A Preliminary Study on Docetaxel as Treatment for Advanced Epithelial Ovarian Cancer

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Background: Ovarian cancer is one of the most common malignancies in women. Present standard therapeutic regimen produces toxicities that limit the use of these agents as well as cause great discomfort for the patients. It is, therefore, prudent to examine other chemotherapeutic agents which may have similar efficacy to the standard regimen but may cause less toxic effects. **Objective**: The main purpose of this study is to determine the response rate and the toxicity profile of docetaxel as treatment for persistent and recurrent ovarian epithelial malignancies. **Methodology**: A retrospective review of medical records of patients with persistent or recurrent ovarian cancer who had treatment with docetaxel from 1999-2003 was conducted at the PGH Cancer Institute. Docetaxel 100 mg/m^2 was given in combination with either carboplatin or cisplatin every three weeks for up to 6 cycles. Active follow up was done on each patient, which included complete physical examination as well as laboratory results. **Results**: Fifteen patients were included in the study. The age range of the subjects was from 30 to 66 years of age with a median of 48 years of age. Median gravidity was 3 $\pm$ 2.7. The most common histologic type was mucinous cystadenocarcinoma (40%), followed by serous cystadenocarcinoma (33.33%), endometrioid cystadenocarcinoma (3%) and clear cell cystadenocarcinoma (6.66%). Complete clinical response (CCR) was observed in 4 patients (26.67%). Median time to progression was noted to be 204 days, with a range of 79 to 1065 days or 2.6 to 35.5 months. Toxicities noted include neutropenia, anemia, fluid retention, nausea, vomiting, alopecia, paresthesia and diarrhea. **Conclusion**: Docetaxel shows activity in treating ovarian malignancy similar to that of paclitaxel, the accepted standard therapy. The overall response rate obtained in our study is similar to the response rate in other studies using the same regimen. Neutropenia, peripheral edema, and other non-hematologic toxicities were similar to that seen in patients included in other studies on docetaxel but no treatment-related deaths were noted.

Key words: Docetaxel, ovarian epithelial carcinoma

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In the Philippines, ovarian cancer is the second most common gynecologic cancer. At the UP-Philippine General Hospital from 1987-1998, 120 new cases of ovarian cancer were reviewed. Among these new cases reviewed, about 46 percent belong to Stages III and IV malignancy. There were 55 advanced cases of ovarian cancer registered for continuation of treatment in the Section of Gynecologic Oncology of the UP-PGH.

In advanced epithelial ovarian cancer, tumor-reductive surgery is performed before chemotherapy using cisplatin-based regimen is initiated. Of the 120 patients seen from 1987 to 1998, 44 had measurable disease and 24 of the patients were noted to have measurable clinical response. The patients may be in remission for a few months but recurrences were noted in 15 percent of our cases despite these treatments.

It, therefore, becomes predictable that the number of cases with advanced epithelial ovarian cancer in our institution continues to comprise the bulk of our most difficult cases to manage in the spectrum of ovarian cancer behavior. In 1987-1998, on the average, 50 cases of advanced epithelial ovarian cancer were treated.

In the treatment of advanced epithelial ovarian cancer, cisplatin has a response rate of 60%. However, the overall survival of 30-35% has not significantly improved over the past decades. There was, therefore, a need to find new chemotherapeutic agents for advanced ovarian cancer. A new class of chemotherapeutic agents, the taxanes, which act by promoting assembly of microtubules and stabilizing formed tubules, have been found to have clinical activity in epithelial ovarian cancers including platinum resistance.

In women with advanced ovarian cancer, combination chemotherapy of cisplatin and cyclophosphamide as adjuvant treatment resulted in higher response rate and longer survival rate in those with adequate surgical therapy. Thus, cisplatin plus cyclophosphamide became the standard treatment in ovarian cancer. However, in women with advanced ovarian cancer, lower response rate is noted. The long term disease control is less than 10% in women with incompletely resected stage III disease and less than 5% in women with stage IV disease.

In 1996, McGuire, et al. (GOG-111) compared cisplatin plus cyclophosphamide to paclitaxel and cisplatin in patients with advanced ovarian cancer.[1] The overall response rate is 60% in the cisplatin plus cyclophosphamide group with a median survival of 24 months. While the paclitaxel plus cisplatin group had an overall survival rate of 73% with a median survival of 38 months. Thus, the study provided a strong evidence paclitaxel plus cisplatin regimen is more effective than the cisplatin plus cyclophosphamide group.

However, both cisplatin and paclitaxel produce neurotoxicity that is predominantly sensory and there is evidence that paclitaxel-induced neurotoxicity is dose-dependent.[2] The neurotoxicity may be decreased using shorter 3-hour infusion time. However, the longer 24-hour infusion time produced greater neutropenia and increased patient inconvenience.[3]

As the paclitaxel-cisplatin combination has become established as the standard treatment of advanced epithelial ovarian cancer and further toxicity information emerges, it is appropriate to evaluate other anti-cancer drugs with the same or greater efficacy with less toxicity.

Docetaxel (Taxotere) is a chemical entity belonging to the taxoid family. Docetaxel is prepared by semi-synthesis involving a natural product extracted from the renewable needle biomass of yew plants. It is a white powder which is insoluble in water. Like paclitaxel, docetaxel, also a taxane, acts by promoting the assembly of microtubules and stabilizing formed tubules.[4] Both drugs have very similar mechanism of action and anti-cancer activity in epithelial ovarian cancer, including the platinum-resistant tumors.

Docetaxel has been shown to be more potent than paclitaxel in promoting assembly of tubulin and in inhibiting microtubule depolymerization. In 1994, Verweil, et al. noted that there is a difference in the tubulin polymer generation between paclitaxel and docetaxel. They noted that docetaxel appears twice as active in depolymerization

inhibition. Docetaxel also showed equal or greater cytotoxicity in relevant pre-clinical models.[5]

Docetaxel had been demonstrated to be active in ovarian carcinoma. Fujiwara, et al. has shown in their Phase II dose escalation trial for Taxotere in ovarian cancer patients previously treated with platinum-based regimen that the maximum allowable dose (MAD) for Taxotere is 70 mg/m^2 every 3 weeks.[6]

Docetaxel can produce a fluid retention syndrome characterized by peripheral edema and weight gain. Pleural and pericardial effusions and ascites have also been reported.

The development of fluid retention seems to be related to the cumulative dose of docetaxel. Premedication with corticosteroids has been shown in a randomized trial to delay the onset of this syndrome.[7]

In a Scottish Trial Group headed by Vasey, the use of docetaxel-cisplatin combination as first line treatment was studied in 100 patients with advanced disease from September 1995 to March 1997. Cisplatin was given at 75 mg/m^2 and docetaxel at 75 or 85 mg/m^2 every 3 weeks for 6 cycles. The endpoint of the study is to determine treatment-induced pulmonary edema. Results showed that 66 patients were able to continue the treatment regimen. Cisplatin related toxicity was the main reason for the discontinuation. However, no patient withdrew from the study due to pulmonary edema. Grade III / IV neutropenia was noted in 70 percent of patients with neutropenic deaths with use of docetaxel at 85 mg/m^2. The overall response rate was 69%. Median progression-free survival for the group was 12 months.[8]

Another Scottish trial was conducted from April 1997 to March, 1998 using docetaxel-carboplatin regimen.[9] There were 141 patients enrolled at 5 dose levels. Docetaxel was given from 60 to 85 mg/m^2 and carboplatin was given from AUC 5 to 7. The regimen was given every 3 weeks for 6 cycles. The results showed that the optimal dose of docetaxel is at 75 mg/m^2 and carboplatin at AUC 5. Ninety one percent of patients were able to complete all 6 cycles. Grade III / IV neutropenia was noted in 86 percent of patients but was prolonged only in 18 percent. There were 14 percent of patients with Grade III / IV thrombocytopenia. One patient had dose delay and reduction. The following toxicities were noted:

Alopecia	64%
Edema	11%
Myalgia	6%
Sensory neuropathy	5%

The overall response rate is 67%. They concluded that docetaxel-carboplatin regimen is safe, effective and well-tolerated regimen with over 90 percent of patient completing the cycles. Only 5 percent of patients experienced neurotoxicity.

From these studies, docetaxel showed an overall efficacy of 70% objective response rate, which is equal to paclitaxel. However, docetaxel is less neurotoxic. Docetaxel is also more convenient because it can be given on outpatient basis as a 1-hour infusion. It is, therefore, the objective of this study to determine the response rate and the toxicity profile of docetaxel in combination with cisplatin or carboplatin as adjuvant treatment for persistent and recurrent ovarian epithelial malignancies.

Materials and Methods

Patient Population

This study included gynecologic cancer patients who had persistent or recurrent ovarian cancer who received the docetaxel alone or in combination with cisplatin or carboplatin from 1999-2003 at the Philippine General Hospital.

Inclusion Criteria

Patients meeting the following criteria were eligible for inclusion in the study:

1. Patient is at least 18 years of age or more.
2. Patient has a histologically proven ovarian cancer.
3. Patients with advanced sub-optimally debulked epithelial ovarian cancer (residual tumor $\geq$ 2 cm)

4. Patient must have measurable or evaluable disease (See Appendix A – definitions of disease and response)
5. Patient has an ECOG performance score of 0-2 (Appendix B)
6. Patient has normal organ function, except if abnormal due to tumor involvement.
   Normal bone marrow function as indicated:
   Platelet ≥ 100,000 mm^3
   Hemoglobin ≥ 10g/dl
   Neutrophil > 1.5 x 10^3/ mm^3
   Adequate renal function as indicated by:
   Serum creatinine < 2.5 mg/dl
   Adequate liver function as indicated by:
   Bilirubin and AST or ALT < 2 times the upper limit of normal
   Unless related to primary disease

Exclusion Criteria

Patients were not included in the study if the following criteria were present:

1. History of cardiac disease, with New York Heart Association Class II or greater (See Appendix C).
2. Clinically significant hepatic disease ad evidenced by deranged liver enzymes.
3. Patient has uncontrolled viral, bacterial or fungal infection.
4. Patient exhibits confusion or disorientation.
5. Patients with any other active primary tumor, under treatment.
6. Patients with symptomatic metastasis to the brain.
7. Prior radiation therapy to more than one third of the hematopoietic sites.
8. Prior biologic response modifiers or any other investigational drug.

Methodology

A retrospective review of medical records of gynecologic cancer patients who received docetaxel in combination with carboplatin or cisplatin for advanced ovarian epithelial cancer from 1999 to 2003 was done. Demographic data such as age, gravidity and parity were noted.

For 10 patients in the study, docetaxel 100 mg/ m^2 was administered as a 1-hour infusion in 500 cc of D_5W after pre-medication with oral dexamethasone 8 mg/tab twice a day previous to the docetaxel infusion. This was followed by infusion of either cisplatin 100 mg/m^2 or carboplatin 450 mg/m^2 after adequate hydration and administration of anti-emetics (5HT3 antagonists). This constituted one cycle of chemotherapy and each cycle was administered every 3 weeks for up to 6 cycles. Three patients, on the other hand, received the docetaxel – carboplatin regimen after having undergone previous chemotherapy with paclitaxel - carboplatin and paclitaxel-cisplatin. Lastly, one patient with previous chemotherapy with a carboplatin-cyclophosphamide combination and another with a previous chemotherapy of cisplatin-cyclophosphamide each received chemotherapy using docetaxel as single agent chemotherapy.

The dose-limiting toxicity of docetaxel is neutropenia, fluid retention and hypersensitivity reaction. These adverse reactions were assessed carefully prior to and during the administration of each cycle.

Active follow up was done for each patient, including physical and pelvic examinations, laboratory tests and evaluation of adverse experiences. Complete blood count was determined for each patient regularly as well as serum electrolytes and liver enzyme values. Appropriate radiological imaging (i.e. x-ray, CT scan, MRI, ultrasound) was done and tumor markers, such as CA-125, were determined depending on the needs of each particular patient.

Patients were followed up every three weeks for examination and monitoring. The hematologic, renal, and hepatic functions were also monitored and were graded according to the Gynecologic Oncology Group common toxicity criteria grade (See Appendix D). Radiological imaging was repeated after 2 cycles to assess disease status. Patients who achieved complete and partial response were re-evaluated 4 weeks later to confirm the initial observation of response. Patients who completed

at least 2 cycles were considered evaluable and were included in the study.

The primary endpoint of this study is the objective response rate as determined by physical examination and radiologic assessment of each patient. Secondary endpoints include time to response, duration of response and time to progression of the disease. Adverse events and clinical laboratory data were noted to examine the safety of the chemotherapeutic agent.

Sample Size

The sample size was not calculated since this was a case series study.

Data Analysis

Descriptive statistics using mean, range, and standard deviations were performed on the quantitative data gathered. Percentages alone were calculated for qualitative data. Mean time to response, duration of response and time to progression in months were also calculated.

Results

Patient Characteristics

A total of 15 patients were included in the study. The age range of the subjects was from 30 to 66 years of age with a median of 48 years of age. Median gravidity was 3 ± 2.7. The most common histologic type was mucinous cystadenocarcinoma (40%), followed by serous cystadenocarcinoma (33.33%), endometrioid cystadenocarcinoma (3%) and clear cell cystadenocarcinoma (6.66%). Majority (60%) of the patients were diagnosed with Stage II to Stage IV disease prior to chemotherapy. Four patients (26.67%) were diagnosed with stage IB or IC disease while 2 patients (13.33%) were inadequately staged. Five patients (33.33%) underwent prior chemotherapy for persistent or recurrent disease. Two of these patients received one cycle of paclitaxel – carboplatin, one underwent 6 cycles of chemotherapy with cisplatin-paclitaxel, one received three cycles of carboplatin – cyclophosphamide, and the last patient underwent four cycles of chemotherapy with cisplatin – cyclophosphamide.

Response to Therapy

All in all, complete clinical response (CCR) was observed in 4 patients (26.67%). Two patients had no evidence of disease for up to 63 months and 54 months from the start of the chemotherapy until the time this study was conducted. The other two patients achieved complete clinical response for 7 months and 4 months, respectively but were subsequently lost to follow up. One patient was noted to have partial disease response for more than three months before recurrence of the disease. Another patient was noted to have stable disease for 9 months before she was lost to follow up.

