 mg/m2 IV
	1-5	Ifosfamide	1200 mg/m2 IV
	1-5	Etoposide	75 mg/m2 IV

EMA/CO, etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine; actD,
actinomycin-D (Cosmegan, Whitehouse Station, NJ); IV, intravenous; MTX, methotrexate; IM, intramuscular; PO,
by mouth; EMA/EP, etoposide, methotrexate, actinomycin D, and cisplatin.

Table 4. Clinicopathological characteristics of 35 cases of non-gestational pure ovarian choriocarcinoma

Variable	Value
Mean age, years	14.3±4.2
Duration of abdominal pain	weeks 3-16
Side, %	
Right	69
Left	31
Stage, %	
I	49
II	17
III	17
IV	17
Surgery, %	
UO/SO	74
AH+BSO	20
BSO	4
hCG, mU/ml	0.034-200,000
Treatment, n	
Bone marrow transplant	2
Chemotherapy	
Methotrexate-based	11
Vinblastin, bleomycin and cisplatin	4
Cisplatin, etoposide and bleomycin	5
Outcome, %	
Succumbed	31
Alive	69

UO/SO, unilateral oophorectomy/salpingo-oophorectomy; hCG, human chorionic gonadotropin; BSO, bilateral salpingo-oophorectomy; AH, abdominal hysterectomy