Seven patients included in the study were noted to have disease progression. Median time to progression was noted to be 204 days, with a range of 79 to 1065 days or 2.6 to 35.5 months. Two patients were lost to follow up even before the completion of the 6 cycles of chemotherapy.

Among the six patients receiving docetaxel – carboplatin as first line chemotherapy, two patients showed complete clinical response. The first patient had no evidence of disease for up to 63 months from the start of treatment while the second patient had no evidence of disease for 7 months. She was, however, subsequently lost to follow-up. The rest of the patients in this group were noted to have disease progression. The shortest time to progression was 3 months and 17 days while the longest time was 1065 days or approximately 35 months. The median time to progression for this group was 345 days or 11 months.

Four patients in the study received the docetaxel – cisplatin combination as first line treatment. Of these, one patient was noted to have no evidence of disease after 4 months. But the patient was lost to follow up. The other three patients had progression of the disease, with the time to progression ranging from 91 days to 204 days from the start of treatment. The median time to progression was noted to be 196 days or 6 months.

The remaining patients in the study received chemotherapy with other agents prior to receiving docetaxel. Two patients had one cycle each of paclitaxel-carboplatin before shifting to the docetaxel-carboplatin combination. One of these patients received three cycles before being lost to follow up. The other patient had no evidence of the disease for up to 5 years and three months, or 63 months.

One patient in the study previously received three cycles of carboplatin-cyclophosphamide before shifting to docetaxel because of disease progression. She received three cycles of docetaxel and was found to have rectal metastasis 79 days after the first cycle. Another patient previously underwent chemotherapy with cisplatin-cyclophosphamide for 4 cycles before shifting to docetaxel. This patient was noted to have stable disease for 9 months. The last patient received six cycles of paclitaxel-cisplatin before shifting to docetaxel because of disease progression. She received three cycles of docetaxel-carboplatin before being lost to follow up.

Toxicities

A total of 82 cycles of chemotherapy with docetaxel alone or docetaxel combined with either cisplatin or carboplatin were administered to the patients included in this study. The median number of cycles per patient was 6 cycles.

All patients were monitored for any adverse drug reactions or toxicity. One patient was reported to have grade 4 neutropenia with an ANC of 0.42×10^9 cells/L. This necessitated a delay in the interval of the chemotherapy as well as administration of Granulocyte-Colony Stimulating Factor (G-CSF) and antibiotics. Three patients were noted to have low hemoglobin counts requiring the patients to undergo blood transfusion prior to their next chemotherapy cycle. All these patients received Docetaxel-carboplatin as first line treatment and they each received at least 6 cycles of chemotherapy.

Edema was also common side effect in the patients included in the study. Five (33%) of the patients had grade I to grade II bipedal edema. Gastrointestinal side effects included grade 2 diarrhea which was present in two patients. One patient complained of alopecia, another complained of grade II stomatitis and a third patient complained of grade I paresthesia.

There was only one recorded death due to disease progression.

Discussion

Ovarian cancer is a lethal malignancy and is one of the most common causes of death in patients with cancer of the female genital tract. The standard treatment for advanced epithelial ovarian cancers has been chemotherapy with a platinum agent and a taxane, which is commonly paclitaxel. However, because of the adverse effects of these agents, commonly neurotoxicity, another chemotherapeutic agent with less toxicity and equal potency may be more beneficial to patients.

The objective of this study was to determine and assess the efficacy and safety of docetaxel, either given alone or in combination with either cisplatin or carboplatin. The overall clinical response rate in this study was 33.34% (complete clinical response = 26.67%; partial clinical response = 6.67%). Toxicities noted included edema, neutropenia, anemia, diarrhea and stomatitis. No patients, however, stopped treatment due to these toxicities.

As a single agent, docetaxel has been studied as possible treatment for advanced epithelial ovarian cancer. During the 1990's, trials have been performed to assess the efficacy of the drug given at 100 mg/m^2 every three weeks. Overall response rates from these trials ranged from 23 to 40%, similar to the 26% complete clinical response rate noted in our study.[10,11,12] Likewise, in a prospective, non randomized study by Vasey, et al. which was conducted to assess the feasibility of using docetaxel and cisplatin as first-line chemotherapy for advanced epithelial ovarian cancer, the complete clinical response rate was 38%.[9] These response rates are comparable to that reported in studies assessing the efficacy of the paclitaxel - cisplatin combination.

For example, in a randomized inter-group trial conducted by Piccart, et al.[13] wherein a comparison between paclitaxel-cisplatin versus cisplatin-cyclophosphamide was done, they noted a complete clinical response rate of 41 percent in patients receiving the paclitaxel-cisplatin combination. This supports that there is analogous response rates between docetaxel and paclitaxel.

Neutropenia is the most common toxicity noted in studies using docetaxel. In the study done by the Scottish Gynaecological Cancer Trials Group, 75 percent of the patients experienced grade 4 neutropenia.[9] Five patients experienced grade 4 neutropenia with fever and there were two treatment-related deaths noted. Similarly, in the study done by Francis, et al.[12], grade 4 neutropenia was noted in 83 percent of patients and 11 patients experienced febrile neutropenia. Other studies[11,13] also noted similar occurrence of neutropenia ranging from 83 to as high as 90 percent of patients. In our study, however, neutropenia was noted in only one patient (~6%) and no dose reduction was necessary for these patients, although treatment was delayed.

Anemia was an effect also noted in other studies. Francis, et al. noted that 42 percent of the patients in their study who received docetaxel developed grade 3 anemia. In our study, however, only three patients (18%) developed anemia necessitating blood transfusion before administration of subsequent cycles. It is important to note, however, that because anemia may be associated to the underlying malignancy, docetaxel as a direct cause of the anemia may be difficult to determine.

Fluid retention is also a known toxicity brought about by docetaxel. It usually manifests as peripheral edema which can progress to generalized edema and pleural effusion. In our study, 33 percent of the patients developed grade I to II bipedal edema. This is lower than the results in the study by Piccart[13] wherein 44 percent of patients developed peripheral edema, with 17 other patients developing pleural effusion. Katsuma, et al.[11] also reported edema in 16 percent of the patients in their study. Although this may be a common toxicity secondary to docetaxel, there has been no known permanent effect of the fluid retention, with most occurrences resolving after the completion of the chemotherapy cycle. The practice of administering corticosteroids and antihistamines prior to the administration of docetaxel has been known to reduce the incidence and severity of fluid retention.

Other non-hematologic effects of docetaxel include alopecia, nausea and vomiting, diarrhea, mouth sores and paresthesia. These toxic effects have also been noted in other studies involving docetaxel and were not as significant and were well tolerated. No patient in our study had to stop treatment due to these side effects.

Conclusion

Docetaxel shows activity in treating ovarian malignancy similar to that of paclitaxel, the accepted standard therapy. The overall response rate obtained in our study is similar to the response rate in other studies using the same regimen. Neutropenia, peripheral edema, and other non-hematologic toxicities were similar to that seen in patients included in other studies on docetaxel but no treatment related deaths were noted.

APPENDIX A

Definition of Disease and Response

Measurable Disease

Bidimensionally measurable lesions with clearly defined margins by 1) Chest x-ray with at least one diameter ≥ 0.5 cm, or 2) by CT scan, MRI or other imaging scan with both diameters greater than the distance between cuts of the imaging study, or 3) by palpation with both diameters ≥ 2 cm. Both lesions are not included.

Evaluable Disease

Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters ≤0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter ≤ 2 cm bone disease.

Non-evaluable Disease

Pleural effusions, ascites, disease documented by indirect evidence only (e.g. by laboratory values).

Definitions of Response

If an organ has too many measurable lesions to measure at each evaluation, choose 3 to be followed before the patient has entered the study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions have been assessed using the same methodology as at baseline. Responses will be categorized as follows:

Complete Response (CR)

Complete disappearance of all measurable and evaluable disease. No new lesions. No disease-related symptoms. No evidence of non-evaluable disease, including normalization of markers and other abnormal laboratory values. A durable response must persist for 2 separate measurements taken 4 weeks apart.

Partial Response (PR)

A 50% decrease in the sum of the products of bidimensional perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. A durable response must persist for 2 separate measurements taken 4 weeks apart. A response will be considered durable if it persists when assessed again 4 weeks later.

Stable Disease (SD)

Does not qualify for CR, PR, or progressions.

Progressive Disease (PD)

A greater than 25% increase in the sum of the products of the longest perpendicular diameters of lesions or appearance of new lesions.

Time to Response

From the start of study drug to first observation of durable response (the first of 2 confirmatory measurements).

Duration of Response

From the first observation of durable response (the first of 2 confirmatory measurements) to the first observation of progressive disease, or to death due to any cause, or early discontinuation of treatment due to progressive disease.

Time to Progression

From the start of study drug to the first evidence of progression.

Survival

From the time of start of study drug to death due to any cause.

Patient Populations

All patients receiving any study medication will be considered evaluable for safety analyses. In addition to analysis of evaluable patients, intent-to-treat analysis of all patients enrolled in the trial will also be performed.

Evaluable Patient Population

All patients who meet all inclusion and exclusion criteria, receive at least 2 cycles of study drug as prescribed, and complete all visits according to schedule will be considered evaluable for the primary efficacy analysis

Intent to Treat (ITT) Population

All patients who receive at least one dose of study drug (partial or complete dose) will be included in the ITT analyses.

Evaluable for Safety

All patients who receive at least one dose of study drug (partial or complete dose) will be evaluable for safety.

APPENDIX B

Eastern Cooperative Oncology Group (ECOG) Performance Scale

SCORE	ACTIVITY LEVEL
0	Fully active; Unrestricted activities of daily living.
1	Ambulatory but restricted in strenuous activity.
2	Ambulatory but capable of self care; Unable to work; Out of bed greater than 50% of waking hours.
3	Limited self care; Confined to bed or chair 50% of waking hours; Needs special assistance
4	Completely disabled; No self-care.
5	Dead

RECOMMENDATIONS		
Surgery	:	ECOG Score 0-2
Chemotherapy	:	ECOG Score 0-2
Radiotherapy	:	No specific recommendation

APPENDIX C

New York State Heart Association Classification

CLASS I	Patients in whom angina is provoked by strenuous exertion. Patients with cardiac disease without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain
CLASS II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
CLASS III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
CLASS IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest.

APPENDIX D

Gynecologic Oncology Group (GOG) Common Toxicity Criteria Grade (October 1988)

ORGAN	TOXICITY	0	1	2	3	4
Blood and Bone Marrow	WBC	> 4.0	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
	PLT	WNL	75.0 – normal	50.0-74.9	25.0-49.9	< 25.0
	Hgb	WNL	10.0- normal	8.0-10.0	6.5-7.9	< 6.5
	Granulocytes/ Bands	> 2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
	Lymphocytes	≥ 2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
	Hemorrhage (clinical, including intraoperative)	None	Mild; no transfusion	Gross; 1-2 units transfusion per episode	Gross: 3-4 unites transfusion per episode	Massive: > 4 units transfusion per episode
	Infection	None	Mild	Moderate	Severe	Life threatening
Gastro-intestinal	Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat	No significant intake	
	Vomiting	None	1 episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hours	> 10 episodes in 24 hours or requiring parenteral support
	Diarrhea	None	Increase of 2-3 stools per day over pre-Rx	Increase of 4-6 stools/day or nocturnal stools or moderate cramping	Increase of 7-9 stools/day or incontinence or severe cramping	Increase of ≥ 10 stools per day or grossly bloody diarrhea or need for parenteral support
	Stomatitis	None	Painless ulcers, edema, erythema, or mild soreness	Painful erythema, edema, or ulcers but can eat	Painful erythema, edema, or ulcers but cannot eat	Requires parenteral or enteral support
	Mechanical Problems	None	Temporary ileus of 3 days or less duration	Ileus requiring tube decompression, narrowing of intestinal segment on X-ray or moderate mucosal edema on proctoscopy	Surgically correctable defect – no stoma	Fistula, perforation, chronic bleeding, requiring diversion
	Operative	None	Repair of mucosal disruption	Resection for enterotomy	Temporary diversion	Permanent diversion

ORGAN	TOXICITY	0	1	2	3	4
Liver	Bilirubin	WNL		<1.6 x N	1.6 x 3.0 x N	> 3.0 x N
	Transaminases	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20 x N	> 20.0 x N
	Alk Phos	WNL	≤ 2.5 x N	2.6 x 5.0 x N	5.1-20 x N	> 20.0 x N
	Liver-clinical	No change from baseline			Pre coma	Hepatic Coma
Kidney and Bladder	Creatinine	WNL	<1.5 x N	1.5-3.0 x N	3.1-6.0 x N	
	Proteinuria	No change	1+ or < 0.3 g% or < 3 g/L	2-3 + or 0.3-1.0 g% or 3-10 g/L	4+ or > 1.0g% or > 10 g/L	
	Hematuria	Negative	Microscopic only	Gross, no clots	Gross, (+) clots	
	Bladder and ureter, acute	No problems	Dysuria, frequency, and/or microscopic hematuria; injury of bladder with primary repair	Bacterial infection; gross hematuria not requiring transfusion (< 2 gm% in Hgb); injury requiring re-anastomosis or re-implantation	Gross hematuria requiring transfusion (> 2 gm % in Hgb); sepsis, fistula or obstruction requiring secondary operation; loss of one kidney	Life threatening hematuria or septic obstruction of both kidneys or vesico-vaginal fistula requiring diversion
	Bladder and ureter, chronic	None	Dysuria, frequency, minimal telangiectasia with edema by cystoscopy	Superficial ulceration; moderate telangiectasia,; gross hematuria (< 2 gm% in Hgb; bladder volume less than 150 cc	Deep ulceration, severe pain; gross hematuria requiring transfusion (> 2 gm% Hgb); permanent unilateral loss of kidney	Decreased bladder volume requiring diversion or catheter drainage; fistula; necrosis; permanent bilateral obstruction or loss of renal function requiring dialysis
	Operative	None	Bladder atony immediately post operative	Bladder atony > 6 weeks but transient	Bladder atony requiring intermittent catheterization	
Alopecia	Alopecia	No loss	Mild hair loss	Pronounced or total hair loss		

ORGAN	TOXICITY	0	1	2	3	4
Heart	Pulmonary	None or no change	Asymptomatic, with abnormality in PFTs	Dyspnea on significant exertion	Dyspnea at normal level of activity	Dyspnea at rest
	Cardiac dysrrhythmias	None	Asymptomatic, transient, requiring no therapy	Recurrent or persistent, no therapy required	Requires treatment	Requires monitoring or hypotension or ventricular tachycardia or fibrillation
	Cardiac function	None	Asymptomatic, decline of resting ejection fraction by less than 20% of baseline value	Asymptomatic, decline of resting ejection fraction by more than 20% of baseline value	Mild CHF responsive to therapy	Severe or refractory CHF
	Cardiac ischemia	None	Non-specific T wave flattening	Asymptomatic ST and T wave changes suggesting ischemia	Angina without evidence for infarction	Acute Myocardial Infarction
	Cardiac pericardial	None	Asymptomatic effusion, no intervention required	Pericarditis (rub, chest pain, ECG changes)	Symptomatic effusion; drainage required	Tamponade, drainage urgently required
Blood Pressure	Hypertension	None or no change	Asymptomatic; transient increase by > 20 mm Hg (D) or to 150/100 if previously WNL; no treatment required	Recurrent or persistent increase by > 20 mm Hg (D) or to 150/100 if previously WNL; no treatment required	Requires therapy	Hypertensive crisis
	Hypotension	None or no change	Changes requiring no therapy (including transient orthostatic hypotension)	Requires fluid replacement or other therapy but not hospitalization	Requires therapy and hospitalization but resolves within 48 hours of stopping the agent	Requires therapy and hospitalization for > 48 hours after stopping the agent
	Venous problems	None	Superficial phlebitis; primary suture repair for injury with grade 0 or 1 blood loss	Pelvic or deep vein phlebitis; primary suture repair for injury with grade 2 or greater blood loss	Pulmonary embolus; bypass for injury	Pulmonary embolus requiring embolectomy or caval ligation
	Arterial problems	None	Spasm; primary suture repair for injury with grade 0 or 1 blood loss	Ischemia not requiring surgical treatment; primary suture repair for injury with grade 2 or greater blood loss	Vascular thrombosis requiring resection with anastomosis; vascular occlusion requiring surgery; bypass for injury	Myocardial infarction; resection of organ (bowel, limb, etc.)

ORGAN	TOXICITY	0	1	2	3	4
Skin	Skin	None or no change	Scattered macular or popular eruption or erythema that is asymptomatic	Scattered macular or popular eruption or erythema with pruritus or other associated symptoms	General symptomatic macular, popular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
	Wound infectious	None	Cellulitis	Superficial infection	Abscess	Necrotizing fasciitis
	Wound- non infectious	None	Incisional separation	Incisional hernia	Fascial disruption without evisceration	
	Allergy	None	Transient rash: drug fever < 38°C, 100.4 °F	Urticaria; drug fever < 38 ° C, 100.4 °F; mild bronchospasm	Serum sickness; bronchospasm requiring parenteral medication	Anaphylaxis
	Fever in absence of infection	None	37.1-38.0 °C 98.7-100.4 °F	38.1-40.0 ° C 100.5- 104.0 °F	> 40.0 ° C or > 104.0°F for less than 24 hours	> 40.0 ° C or > 104.0°F for more than 24 hours or fever accompanied by hypotension
	Local	None	Pain	Pain and swelling with inflammation or phlebitis	Ulceration	Plastic surgery indicated
	Lymphatics	None	Mild lymphedema	Moderate lymphedema requiring compression; lymphocyst	Severe lymphedema limiting function; lymphocyst requiring surgery	Severe edema limiting function with ulceration
Metabolic	Weight gain/loss	< 5.0%	5.0-9.9%	10.0-19.9%	> 20.0%	
	Hyperglycemia	< 116	116-160	161-250	251-500	> 500 or ketoacidosis
	Hypoglycemia	> 64	55-64	40-54	30-39	< 30
	Amylase	WNL	< 1.5 x N	1.5-2.0 x N	2.1-5.0 x N	> 5.1 x N
	Hypercalcemia	< 10.6	10.6-11.5	11.6-12.5	12.6-13.5	> 13.5
	Hypocalcemia	> 8.4	8.4-7.8	7.7-7.0	6.9-6.1	≤ 6.0
	Hypomagnesemia	> 1.4	1.4-1.2	1.1-0.9	0.8-0.6	≤ 0.5
Coagulation	Fibrinogen	WNL	0.99-0.75 x N	0.74-0.50 x N	0.49-0.25 x N	≤ 0.24 x N
	Prothrombin Time	WNL	1.01-1.25 x N	1.26-1.50 x N	1.51-2.00 x N	> 2.00 x N
	Partial thromboplastin time	WNL	1.01-1.66 x N	1.67-2.33 x N	2.34 – 3.00 x N	> 3.00 x N

ORGAN	TOXICITY	0	1	2	3	4
Neurologic	Neurosensory	None or no change	Mild parethesias, loss of deep tendon reflexes	Mild or moderate objective sensory loss; moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	
	Neuromotor	None or no change	Subjective weakness; no objective findings	Mild objective weakness without significant impairment	Objective weakness with impairment	Paralysis
	Neurocortical	None	Mild somnolence or agitation	Moderate somnolence or agitation	Severe somnolence, agitation, confusion, disorientation, hallucination	Coma, seizures, toxic psychosis
	Neurocerebellar	None	Slight incoordination, dysdiadochokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis
	Neuro-mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
	Neuro-headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	
	Neuro-constipation	None or no change	Mild	Moderate	Severe	Ileus > 96 hours
	Neuro-hearing	None or no change	Asymptomatic; hearing loss on audiometry only	Tinnitus	Hearing loss interfering with function but correctable with hearing aid	Deafness not correctible
	Neuro-vision	None or no change			Symptomatic subtotal loss of vision	Blindness

References

1. McGuire WP, William JH, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage II and stage IV ovarian cancer. New Engl J Med 1996; 334(1): 1-6.
2. Postma TJ, Vermoken JB, Leifting AJM, et al. Paclitaxel-induced neuropathy. Ann Oncol 1995; 6: 489-494.
3. Eisenhauer EA, Bokkei HW, Swenerton KD, et al. European- Canadian randomized trial of paclitaxel in relapsed ovarian cancer. High dose versus low-dose and long versus short infusion. J Clin Oncol 1994; 12: 2654-2666.
4. Product insert. Taxotere (Docetaxel) Injection concentrate. Sanofi-Aventis, December 2006.
5. Picart MJ, Bokkei HW, et al. Docetaxel: an active new drug for treatment of advanced epithelial ovarian cancer. J Natl Cancer Inst 1995; 387(9): 676-681.
6. Fujiwara K, Kohno I, Tanaka K, et al. Phase II dose escalation: a novel approach to balancing efficacy and toxicity of anticancer agents. Japanese Docetaxel Ovarian Cancer Study Group. Anticancer Res 1999; 19 (191B): 639-644.
7. Kavanaugh J, Kudellka A, Freedman R, et al. Taxotere (Docetaxel): Activity in platinum refractory ovarian cancer and amelioration of toxicity. Proc Am Soc Clin Oncol 1994; 13: 237.
8. Vasey PA, Paul J, Birt A, et al. Docetaxel and cisplatin in combination as first-line chemotherapy for advanced epithelial ovarian cancer. J Clin Oncol 1999; 17: 2069-2080.
9. Vasey PA, Atkinson R, Coleman R, et al. Docetaxel-carboplatin as first-line therapy for epithelial ovarian cancer. Br J Cancer 2001; 84: 170-178.
10. Vasey PA. Role of docetaxel in the treatment of newly diagnosed advanced ovarian cancer. J Clin Oncol 2003; 21:136s-144s.
11. Katsumata N, Tsunematsu R, Tanaka K, et al. A phase II trial of docetaxel in platinum pre-treated patients with advanced epithelial ovarian cancer: a Japanese Cooperative study. Ann Oncol 2000; 11: 1531-1536.
12. Francis P, Schneider J, Hann L, et al. Phase II trial of docetaxel in patients with platinum-refractory advanced ovarian cancer. J Clin Oncol 1994; 11: 2301-2308.
13. Piccart MJ, Bertelsen K, Cassidy J, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000; 9: 699-708.

Diagnostic Value of Ultrasound and Urine Cytology in the Staging of Cervical Cancer*

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Background: The International Federation of Gynecology and Obstetrics (FIGO) staging classification for cervical cancer is based on clinical evaluation and limited radiologic assessment of disease extent. For bladder involvement, cystoscopy is the only accepted diagnostic procedure. Even with flexible instruments, cystoscopy remains invasive and bothersome to the patient. Clinical research in cervical cancer has been searching for alternative, less invasive methods to detect bladder involvement or at least to indicate further investigation. Alternative diagnostic tools include ultrasound and urine cytology. **Objective**: The study aims to establish the diagnostic values of ultrasound and urine cytology in assessing bladder involvement in cervical cancer. **Method**: Using a cross-sectional study design, all newly diagnosed cervical carcinoma patients stage IIB and up were included in the study. The standard staging investigations were done on all patients. In addition, urine sample collected midstream were sent for cytology. Transvaginal sonography was likewise done on all patients. Cystoscopy and biopsy were performed on all subjects. **Results**: Twenty-six patients were enrolled into this study. Transvaginal sonography has a sensitivity of 100% and specificity of 92%. Ultrasound has a positive predictive value of 50% and a negative predictive value of 100%. On the other hand, urine cytology has a sensitivity of 50% and specificity of 96% for bladder mucosa infiltration. The predictive value of a positive test is 50% and for a negative test is 96%. **Conclusion**: Ultrasound and urine cytology are very useful screening tests for bladder infiltration in patients with cervical cancer. Cystoscopy should be reserved for patients with abnormal ultrasound and urine cytology in resource-poor settings with a large burden of disease.

Key words: urine cytology, cervical carcinoma

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Cervical cancer is an important public health problem among women in developing countries.[1] In the Philippines, it is the fifth leading site for both sexes combined and the second among women.[2] It is the most common gynecologic malignancy in the country. This is mostly due to the lack or inefficiency of existing prevention programs.[1]

Majority of patients present at an advanced stage of the disease. It is recognized that the survival of women with cervical cancer is directly determined by the extent of disease at the time of diagnosis.[3] Evaluation of the local spread of invasive cervical cancer is crucial in assigning the proper stage, programming the appropriate treatment and predicting the outcome.[4] According to FIGO, local staging of the tumor should be based mainly upon clinical findings.[5] However, the accuracy of this system is reported to be low, particularly with respect to infiltration of the bladder. [6,7,8]

FIGO has recommended the use of cystoscopy in ruling out bladder involvement. However, invasive staging with histopathologic evaluation of the extent of the disease leads to increased morbidity. Cystoscopy may result in pain, urinary frequency (37%), hematuria (19%) and urinary tract infection (2.7%).[9] This procedure is limited only to diagnosis of those tumors that can be visualized. Most importantly, the cost of cystoscopy is prohibitive. In resource-poor settings with a high burden of disease like the Philippines, it is of utmost importance that new and innovative ideas are constantly being investigated to assist in the efficient spending of limited resources without compromising on quality.

Ultrasonography and urine cytology have been shown to be accurate investigations in primary bladder neoplasms and to reduce the need for cystoscopy. Cystoscopy yields only a 7-14% positive rate and thus more than 80% of cystoscopies can be avoided.[10,11]

General Objective

To determine the diagnostic accuracy of urine cytology and ultrasound in predicting bladder involvement among advanced-stage cervical cancer patients.

Specific Objective

1. To determine the sensitivity and specificity of ultrasound and urine cytology as predictive tools for bladder involvement among cervical cancer patients with FIGO stage IIB and above.
2. To determine the positive (PPV) and negative predictive value (NPV) of ultrasound and urine cytology as predictive tools for bladder involvement among cervical cancer patients with FIGO stage IIB and above.

Materials and Methods

Study Design: This is a cross-sectional study.

Sample size determination

A. Sensitivity determination

For urine cytology, the following assumptions were used: 95% confidence level, 70% sensitivity and 10% margin of error.
For ultrasound, 95% confidence level, 97% sensitivity and 10% margin of error were used.

B. Specificity determination

For both ultrasound and urine cytology, a specificity of 90% was used. Therefore a sample size of 35 patients found negative for bladder extension on biopsy/cystoscopy was needed based on the following assumptions: 95% confidence level, 90% specificity and 10% error.

Methods

New patients diagnosed with cervical cancer FIGO stage IIB and up from the Section of Gynecologic Oncology and Trophoblastic Disease of Jose R. Reyes Memorial Medical Center from March to August, 2008 were included in this cross-sectional study. Written informed consent was

obtained from all the participants. Staging investigations included cervical biopsy, complete blood count, liver and kidney function tests, electrolytes, and chest radiograph. In addition, transvaginal sonography was done and a midstream urine specimen was collected for cytology.

Transvaginal sonography was performed on all patients in the supine position using Philips HD5540R. The ultrasound was performed by one radiologist. The endovaginal sector probe with a frequency of 7.5 MHz was used. The transvaginal transducer was inserted into the anterior fornix of the vagina and the bladder wall was studied in the sagittal plane. The movability of the bladder wall was assessed by the ability of the bladder to slide along the uterine cervix when the probe is pushed up against the bladder from the anterior fornix. Movability was considered as an indication of an intact bladder wall. The ultrasonographer reported on the findings of the posterior bladder wall as thickened or normal as well as the bladder mucosa as either normal or suspicious of infiltration.

The voided urine (40-80ml) samples were collected from all patients and was centrifuged for 10 minutes and the sediment was placed on glass slides. The slides were fixed using 95% ethyl alcohol. The slides were stained according to Papanicolaou. Specimens negative for malignancy or with atypia of any degree were categorized as "negative' and specimens considered suspicious or positive for malignancy as "positive."

Rigid cystoscopy and biopsy was performed on all subjects by a Urology resident. Patients were under intravenous anesthesia. Cystoscopically-directed biopsy specimens were taken from all areas in the bladder which were suspected of cancer. If there was no suspicious lesion on cystoscopy, biopsies were taken from the trigone and posterior wall of the bladder. Slides of tissue specimens stained with hematoxylin and eosin were reviewed by one pathologist who confirmed the presence or absence of bladder invasion by cervical cancer.

Statistical Analysis

Sensitivity is defined as the ratio of cervical cancer patients with bladder involvement with positive cytology on urine cytology to the total number of cervical cancer patients with bladder involvement included in the study.

Specificity is defined as the ratio of cervical cancer patients with no bladder involvement with negative cytology on urine cytology to the total number of individuals without bladder involvement.

Positive predictive value is defined as the probability that an individual with positive cytology on urine cytology has bladder involvement.

Negative predictive value is defined as the probability that an individual with negative cytology on urine cytology does not have bladder involvement.

A 95% confidence interval was computed for all parameters.

Results

Table 1 shows the mean age, gravidity, cancer type and stage of cancer. Mean age was 48.9 years. The most common gravidity were Gravida1 and Gravida 5. The most common histologic type was squamous cell carcinoma, large cell non-keratinizing (SCCA LCNK). The most common stage at diagnosis was IIIB (17).

Table 1. Age, gravidity, histologic type and stage of cancer.

ID	Age/Gravidity	Histologic Type	Stage
1	41 / G1P1(1001)	SCCA, LCK	IIIB
2	45 / G3P3(3003)	Adenosquamous CA	IIIB
3	56 / G7P5(5023)	Papillary Squamous Cell CA	IIIB
4	44 / G4P2(2022)	SCCA, LCNK	IIB
5	46 / G6P6(6006)	Adenocarcinoma	IIB

ID	Age/Gravidity	Histologic Type	Stage
6	56 / G5P5(5005)	SCCA	IIIB
7	46 / G5P5(5005)	SCCA, LCNK	IIIB
8	36 / G5P5(4104)	SCCA, LCNK	IIIB
9	50 / G1P1(1001)	SCCA, LCNK	IIIB
10	47 / G2P2(2002)	SCCA, LCK	IIIB
11	47 / G4P4(4004)	Adenocarcinoma	IIB
12	49 / G2P2(0020)	SCCA, small cell type	IIIB
13	44 / G2P2(2002)	SCCA, LCNK	IIIB
14	69 / G8P8(8007)	SCCA, LCNK	IIB
15	57 / G1P1(0101)	Adenocarcinoma	IVB
16	43 / G4P3(2112)	SCCA, LCNK	IIB
17	37 / G3P3(3003)	SCCA, LCK	IIIB
18	50 / G5P4(4014)	SSCA, LCNK	IIB
19	34 / G1P1(1001)	SCCA, LCNK	IIIB
20	47 / G2P2(2002)	SCCA, LCNK	IIIB
21	47 / G7P6(6016)	SCCA, LCNK	IIB
22	76 / G9P9(9009)	SCCA, LCNK	IIIB
23	54 / G4P4(4004)	Adenocarcinoma	IIIB
24	55 / G7P6(6016)	SCCA,LCNK	IIIB
25	45 / G1P1(1001)	Adenocarcinoma	IIIB
26	51 / G5P5(5004)	SCCA, LCNK	IIB
	Mean ± age= 48.9 ± 9.19 Mode gravidity= G1 and G5	Most common =SCCA LCNK (18)	Most common stage=3B (17)

Table 2 shows the list of patients and their ultrasound, urine cytology, cystoscopy ,and biopsy findings. It can be seen that ultrasound found 4 subjects with suspicious infiltrates while urine cytology found only two. One subject had acellular smear so there was no finding in the urine cytology test. Biopsy found only two positive for tumor.

Table 2. Patients' ultrasound, urine cytology, cystoscopy and biopsy findings.

ID Number	Ultrasound	Urine Cytology	Cystoscopy & Biopsy
1	Bladder thickness: 7.0 mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings: Normal bladder mucosa; Biopsy: Negative for tumor
2	Bladder thickness: 17.0 mm Fixed Floaters within the bladder Suspicious of infiltration	Negative for malignant cells	Intraoperative findings: Posterior wall slightly elevated; Multiple bladder mass measuring 0.5-1.0cm; Biopsy: Positive for tumor
3	Bladder thickness: 13.5 mm Fixed Suspicious infiltrates within the bladder wall	Positive for malignant cells	Intraoperative findings: Elevated posterior walll; Biopsy: Positive for tumor

ID Number	Ultrasound	Urine Cytology	Cystoscopy & Biopsy
4	Bladder thickness: 4.6 mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings: Smooth bladder mucosa, Elevated trigone, No mass Biopsy: Negative for tumor
5	Bladder thickness: 5.0 mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal bladder mucosa; Biopsy: Negative for tumor
6	Bladder thickness: 4.5 mm Moveable Normal bladder mucosa	Positive for malignant cells	Intraoperative findings:Normal bladder mucosa; Biopsy: Negative for tumor
7	Bladder thickness: 3.9mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Smooth bladder mucosa; Biopsy: Negative for tumor
8	Bladder thickness: 14.0mm FixedSuspicious of infiltration	Negative for malignant cells	Intraoperative findings:Normal bladder mucosa; Biopsy: Negative for tumor
9	Bladder thickness: 11.0mm FixedSuspicious of infiltration	Negative for malignant cells	Intraoperative findings:Smooth bladder mucosa; Biopsy: Negative for tumor
10	Bladder thickness: 4.7mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Smooth bladder mucosa; Biopsy: Negative for tumor
11	Bladder thickness: 4.7mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings: Smooth bladder mucosa; Biopsy: Negative for tumor
12	Bladder thickness: 4.8mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal bladder mucosa; Biopsy: Negative for tumor
13	Bladder thickness: 5.0mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Smooth bladder mucosa, No mass noted Biopsy: Negative for tumor
14	Bladder thickness: 4.9mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings: No mass noted; Biopsy: Negative for tumor

ID Number	Ultrasound	Urine Cytology	Cystoscopy & Biopsy
15	Bladder thickness: 8.2mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings: Normal looking mucosa; Biopsy:Negative for malignant cells
16	Bladder thickness: 3.4mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal looking mucosa, No mass noted Biopsy:Negative for tumor
17	Bladder thickness: 5.8mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal bladder mucosa; Biopsy: Negative for tumor
18	Bladder thickness: 4.8mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal looking mucosa Biopsy: Negative for tumor
19	Bladder thickness: 6.5mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal looking mucosa, No mass noted Biopsy: Negative for tumor
20	Bladder thickness: 6.9mm Moveable Normal bladder mucosa	Acellular smear	Intraoperative findings:Normal looking mucosa, No mass noted Biopsy: Negative for tumor
21	Bladder thickness: 6.9 mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal looking mucosa, No mass noted Biopsy: Negative for tumor
22	Bladder thickness: 5.2mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal looking mucosa, No mass noted Biopsy: Negative for tumor
23	Bladder thickness: 4.0mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings: Normal looking mucosa Biopsy: Negative for tumor

ID Number	Ultrasound	Urine Cytology	Cystoscopy & Biopsy
24	Bladder thickness: 5.7mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal looking mucosa Biopsy:Negative for tumor
25	Bladder thickness: 6.2mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings: Normal looking mucosa, No mass noted Biopsy:Negative for tumor
26	Bladder thickness: 8.2mm Moveable Normal bladder mucosa	Negative for malignant cells	Intraoperative findings:Normal looking mucosa, No mass noted Biopsy:Negative for tumor

Tables 3A and 3B show the 2x2 tables for the computation of the validation parameters. For ultrasound, sensitivity and negative predictive values were 100%, specificity was 92% and positive predictive value was 50%.

Table 3B shows that urine cytology had a sensitivity and positive predictive values of 50% while specificity and negative predictive values were both 96%.

Table 4 summarizes the validation parameters and their confidence intervals for ultrasound and urine cytology. It can be seen that ultrasound has a higher sensitivity than urine cytology but slightly lower specificity than urine cytology. PPV was the same for both tests, while NPV was higher for ultrasound than urine cytology. Confidence intervals showed wide ranges for both tests for sensitivity and PPV mainly because of the very small number with positive results. Specificity and NPV had more accurate results as shown by the narrow confidence intervals. There is a trend indicating that both tests are better at identifying those who have truly no malignancy in the bladder (specificity), than in identifying those who have the disease (sensitivity). Since this is a pilot study, further testing using bigger sample sizes is recommended.

Table 3A. 2x 2 table for the computation of validation parameters of ultrasound with cystoscopy/biopsy as gold standard.

	Cystoscopy/Biopsy		
Test(USN)	Positive	Negative	Total
Positive	2	2	4
Negative	0	22	22
Total	2	24	26

Table 3B. 2 x 2 table for the computation of validation parameters of urine cytology with cystoscopy/biopsy as gold standard.

	Cystoscopy/Biopsy		
Test(Urine Cytology)	Positive	Negative	Total
Positive	1	1	2
Negative	1	22	23
Total	2	23	25

Table 4. Summary of validation parameters.

	Ultrasound	Urine cytology
Sensitivity /Confidence interval	100% (19.8% - 100%)	50% (2.7% - 97.3%)
Specificity/Confidence interval	92% (72% - 98%)	96% (76%-99.8%)
PPV/Confidence interval	50% (9.2% - 91%)	50% (2.7% - 97.3%)
NPV/Confidence interval	100% (82% - 100%)	96% (76% - 99.8%)

Discussion

Invasive cervical cancer may spread to the lower urinary tract by direct invasion. Examination of the bladder in very important in evaluating the extent of spread in advanced cervical cancer.[12]

In an era of increased cost consciousness, it may be appropriate to estimate the efficiency of the tests used to evaluate bladder involvement.

Cystoscopy is necessary to establish the diagnosis of bladder invasion by cervical cancer.[12] However, it is an invasive investigation and it is expensive.[13] It may also cause several acute urinary symptoms. Not all patients with cervical cancer need cystoscopy to rule out bladder involvement.

Due to the invasive and labor-intensive nature of cystoscopy, there is a challenge to develop better, less costly, and non-invasive approaches which could give us information on bladder involvement.[14] Urine cytology and ultrasound have the potential to give us this information in a non-invasive way.

Transvaginal ultrasound (TVS) is a promising modality for recognizing bladder wall infiltration by cervical cancer. With the use of a high-resolution vaginal probe, transvaginal sonography provides a relatively clear demonstration of the tissue planes between the cervix and lower urinary tract. [15] Researches on ultrasonography show that depending on the severity of tumor invasion, the bladder wall was elevated with a plateau- or hump-like appearance, the wall thickness increased, the mucosal surface became irregular, ragged and bullous, and the inner layers displayed mixed echogenicity.

On the other hand, urine cytology has been an integral part of bladder cancer screening since the first satisfactory technique for demonstrating cancer cells in centrifuged urine was described by Papanicolaou and Marshall in 1945.[16,17]

De Jonge and Miskin showed in their study that ultrasonography is a good screening test for bladder infiltration in patients with cervical cancer.[10,11] Ultrasound has a sensitivity of 100% and specificity of 76.5%. In our study, the sensitivity was 100% while the specificity was 92%. It had a positive predictive value of 50% and a negative predictive value of 100%.

Ultrasound showed 4 subjects with suspicious infiltrates and fixed bladder wall. The two positive sonologic findings were confirmed by the biopsy results while the other two revealed negative biopsy results.

On the other hand, urine cytology is the first non-invasive method with good overall median specificity of 99% (83-100%) and acceptable overall median sensitivity of 34% (20-53%) to detect bladder cancer reported in a comprehensive literature review and meta-analyses.[19,20] The present study likewise confirmed a high specificity rate (96%) in the urine cytology but the sensitivity rate was higher at 50% compared with the previous studies.

Results in the study showed 2 subjects with malignant cells on urine cytology. One subject had positive biopsy result while the other subject failed to reveal a positive result on tissue biopsy. Among the 26 subjects who had urine cytology test, there was one acellular smear. The smear had no adequate cells for the pathologist to make a diagnosis.

The preliminary results of this study showed that both urine cytology and TVS had high specificity and negative predictive value, indicating good ability to identify those that do not have bladder infiltration. Urine cytology showed a higher specificity than TVS. Estimates of sensitivity for both tests do not have the same accuracy as that of specificity because of the very few positive cases included in the study (estimated sample size to determine sensitivity was 80 for urine cytology and 11 positive cases for TVS; actual number included in the study was only 2 positive cases).

Ultrasound and urine cytology seem to be promising tools in ruling out bladder infiltration in patients with cervical cancer. Cystoscopy can be reserved for patients with abnormal ultrasound findings and abnormal urine cytology, and can reduce the cost of screening in resource-poor settings with a large burden of disease.

Conclusion

Urine cytology and ultrasound are promising screening tools and this study shows evidence that could help influence a change in the practice of screening for bladder infiltration among those with cervical cancer, which in turn could lead to significant future resource savings and a reduction in morbidity from early detection and staging.

Recommendation

The number of positive cases included in the study is too small to allow us to draw any conclusions about the tests' sensitivity and positive predictive value. Thus further investigation using adequate sample size should be undertaken.

References

1. Sankaranarayanan R. Cervical cancer in developing countries. Transactions of the Royal Society of Tropical Medicine and Hygiene 2002; 96: 580-585.
2. Laudico AV, Esteban DB, et al. Major cancer sites. 2005 Philippine Cancer Facts and Estimates; page 12.
3. Allen D and Narayan K. Managing advanced-stage cervical cancer. Best Pract Res Clin Obstet Gynecol 2005; 19(4): 591-609.
4. Chi T, Giunchi S, et al. Three-dimensional transvaginal sonography in local staging of cervical carcinoma: description of a novel technique and preliminary results. Ultrasound Obstet Gynecol 2007; 30: 778-782.
5. Pecorelli S, Odicino F. Cervical cancer staging. Cancer J 2003; 9: 390-394.
6. Benedet JL, Bender H et al. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynecol Obstet 2000; 70: 209-262.
7. Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. Int J Gynecol Obstet 2003; 83 (Suppl.1): 41-48.
8. Hertel H, Kohler C, et al. Laparoscopic staging compared with imaging techniques in the staging of advanced cervical cancer. Gynecol Oncol 2002; 87: 46-51.
9. Rockall AG, Ghosh S, et al. Can MRI rule out bladder and rectal invasion in cervical cancer to help select patients for limited EUA? Gynecol Oncol 2006; 244-249.
10. Snyman LC, Zondagh BA, et al. Urine cytology as a screening test for bladder infiltration in cervical cancer. Int J Gynecol Cancer 2006; 16: 1587-1590.
11. Du Toit JP. A cost-effective but safe protocol for the staging of invasive cervical carcinoma in a third world country. Int J Gynecol Obstet 1988; 26: 261-264.
12. Ching-Chung Liang, Chih-Jen Tseng, et al. The usefulness of cystoscopy in the staging of cervical cancer. Gynecol Oncol 2000; 76: 200-203.
13. Vriesema JLJ, Pouckin MH, et al. Patient opinion of urinary tests versus flexible urethrocystoscopy in follow-up examination for superficial bladder cancer: a utility analysis. Urology 2000; 56: 793-797.
14. Vlahou A, Schellhammer PF, et al. Development of a novel proteomic approach for the detection of transitional cell carcinoma of the bladder in urine. Am J Pathol 2001; 158: 1491-1502.
15. Huang WC, Yang JM, et al. Ultrasonographic characteristics and cystoscopic correlates of bladder wall invasion by endophytic cervical cancer. Ultrasound Obstet Gynecol 2006; 27: 680-686.
16. Ramakumar S, Bhuiyan J, et al. Comparison of screening methods in the detection of bladder cancer. J Urol 1999; 161: 388-394.
17. Raitanen MP, Aine R, et al. Differences between local and review urinary cytology in diagnosis of bladder cancer. An interobserver multicenter analysis. Eur Urol 2002; 41: 284-289.
18. De Jonge ETM, Miskin S. Transabdominal ultrasonography of the bladder as a staging examination for cervical carcinoma. South Africa Med J 1995; 85: 1076-1080.
19. Planz B, Jochims E, et al. The role of urinary cytology for detection of bladder cancer. J Cancer Surg 2005; 31: 304-308.
20. Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. Urology 2003; 6 (1): 109-118.

Magnesium and Potassium Depletion in Cervical Cancer Patients Receiving Weekly Cisplatin Chemotherapy Concurrent with Radiotherapy: A Retrospective Cohort Study*

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Objectives: This retrospective cohort study was conducted to determine the association of a low dose weekly cisplatin chemotherapy with the serum magnesium and potassium levels of cervical cancer patients undergoing concurrent chemoradiation. **Methods:** One hundred fourteen cervical cancer patients who underwent radiotherapy concurrent with Cisplatin 40mg/m^2 weekly for at least 3 cycles from January to December 2007 were included in this study. Sociodemographic and clinicopathologic data, as well as the details of each chemotherapy cycle and laboratory results were obtained. Mean and standard deviation were employed for quantitative variables while frequencies and percentages were used for qualitative variables. Repeated measures analysis of variance was used to determine the difference in change of magnesium and potassium during chemotherapy. Sidak multiple comparison test was used to determine which among the time points were different. Rank correlation was used to determine the correlation of the change in magnesium and potassium during chemotherapy. A logistic regression model was derived to show the association of factors with either hypomagnesemia and hypokalemia. All statistical tests were computed at 95% level of significance, alpha=0.05. **Results:** Calculation of the relative mean change in magnesium, creatinine and potassium showed a significant decrease in the serum magnesium levels (p value = 0.001) but not with potassium (p=0.27) and creatinine (p=0.47). The incidence of hypomagnesemia is 46.49% with the degree of hypomagnesemia being mild in 55 percent of patients, moderate in 30 percent and severe to life-threatening in 15 percent of patients. There is progressive decline in serum magnesium levels with each successive cycle by 17.4% from the

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baseline after the 1st cycle, 30.9% after the 2nd cycle and 45.4% after the 3rd cycle. There is poor correlation observed between the occurrence of hypomagnesemia and hypokalemia with a correlation coefficient of 8%. The median time to development of hypomagnesemia is 21 days (95% CI 19, 23) while the median time to development of hypokalemia is 28 days (95% CI 28, 30). The difference in rate is statistically significant. Only the cumulative dose of the chemotherapy was statistically associated with hypomagnesemia and hypokalemia. Elevated creatinine and body surface area were not significantly associated with the decline in level of magnesium and potassium. **Conclusion**: This study is the first one conducted with regards the serum magnesium and potassium levels of cervical cancer patients receiving cisplatin chemotherapy at 40 mg/m^2 weekly, a dose given as a radiosensitizer and a dose that is lower than those analyzed in other studies. It is noteworthy to point out that even at such a low dose of cisplatin, hypomagnesemia still developed. The cumulative dose of the chemotherapeutic agent is the only factor noted to significantly affect the level of decline in serum magnesium levels. In this study, a minimal cumulative dose of only 120 mg/m^2 of cisplatin is needed to induce hypomagnesemia.

Key words: cisplatin, cervical cancer, concurrent chemoradiation, magnesium, potassium

Since its clinical introduction in 1971, cisplatin has proven to be a very important cytostatic agent effective against a variety of solid tumors. In 1999, the National Cancer Institute has made a consensus statement on concurrent chemoradiation as the standard of care for locally advanced cervical cancer and this concept has gained widespread acceptance since. Weekly cisplatin was introduced as a standard component of such treatment, with its potential to increase killing of tumor cells, inhibiting repair of radiation damage, inducing cell synchronization, recruiting non-proliferating cells into the cell cycle and the sensitization of hypoxic cells.[1]

In recent years, with the availability and refinement of techniques, studies on magnesium were made possible on a larger scale. These studies have elucidated the role of magnesium in many cellular processes particularly in cellular energy metabolism involving ATP, muscle Na K-pump activity, calcium channel activity, stabilization of membrane structures, mRNA translation and transcription and replication of DNA.[2]

Hypomagnesemia is a well known side-effect in patients undergoing chemotherapy with cisplatin. It is now the most common renal defect associated with cisplatin therapy. The reported incidence varies between 29-100 percent of patients, depending on the definition and different studies.[3] The exact mechanism by which cisplatin causes hypomagnesemia is not clear but appears to be dependent on the applied cumulative dose of the drug. The clinical features of magnesium depletion are wide ranging, and the condition can be difficult to diagnose. The symptoms and signs can be variable, and may be attributed to the underlying malignancy or treatment. Clinical manifestations are predominantly neuromuscular abnormalities, such as irritability, tremor, hyper-reflexia, ataxia, fits and carpo-pedal spasm. Other manifestations include psychiatric disturbances, such as confusion

and hallucinations, and electrocardiograph changes, such as a prolonged QT interval, broad flattened T waves and occasional shortening of the ST interval. Furthermore, many symptoms of moderate to severe hypomagnesemia are non-specific and symptomatic magnesium depletion is usually associated with additional ion abnormalities, such as hypocalcemia, hypokalemia and metabolic alkalosis.[3]

In patients with hypomagnesemia, a six-fold increase in the prevalence of hypokalemia has been reported. This may result from the proximal tubular injury by cisplatin leading to an increased delivery of sodium, potassium and water to the distal nephron, creating a sodium-load dependent potassium secretion. Hypomagnesemia may also lead to an impairment of the Mg-dependent Na, K-ATPase resulting in increased cellular potassium loss, which is aggravated by the hyperhydration used during treatment with cisplatin. Hypomagnesemia also increases renin release and thereby increasing aldosterone levels, further enhancing potassium excretion. Whatever the cause is, attempts should be made to correct both conditions since hypokalemia, probably on the basis of the Mg-dependent Na,K-ATPase, may fail to resolve without simultaneous administration of magnesium.[2]

Review of Literature

Hypomagnesemia in association with cisplatin therapy was initially described by Schilsky and Anderson[4] in 1979 and this has been repeatedly confirmed.[5,6,7,8] The kidney is the major regulator of the circulating magnesium concentration and renal tubular magnesium wasting is thought to be the mechanism of cisplatin-induced hypomagnesemia.[9] It appears that the resultant hypomagnesemia is dependent on the applied cumulative dose of the cisplatin chemotherapy.[8] Ariceta, et al.[10] found that the minimal cumulative dose required to induce hypomagnesemia was 300 mg/m^2 of cisplatin. Martin, et al.[11] suggested that most patients who receive cumulative doses of cisplatin in excess of 400 mg/m^2 will develop some degree of hypomagnesaemia.

The percentage of patients developing hypomagnesemia at some point during treatment vary among observers depending on the regimen of treatment used. Schilsky, et al.[4] retrospectively analyzed serum electrolytes in 44 patients receiving cisplatin chemotherapy and found that 52 percent (23/44) of patients developed hypomagnesemia (< 1.4 meq/l) during treatment with doses of 70 mg/m^2 at three weekly intervals with a median of four courses. Buckley, et al.[5] found out that the incidence of hypomagnesemia in 50 patients receiving cisplatin 50mg/m^2 at four weeks interval increased during treatment from 41% after one course of chemotherapy to 100% in patients receiving six courses of chemotherapy. Bell, et al.[12] prospectively evaluated 50 patients receiving different regimens of cisplatin and found all patients to be hypomagnesemic (< 0.69 mmol/l) after 4 courses of chemotherapy irrespective of the dosage applied (50–100 mg/m^2). Lastly, Stewart, et al.[7] prospectively evaluated 17 patients treated with cisplatin 50 mg/m^2 at 4-week intervals for a mean of 13 courses. Hypomagnesemia (< 1.8 mg/dl) developed in 88 percent of patients at some point during treatment and was considered moderate/severe (< 1.4 mg/dl) in 53 percent of cases.

Hodgkinson, et al.[13] assessed the incidence of hypomagnesemia, the influence of different cisplatin dosages on the degree of hypomagnesemia and the effect of routine magnesium supplementation on magnesium levels. Multiple regression analysis showed a significant association between dose, frequency and number of cycles given, and the degree of hypomagnesemia. Routine magnesium supplementation significantly reduced the degree of hypomagnesemia if sufficient amounts of magnesium are given. The authors concluded that magnesium levels should be measured routinely in all patients receiving cisplatin and that all cisplatin-based chemotherapy regimens should be supplemented routinely with sufficient doses of magnesium (40-80 mmol magnesium per cycle depending on the regimen).

Experimental and clinical observations support the view that uncorrected magnesium deficiency impairs repletion of cellular potassium. This is consistent with the observed close association between potassium and magnesium depletion. Concomitant magnesium deficiency in potassium-depleted patients ranges from 38% to 42%. Refractory potassium repletion due to unrecognized concurrent magnesium deficiency can be clinically perplexing.[14] Rodriguez, et al.[15] described two patients with hypomagnesemia-associated refractory hypokalemia following cisplatin therapy. Potassium supplementation failed to replace the potassium deficit. Profound hypokalemia persisted until hypomagnesemia was recognized and corrected. In another patient was the concurrent hypomagnesemia recognized until the 11th and 9th hospital days. These two cases demonstrated the association of a refractory potassium repletion and magnesium deficiency. They concluded that both serum potassium ion and magnesium levels should routinely be assessed in patients who require cisplatin therapy.

Chemoradiation is the standard of treatment for cervical cancer. Cisplatin at the dose of 40mg/m^2 is the standard radiosensitizer given weekly for 6 courses concurrent with radiotherapy. There has been no study conducted with regards the serum magnesium and potassium levels of patients receiving this dose and frequency of cisplatin, thus, this study is undertaken.

Objectives

1. To determine the association of weekly cisplatin chemotherapy with hypomagnesemia and hypokalemia in patients with cervical cancer.
2. To determine the clinico-pathologic profile of cervical cancer patients undergoing cisplatin chemotherapy.
3. To determine the time to decline of magnesium and potassium in cervical cancer patients undergoing weekly cisplatin chemotherapy.
4. To determine the factors associated with hypomagnesemia and hypokalemia.

Materials and Methods

Study Design

This is a retrospective cohort study on cervical cancer patients who underwent concurrent chemoradiation as primary or adjuvant therapy at the Cancer Institute from January to December 2007.

Patient Inclusion

Patients who satisfied the following criteria were included in this analysis and comprised the study population:

1. Age 18-75 years
2. Those with squamous cell, adenocarcinoma or adenosquamous histologic types of cervical cancer
3. All stages of cervical cancer for which chemoradiation is given as the primary treatment or adjuvant treatment after a radical hysterectomy
4. Baseline serum creatinine, magnesium and potassium levels within the normal range
5. Those who have received at least 3 courses of weekly cisplatin chemotherapy as a radiosensitizer.

Methods

Outpatient medical records of these patients who fulfilled the inclusion criteria were retrieved and reviewed. A case registry form that included sociodemographic data, height, weight, baseline internal examination, histologic diagnosis and stage, and for each cycle of chemotherapy: the date of treatment, baseline and postchemotherapy serum creatinine, magnesium and potassium levels were filled up by the principal investigator. Data were encoded in excel and analyzed using Stata version 8.3.

Statistical Analysis

Descriptive statistics utilized means and standard deviation for quantitative variables while frequencies and percentages were used for qualitative variables. To determine the difference in change of magnesium and potassium during chemotherapy, repeated measures analysis of variance was used and the Sidak multiple comparison test was used to determine which among the time points were different. Rank correlation was used to determine the correlation of the change in magnesium and potassium during chemo-cycle 3.

A Kaplan-Meier survival graph was made to show the time to development of hypomagnesemia and hypokalemia. The median time to decline was computed with the corresponding 95% confidence interval. To determine the difference in rate of development of hypomagnesemia and hypokalemia, the log rank test was used.

A logistic regression model was derived to show the association of factors with either hypomagnesemia and hypokalemia.

All statistical tests were computed at 95% level of significance, alpha=0.05.

Results

A total of 114 patients with cervical cancer who underwent at least 3 courses of weekly cisplatin chemotherapy and radiotherapy were included in the study. Table 1a shows the clinical profile of these patients. The mean age was 49.4 years and the patients were multigravid. The mean body mass index was 22.8 and this is below the cut-off for obesity (BMI³25, International Obesity Task Force)

Table 1a. Clinical profile of patients with cervical cancer undergoing weekly cisplatin and radiotherapy.

Characteristics	Mean (SD)
Age	49.4 (9.2)
Gravida	4.7 (2.7)
Parity	4.1 (2.6)
Body Mass Index	22.8 (4.0)
Body Surface Area	1.5 (0.2)

Table 1b shows the clinicopathologic profile of patients with cervical cancer undergoing weekly cisplatin and radiotherapy. One third of the patients did not have vaginal involvement while the upper third of the vagina was involved in 30 percent of the patients. The corpus uteri were normal in size in majority of patients. Majority of the patients had parametrial involvement, which was either nodular or nodular and fixed which puts them at stage IIB or IIIB. Approximately 75 percent of cervical tumors were of the squamous cell carcinoma type, with the SCCA, LCNK type still the most predominant, followed by adenocarcinoma in approximately 20 percent of patients. The clinical and pathologic profiles of patients in this study are consistent with those in the literature.

Table 1b. Clinico-pathologic profile of patients with cervical cancer undergoing weekly cisplatin and radiotherapy.

Characteristics	Frequency (Percent) N=114
Vaginal involvement	
Normal	38 (33.4)
Lower third involved	9 (7.8)
Middle third involved	13 (11.4)
Upper third involved	32 (28.1)
Fornix involved	22 (19.3)
Size of corpus uteri	
Absent	11 (9.6)
Normal	93 (81.6)
8-10 weeks	3 (2.6)
10-12 weeks	5 (4.4)
12-14 weeks	2 (1.8)
Parametrial involvement	
Left parametrium	
Normal	45 (39.5)
Nodular	36 (31.6)
Nodular and fixed	33 (28.9)
Right parametrium	
Normal	51 (44.7)
Nodular	36 (31.6)
Nodular and fixed	27 (23.7)
Histology	
SCCA	5 (4.4)
SCCA, LCK	12 (10.5)
SCCA, LCNK	66 (57.9)
SCCA, small cell	3 (2.7)
Adenocarcinoma	25 (21.9)
Adenosquamous carcinoma	3 (2.6)
Tumor stage	
IB1	18 (15.8)
IB2	8 (7.0)
IIA	5 (4.4)
IIB	39 (34.2)
IIIB	39 (34.2)
V	3 (2.6)
V-IIA	1 (0.9)
V-IIIB	1 (0.9)

The relative mean change in magnesium, creatinine and potassium was calculated from the third cycle and the first chemotherapy cycle (Table 2). This is because most of the patients did not undergo chemotherapy from the fourth cycle onward. There is a significant decrease (p value = 0.0001) in magnesium. A decrease in potassium was observed but was not statistically significant (p=0.27). Creatinine showed an increase but was likewise not statistically significant (p=0.47).

The change in magnesium level was significantly different between chemotherapy cycle 1 and cycle 3 (Table 3). All other cycles in all variables did not show significant difference.

The total number of patients who developed hypomagnesemia is 53 (46.49%). Table 4 shows the mean level of magnesium from baseline to after the 3rd cycle of chemotherapy and its relative frequency.

Figure 1 shows the correlation of the change in magnesium and potassium in chemotherapy cycle 3. There is poor correlation observed and the correlation coefficient is 8%. This means that the change in potassium is explained by only 8% of the change in magnesium.

Table 2. Relative change in magnesium, creatinine and potassium after 3 cycles of cisplatin.

Variable	Cycle1 / Mean (SD)	Cycle 2 / Mean (SD)	Cycle 3 / Mean (SD)	F value	P value
Magnesium	-17.4 / (36.6)*	-30.9 / (79.4)	-45.4 / (101.2)*	4.5	0.01
Potassium	-4.2 / (12.9)	-6.4 / (13.3)	-5.1 / (16.3)	1.3	0.27
Creatinine	10.5 / (26.7)	12.9 / (26.9)	15.7 / (29.2)	0.7	0.47

*p=0.02

Table 3. Multiple comparisons of magnesium, potassium and creatinine.

Chemotherapy Cycle	Magnesium P value	Potassium P value	Creatinine P value
Cycle 1 vs Cycle 2	0.46	0.56	0.89
Cycle 1 vs Cycle 3	0.02	0.96	0.43
Cycle 2 vs Cycle 3	0.42	0.86	0.84

Table 4. Mean magnesium level from baseline to after the 3rd cycle of chemotherapy and its frequency.

Level of magnesium	Frequency (Percent)
0.61 to 0.7 (normal)	61 (53.51)
0.51 to 0.6	29 (25.44)
0.41 to 0.5	16 (14.04)
0.3 to 0.4	5 (4.39)
<0.3	3 (2.63)

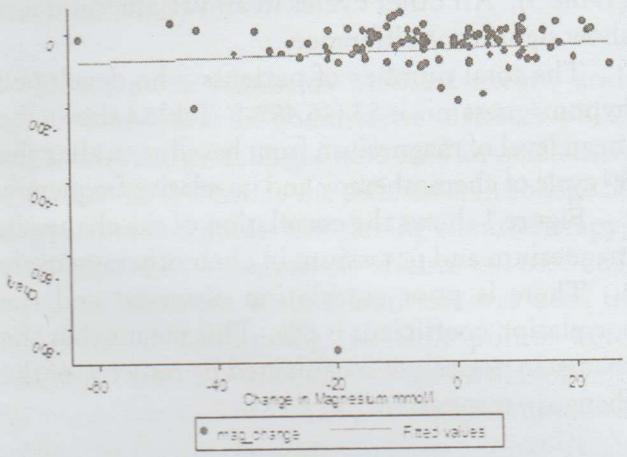

Figure 1. Correlation of change in magnesium and potassium during chemo cycle 3.

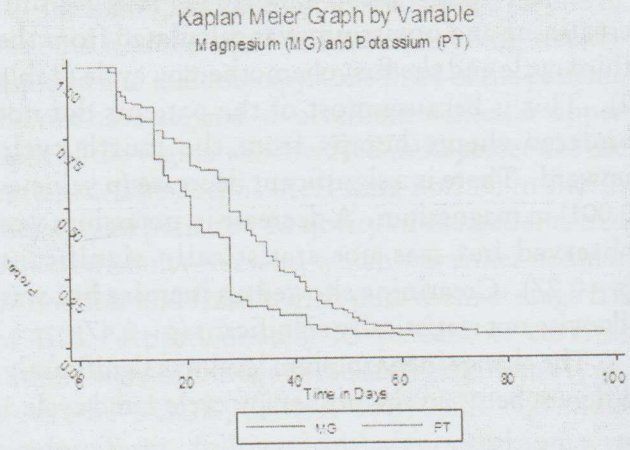

Figure 2. Kaplan-Meier graph of hypomagnesemia and hypokalemia during chemotherapy.

The median time to development of hypomagnesemia is 21 days (95% CI 19, 23) while the median time to development of hypokalemia is 28 days (95% CI 28, 30). The rate of development of hypomagnesemia is significantly (c2 = 10.52, p value = -0.012) faster compared to hypokalemia. Figure 2 shows the Kaplan-Meier graph of hypomagnesemia and hypokalemia during chemotherapy in this study.

Table 5 shows the association of different factors with either hypomagnesemia and hypokalemia. Only the cumulative dose of the chemotherapy was statistically associated with hypomagnesemia and hypokalemia. Elevated creatinine and body surface area were not significantly associated with the decline in level of magnesium and potassium.

Discussion

Since the 1999 National Cancer Institute consensus statement on the role of concurrent chemoradiation as the standard of care for cervical cancer, cisplatin has been the chemotherapeutic drug of choice as a radiosensitizer.[1] As a drug though, it carries numerous side effects, most of which have been well-characterized. Known side effects are mainly nephrotoxicity, neurotoxicity, ototoxicity, myelosuppression, as well as nausea and vomiting. Nephrotoxicity has received most attention as the major dose-limiting factor.[2]

When excreted by the kidneys, cisplatin exerts a direct damage to renal tubules. There is gradually declining rates of proximal reabsorption of sodium

Table 5. Association of factors with magnesium and potassium decline.

Variable	Odds ratio	P value	95% Confidence interval
Magnesium			
Cumulative dose of chemotherapy	1.01	0.007	1.002, 1.01
Elevated creatinine	1.38	0.50	0.54, 3.52
Body surface area	1.01	0.84	0.89, 1.14
Potassium	1.01	0.001	1.005, 1.02
Cumulative dose of chemotherapy	0.59	0.26	0.24, 1.45
Elevated creatinine	1.00	0.97	0.89, 1.12
Body surface area			

and water. Evidently any drug causing tubular [illegible] at the sites of tubular reabsorption of magnesium would be expected to influence magnesium homeostasis.[2]

Previous studies have looked into cisplatin-induced hypomagnesemia[4,5,6,7,8,10,12,13,16,17]. Table 6 gives a summary of the results of these studies. In this study, the relative mean change in magnesium was calculated from the third cycle and the first chemotherapy cycle. There is a significant decrease (p value = 0.001) in the level of serum magnesium. The incidence of hypomagnesemia reported is 46.49%, a value that is relatively low compared to most other studies (incidence 29-100%). This is because very few patients continued chemotherapy until the sixth cycle. Most patients received only 3 cycles of chemotherapy. Since the drop in magnesium levels increases with each cycle, the results presented in this study may underestimate the total effects of cisplatin.

Table 6. Summary of studies investigating cisplatin-induced hypomagnesemia.

Author	Regimen	Diagnosis	# of Patients	Dose of Cisplatin	Duration of Treatment	Incidence of hypomagnesemia	Hypomagnesemia related to
[illegible] et al. [illegible]	Cisplatin + miscellaneous	Squamous cell carcinoma	28	50-120mg/m^2 (3-4 weekly)	1-4 cycles (average 2,9, total 82)	100%	Total dose (P<0.001, r=0.66)
[illegible] et al. 1979[4]	Cisplatin based	Miscellaneous	44	70mg/m^2 (3 weekly)	1-10 cycles (ave. 4.7)	70%	-
[illegible] et al. 1982[6]	Cisplatin based	Nonseminomatous GCT	29	Not specified	Not specified	76%	-
[illegible] et al. 1982[23]	Cisplatin + miscellaneous	Miscellaneous	14	30-50mg/m^2	Single dose	87%	-
Stewart, et al. 1985[7]	Cisplatin + Doxorubicin	Ovarian + uterine cancers	17	50mg/m^2 (4weekly)	4-18 cycles (ave 12.7)	88%, 53%	-
Vogelzang, et al. 1985[22]	Cisplatin, Vinblastine, Bleomycin	Metastatic germ cell cancer	30	100mg/m^2 (3weekly)	4-6 cycles (total 157)	87%	Total dose (P0.001)
Buckley, et al. 1985[5]	Cisplatin based	Metastatic lung cancer	66	50 mg/m^2 (4 and 8 weekly)	Up to 6 cycles	76%	Total dose (P0.001), r = 0.32) and dose interval
Bell, et al. 1985[12]	Cisplatin based	Miscellaneous	50	50-100 mg/m^2 (3 weekly)	5 cycles	100%	Dose and total dose
Ashraf, et al. 1983[23]	Cisplatin + miscellaneous	Gynecological Cancers	57	50-100 mg/m^2 (4 weekly)	2-16 cycles (average 6)	72%	Total dose (P0.01,R=-0.75)
Ariceta, et al. 1997[10]	Cisplatin + miscellaneous	Miscellaneous	22	Not specified	Not specified	45%	Total dose (P0.001,R=-0.36 [not specified]
Hayes, et al. 1979[24]	Cisplatin	Miscellaneous	16	90 mg/m^2 3weekly or 30 mg/m^2 weekly	Not specified	94%	-
Abbasciano, et al. 1991[25]	Cisplatin + Etoposide	Lung cancer	16	100 mg/m^2	Single dose	Magnesium level lower than baseline after 7 days (P0.05)	
Sartori, et al. 1993[16]	Cisplatin + miscellaneous	Miscellaneous	22	50-100 mg/m^2	Up to 6 cycles	Decrease of 21.7% after 6 cycles	Total dose (P0.05 after second, P0.001 after third cycle)
Skinner, et al. 1998[26]	Cisplatin based	Miscellaneous	35	60-200 mg/m^2	2-8 cycles (average 5)	29%	Dose
Blachley, et al. 1981[27]	Not specified	Not specified	25	Not specified	Not specified	56%	-
Markman, et al. 1991[17]	Cisplatin based	Ovarian	26	Not specified	1-8 cycles (average 3)	73%, 27%, <0.5 mmol/l	-
Hodgkinson, et al. 2006[13]	Cisplatin based	Not specified	214	Average of 60mg/m^2	1-8 cycles (average 2)	43%	Total dose, dose per cycle

The degree of hypomagnesemia in other studies was mild at grade 1 National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTC toxicity grading) in 75 percent of cases and with a progressive fall in magnesium levels with each successive cycle.[4,18,19] The degree of hypomagnesemia in this study was mild at grade 1 NCICTC toxicity grading in 55 percent of patients, moderate at grade 2 in 30 percent and severe to life-threatening in 15 percent of patients. There is progressive decline in serum magnesium levels with each successive cycle with a decrease of 17.4% from the baseline after the first cycle, 30.9% after the second cycle and 45.4% after the third cycle. This decrease is statistically significant. Although not demonstrated in this study due to the small number of patients who received the fourth to the sixth cycle, it can be surmised that the administration of more chemotherapy cycles will lead to further decline in the levels of the serum magnesium and the drop further increases with each cycle.

Based on previously reported studies, the number of cycles, which is reflective of the cumulative dose, was the major contributing factor to the severity of hypomagnesemia[5,8,10,11,20]. Ariceta, et al.[10] found, that the minimal cumulative dose required to induce hypomagnesemia was 300 mg/m^2 of cisplatin. Martin, et al.[11] suggested that most patients who receive cumulative doses of cisplatin in excess of 400 mg/m^2 will develop some degree of hypomagnesaemia. It is frequently noted after only two or three cycles of therapy.[13] Among the variables considered in this study, the cumulative dose of chemotherapy was the only contributing factor to the incidence of hypomagnesemia. There was a statistically significant decrease in the level of serum magnesium between cycle 1 and cycle 3 (P value 0.02). This would suggest a minimal cumulative dose of only 120 mg/m^2 of cisplatin needed to induce hypomagnesemia.

There was an increasing trend in the level of creatinine with each successive chemotherapy cycle but the increase was not statistically significant. The level of creatinine was also not significantly associated with the decline in the magnesium level. This supports the fact the Cisplatin nephrotoxicity may lead to increased excretion of magnesium even before renal function becomes affected.[2]

The body surface area was another factor analyzed as this would represent the absolute dose of cisplatin given per cycle of chemotherapy. It was not found to be significantly associated with the decline in the level of magnesium.

In patients with hypomagnesemia, a six-fold increase in the prevalence of hypokalemia has been reported.[2] An attempt to look into the association between hypomagnesemia and hypokalemia was done in this study. Although there was a decline in the level of serum potassium with successive cycles of chemotherapy, it was not statistically significant. There is poor correlation observed between the change in the level of magnesium and potassium with a correlation coefficient of only 8%. This means that the change in potassium is explained by only 8% of the change in magnesium.

The median time to development of hypomagnesemia is 21 days (95% CI 19, 23) while the median time to development of hypokalemia is 28 days (95% CI 28, 30). The rate of development of hypomagnesemia is significantly ($c2 = 10.52$, p value = -0.012) faster compared to hypokalemia.

Conclusion

This study is the first one conducted with regards the serum magnesium and potassium levels of cervical cancer patients receiving cisplatin chemotherapy at 40 mg/m^2 weekly, a dose given as a radiosensitizer and a dose that is lower than those analyzed in other studies. It is noteworthy to point out that even at such a low dose of cisplatin, hypomagnesemia still developed. The cumulative dose of the chemotherapeutic agent is the only factor noted to significantly affect the level of decline in serum magnesium levels. In this study, a minimal cumulative dose of only 120 mg/m^2 of cisplatin is needed to induce hypomagnesemia.

There is a decreasing trend in the level of potassium with each successive chemotherapy cycle but this was not statistically significant. Contrary

studies, there is poor correlation between and hypomagnesemia.

Recommendation

levels should be routinely measured cervical cancer patients undergoing weekly chemotherapy as a radiosensitizing agent. clinical features of magnesium depletion are ranging and the condition can be difficult to . The symptoms and signs can be variable may be attributed to the underlying malignancy the treatment instituted. It is therefore not surprising that no studies have been able to objectively by clinical parameters which hypomagnesemia should be considered the for supplementation. This is one area of that can be looked into. It seems reasonable to avoid hypomagnesemia and consequently possible complications associated with it. Determination of the ideal regimen of supplementation that will be fully protective against hypomagnesemia caused by cisplatin is another area of research.

References

1. Serkies K, Jassem J. Concurrent weekly cisplatin and radiotherapy in routine management of cervical cancer: a report on patient compliance and acute toxicity. Int J Rad Oncol Biol Phys 2004; 60(3): 814-821.
2. Lajer H, Daugaard G. Cisplatin and hypomagnesemia. Cancer Treatment Reviews 1999; 25: 47-58.
3. Weisinger JR, Bellorin-Font E. Magnesium and phosphorus. Lancet 1998; 352: 391-396.
4. Schilsky RL, Anderson T. Hypomagnesaemia and renal magnesium wasting in patients receiving cisplatin. Ann Intern Med 1979; 90: 929-931.
5. Buckley JE, Clark VL, Meyer TJ and Pearlman NW. Hypomagnesemia after cisplatin combination chemotherapy. Arch Intern Med 1984; 144: 2347-2348.
6. Schilsky RL, Barlock A, Ozols RF. Persistent hypomagnesemia following cisplatin chemotherapy for testicular cancer. Cancer Treat Rep 1982; 66: 1767-1769.
7. Stewart AF, Keating T and Schwartz PE. Magnesium homeostasis following chemotherapy with cisplatin: A prospective study. Am J Obstet Gynecol 1985; 153: 660-665.
8. Lam M and Adelstein DJ. Hypomagnesemia and renal magnesium wasting in patients treated with cisplatin. Am J Kidney Dis 1986; 8: 164-169.
9. Safirstein R, Winston J, Goldstein M, et al. Cisplatin nephrotoxicity. Am J Kidney Dis 1986; 5: 356-367.
10. Ariceta G, Rodriguez-Soriano J, Vallo A and Navajas A. Acute and chronic effects of cisplatin therapy on renal magnesium homeostasis. Med Pediatr Oncol 1997; 28: 35-40.
11. Martin M, Diaz-Rubio E, Casado A, et al. Intravenous and oral magnesium supplementations in the prophylaxis of cisplatin-induced hypomagnesemia. Am J Clin Oncol 1992; 15: 348-351.
12. Bell DR, Woods RL and Levi JA. Cis-diamminedichloroplatinum-induced hypomagnesemia and renal magnesium wasting. Eur J Cancer Clin Oncol 1985; 21: 287-290.
13. Hodgkinson E, Neville-Webbe HL. Magnesium depletion in patients receiving cisplatin-based chemotherapy. Clin Oncol 2006; 18: 710-18.
14. Whang R, Whang DD, Ryan MP. Refractory potassium repletion. A consequence of magnesium deficiency. Arch Intern Med 1992; 152(11): 2346.
15. Rodriguez M, Solanki DL, Whang R. Refractory potassium repletion due to cisplatin-induced magnesium depletion. Arch Intern Med 1989; 149 (11): 2592-2594.
16. Sartori S, Nielsen I, Tassinari D, et al. Changes in intracellular magnesium concentrations during cisplatin chemotherapy. Oncology 1993; 50: 230-234.
17. Markman M, Rothman R, Reichman B, et al. Persistent hypomagnesemia following cisplatin chemotherapy in patients with ovarian cancer. J Cancer Res Clin Oncol 1991; 117: 89-90.
18. Evans TRJ, Harper CL, Beveridge IG, Wastnage R and Mansi JL. A randomized study to determine whether routine intravenous magnesium supplements are necessary in patients receiving cisplatin chemotherapy with continuous infusion 5-fluorouracil. Eur J Cancer 31A: 174-178.
19. Winkler CF, Mahr MM, DeBandi H. Cisplatin and renal magnesium wasting. Ann Intern Med 1979; 91: 502-503.
20. Vokes EE, Mick R, Vogelzang NJ, Geiser R and Douglas F. A randomized study comparing intermittent to continuous administration of magnesium aspartate hydrochloride in cisplatin-induced hypomagnesemia. Br J Cancer 1990; 62: 1015-1017.
21. Bitran JD, Desser RK, Billings AA, et al. Acute nephrotoxicity following cis-dichlorodiammine-platinum. Cancer 1982;49:1784-1788.
22. Vogelzang NJ, Torkelson JL, Kennedy BJ. Hypomagnesemia, renal dysfunction, and Raynaud's phenomenon in patients treated with cisplatin, vinblastine, and bleomycin. Cancer 1985; 56: 2765-2770.
23. Ashraf M, Scotchel PL, Krall JM, et al. Cis-platinum-induced hypomagnesaemia and peripheral neuropathy. Gynecol Oncol 1983; 16: 309-318.
24. Hayes FA, Green AA, Senzer N, et al. Tetany: a complication of cis-dichlorodiammineplatinum (II) therapy. Cancer Treat Rep 1979; 63: 547-548.

25. Abbasciano V, Mazzotta D, Vecchiatti G, et al. Changes in serum, erythrocyte, and urinary magnesium after a single dose of cisplatin combination chemotherapy. Magnes Res 1991; 4: 123-125.
26. Skinner R, Pearson ADJ, English MW, et al. Cisplatin dose rate as a risk factor for nephrotoxicity in children. Br J Cancer 1998; 77: 1677-1682.
27. Blachley JD, Hill JB. Renal and electrolyte disturbances associated with cisplatin. Ann Intern Med 1981; 95: 628-632.

Gestational Ovarian Choriocarcinoma: A Case Report

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Primary ovarian choriocarcinoma represents less than 5 percent of all ovarian cancers and its incidence is one in 369 million pregnancies. It can be classified as gestational and non-gestational type.

In this case report, a 37-year old multigravid presented with amenorrhea, vaginal spotting and abdominal pain similar to ectopic pregnancy. The patient underwent exploratory laparotomy and salpingo-oophorectomy for an intraoperative finding of ovarian mass. Histopathologic report showed ovarian choriocarcinoma.

Clinical picture and histologic findings that may help differentiate the two subtypes of choriocarcinoma are discussed. Differentiating the two types of ovarian choriocarcinoma is important for therapeutic and prognostication purposes.

Key words: choriocarcinoma, ovarian choriocarcinoma, gestational trophoblastic neoplasia

Primary ovarian choriocarcinoma is a rare neoplasm and has two subtypes, the gestational and the nongestational types. Differentiating the two subtypes is clinically important due to the difference in treatment and prognosis. Diagnosis is usually based on clinical presentation and histological findings. Newer technology like DNA analysis using DNA flow cytometry and restriction fragment pleomorphism may be used to confirm the diagnosis.

There are several theories on the development of non-uterine primary gestational choriocarcinoma (e.g. fallopian tube, ovary): 1) it can arise from an ovarian pregnancy or as an ectopic chorioepithelioma, 2) the ovary maybe a site of metastasis but the primary genital tumor disappeared and the ovary is mistakenly identified as the primary organ, and 3) the trophoblasts during the normal or molar pregnancy are transported to the secondary organ and underwent malignant transformation.[12]

* Finalist, 7th SGOP Interesting Case Paper Contest, September 2008.

The Case

JF is a 37 year-old multigravid who consulted this institution for vaginal bleeding. Her past and family medical histories are unremarkable. She is a household helper with no vices. Her first coitus was at the age of 17 years and has had two non-promiscuous sexual partners. She has not used any artificial contraception. She denied history of sexually transmitted disease.

Her menarche was at the age of 14 years. Subsequent menses occurred at regular monthly intervals lasting for 3-5 days, soaking 2-3 sanitary pads per day. She had no dysmenorrhea. Her last normal menstrual period was on July 21, 2006 giving her an amenorrhea of 12 weeks and 1 day. She is a gravida 6, para 5 (5005) with all pregnancies carried to term and delivered unremarkably by spontaneous vaginal delivery at home attended by a traditional birth attendant. The last pregnancy was delivered in 1999.

The history of the present illness started two weeks prior to admission, when she had vaginal spotting staining 1 napkin per day associated with intermittent hypogastric pain. One week prior to admission, due to the persistence of symptoms, she consulted a private clinic where a positive pregnancy test was elicited. Pelvic ultrasound revealed a left complex mass, probably an ectopic gestation. She was referred to this institution for management. She presented at the OB Admitting Section with stable vital signs. Her blood pressure was 110/80 and she had pink palpebral conjunctivae with full pulses. Her chest and heart findings were normal. She had normoactive bowel sounds, with direct tenderness on the left lower quadrant and no palpable mass. On internal examination, she had normal external genitalia, parous vagina, cervix closed, smooth, with wriggling tenderness and small corpus. There was a 6 cm x 6 cm cystic mass superior and to the left of the uterus. Rectovaginal examination findings were essentially normal. The admitting diagnosis was ectopic pregnancy.

Transvaginal ultrasound showed an anteverted uterus with smooth contour and hyperechoic endometrium which measured 0.4 cm. No gestational sac was seen. The right ovary was converted into a thin-walled multi-loculated cyst that measured 4.9 cm x 3.3 cm x 3.1 cm with low level echo fluid within. The capsule measured 0.2 cm. The left ovary was not visualized. Posterolateral to the uterus is a complex heterogenous mass that measured 8.4 cm x 6.9 cm x 6.6 cm (Figure 1). There was minimal low level fluid in the cul de sac. The sonographic impression was Left adnexal mass to consider ectopic pregnancy with minimal hemoperitoneum. The plan was to do exploratory laparotomy, left salpingectomy with right contralateral tubal ligation under regional anesthesia.

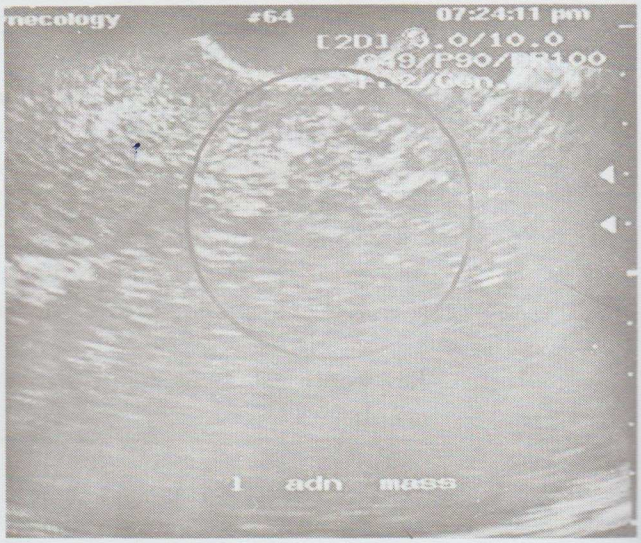

Figure 1. Transvaginal pelvic ultrasound showing the left ovary converted into a multiloculated cyst.

On exploratory laparotomy, there was 200 cc hemoperitoneum. Superior to the uterus was a complex cystic mass that measured 10 cm x 10 cm x 8 cm with smooth and intact capsule. The adnexal mass was attached to the uterus via the utero-ovarian ligament. Its capsule measured 0.1 cm. There was no grossly identifiable normal ovarian tissue. The left fallopian tube was grossly normal and lay medial and inferior to the adnexal mass (Figure 2). The uterus and right fallopian tube were grossly normal. The right ovary was cystic and measured 4 cm x 3 cm x 3 cm. The subdiaphragmatic surface, liver,

spleen, kidneys, small and large omentum and appendix were smooth and normal. Cut section of the left adnexal mass revealed placenta like-tissue (Figure 3). The intraoperative assessment was ruptured ectopic pregnancy, left ovary, rule out choriocarcinoma. She underwent left salpingo-oophorectomy, right tubal ligation and evacuation of hemoperitoneum. The estimated blood loss was 800 cc. She tolerated the procedure well.

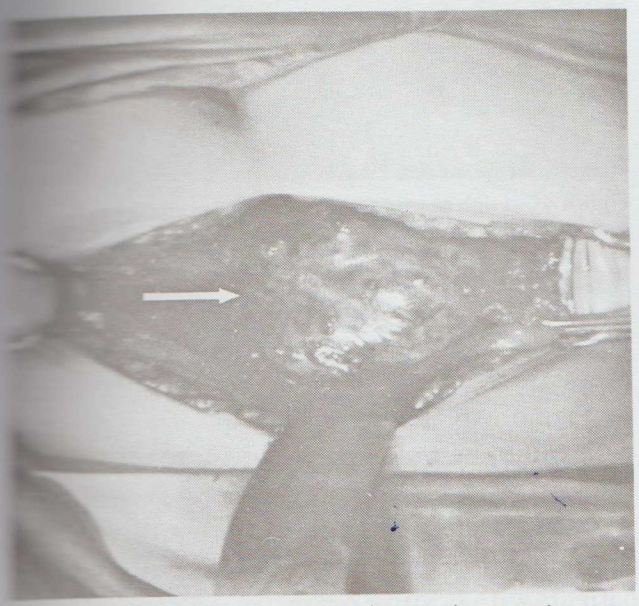

Figure 2. Exploratory laparotomy showing hemoperitoneum. The left ovarian mass is 10 cm x 10cm x 8cm complex cystic mass with smooth capsule (arrow).

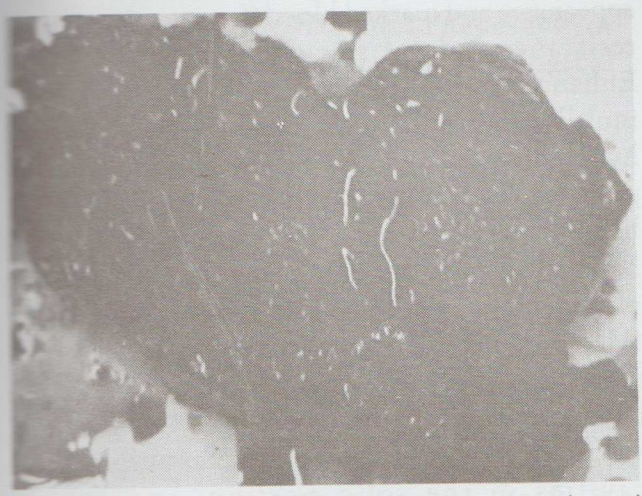

Figure 3. Cut section of the left ovarian mass showed hemorrhage and necrosis.

The preoperative serum BhCG was 268,733 mIU/mL. On the second postoperative day, histopathology report revealed "Left ovarian mass, choriocarcinoma; left fallopian tube and segment of right fallopian tube were unremarkable". She was referred to the Trophoblastic Disease Service with the assessment of Choriocarcinoma Stage I: high risk. The plan was to give multi-agent chemotherapy. However, before further treatment could be initiated, she went home against medical advice. She was lost to follow-up until the time of this write-up.

Discussion

Primary choriocarcinoma of the ovary is a rare but aggressive neoplasm. It accounts for less than 5 percent of all ovarian cancers and its incidence is one in 369 million pregnancies.[1,2] Choriocarcinoma of the ovary is classified into two groups: 1) gestational choriocarcinoma, and 2) non-gestational choriocarcinoma. Gestational choriocarcinoma is further categorized as a primary gestational choriocarcinoma associated with ovarian pregnancy, or as metastatic choriocarcinoma from a primary gestational choriocarcinoma arising from other parts of the genital tract, mainly the uterus. On the other hand, non-gestational choriocarcinoma is a germ cell tumor differentiating toward trophoblastic structures.[3,4] In this institution, there are only six reported cases of primary ovarian choriocarcinoma to date, the first was on 1953 by Dr. Acosta-Sison.[6]

The clinical findings in both types of ovarian choriocarcinoma are non-specific. The patients present with amenorrhea, vaginal spotting and abdominal pain similar to ectopic pregnancy, as seen in the index case. Some patients present with a palpable mass. The elevated β-HCG causes positive pregnancy test and isosexual precocity in young girls and irregular vaginal bleeding in adults.[11]

Grossly, ovarian choriocarcinoma are large, solid, unilateral tumors with necrosis and hemorrhage. Histologically, both non-gestational and gestational choriocarcinoma of the ovary share the same appearance.[1] Tumors are composed of clusters of

cytotrophoblasts separated by streaming masses of syncytiotrophoblasts resulting in a characteristic dimorphic plexiform pattern (Figure 4).

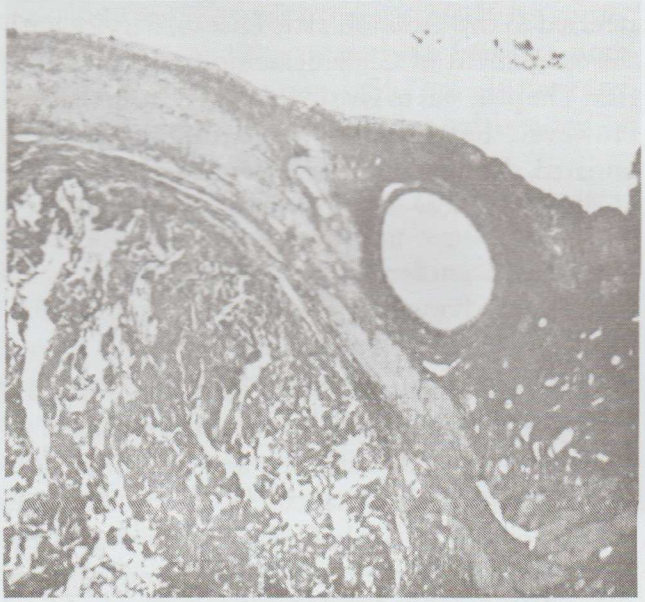

Figure 4A. Low power view of the gestational ovarian choriocarcinoma showing clusters of cytotrophoblast and syncytiotrophoblast.

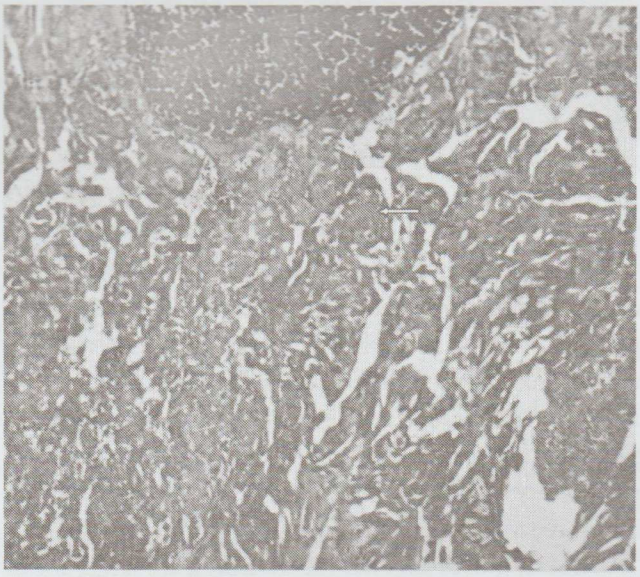

Figure 4B. Another low power magnification of the tumor showing dimorphic pattern of cytotrophoblast (dark arrow) and syncytiotrophoblast (white arrow).

*note the absence of other germ cell elements

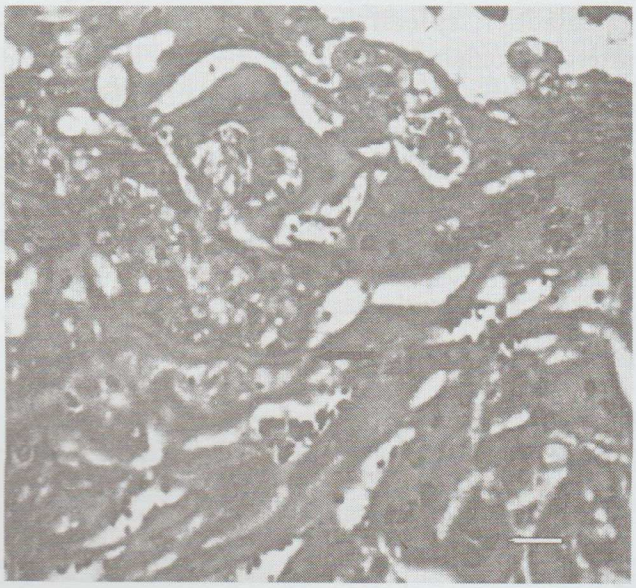

Figure 4C. High power view: cytotrophoblast (dark arrow) and syncytiotrophoblast (white arrow).

Imaging studies which include ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT) scan are not specific. They only determine the presence of pelvic mass and if the said mass is malignant or not. Transvaginal ultrasound, like in this case, can be used to eliminate the possibility of an intrauterine pregnancy in patients with positive pregnancy test or those with uterine involvement. Pelvic ultrasound with Doppler study of ovarian choriocarcinoma shows internal echo of the mass with solid and cystic appearance and marked blood flow signals with low resistance index [8] suggestive of malignancy. Enhanced computed tomography (CT) revealed a multilocular cystic mass containing a peripheral hyperenhanced area. A peripheral irregular solid portion containing small cavities filled with hemorrhagic fluid and a large central portion with hemorrhagic and necrotic changes were suggestive of malignancy on Magnetic Resonance Imaging (MRI). Bazot, et al. reported a case in which imaging study was used to diagnose ovarian choriocarcinoma. In this report, presence of a highly vascularized mass, the presence of multiple cystic cavities in the solid portion, and central hemorrhagic and necrotic changes with high HCG

and an empty uterus are suggestive of ovarian choriocarcinoma.[15]

Gestational choriocarcinoma behaves differently from its non-gestational counterpart and differentiating the two is clinically important for therapeutic and prognostication purposes. The non-gestational type requires more aggressive therapy and has worse prognosis than the gestational type.[1,7,8,9] It is also resistant to chemotherapy.

How can we differentiate one from the other? There are clinical features that may help in the diagnosis of gestational or non-gestational choriocarcinoma.

Age may aid the diagnosis. Non-gestational choriocarcinoma is seen in the premenarchal or postmenopausal age group and virgins.[4] Dilemma arises when ovarian choriocarcinoma is seen in a patient in the reproductive age group, but which is not the gestational variant.

While human chorionic gonadotrophin (β-HCG) is elevated in both gestational and non-gestational choriocarcinoma, the β-HCG level is usually lower in the latter.[10] This is because the cell population in non-gestational choriocarcinoma consists not only of trophoblasts but also other germ cells that do not produce HCG.

Clinically, Ozaki, et al. diagnosed a case of non-gestational choriocarcinoma based on the following clinical features: 1) the long interval from the antecedent pregnancy, 2) the relatively low β-HCG level, 3) the lack of evidence of intrauterine trophoblastic disease, ovarian theca luteum cyst, or corpus luteum cyst on histopathological examination, and 4) the poor prognosis.[8]

Non-gestational ovarian choriocarcinoma is usually associated with other germ cell tumors such as immature teratoma, endodermal sinus tumor, embryonal carcinoma, and dysgerminoma. Though remote, gestational choriocarcinoma may also metastasize to a germ cell tumor of the ovary. The fact is, in the presence of other germ cell elements in the tumor, non-gestational choriocarcinoma is the more likely diagnosis. Also, the presence of other tumor markers like alpha-feto protein, which suggest presence of other germ cell tumors, may aid clinch the diagnosis of non-gestational choriocarcinoma.

Diagnostic dilemma occurs when tumors are purely choriocarcinomatous and devoid of other germ cell elements and found in patients within reproductive age group like the index case, differentiation between the two subtypes by histology alone may be difficult. In humans, unlike in monkeys, the two types of choriocarcinoma cannot be differentiated using immunohistochemistry or electron microscopy.[16,17]

In the index case, the diagnosis is more likely the gestational type of ovarian choriocarcinoma for the following clinical features: 1) the patient is in the reproductive age, 2) her β-HCG was markedly increased, and 3) on histology, only trophoblastic cells, cytotrophoblasts and syncytiotrophoblasts, were seen. There were no other germ cell tumors identified. Deoxyribonucleic acid (DNA) analysis could have confirmed the diagnosis.

Before the 1990s, reported cases of primary ovarian choriocarcinoma are differentiated between gestational and non-gestational types by clinical features mentioned above. However, with the aid of newer technology like DNA analysis, the previously diagnosed non-gestational type was confirmed to be a gestational variant or vice versa[5].

With DNA analysis, the genetic origin of these tumors can be identified. The human genome contains many DNA sequences that occur repeatedly. These repeat sequences may be simple or tandem arrays of complex repeats. DNA polymorphism analysis is performed using tissue from the tumor and matching non-neoplastic tissue of the patient and her partner or spouse to determine non-gestational or gestational origin of the tumor. Koo, et al. described an example of DNA analysis. In this process, the tumor is manually microdissected from the formalin-fixed, paraffin-embedded tissues and DNA is prepared by proteinase K digestion followed by phenol/chloroform extraction.[4] Microsatellite markers from the prepared DNA are amplified using polymerase chain reaction (PCR) to determine allelic size. When all tested microsatellite markers had identical DNA profile with the same allelic sizes between the tumor and the non-neoplastic tissue of the patient, it will be confirmed that the tumor is a non-gestational

variant. But when the markers are similar between the spouse and the tumor, gestational choriocarcinoma is confirmed. Fisher, et al. employed a different method using Y-chromosome-specific probe and locus-specific mini-satellite probes, which identify highly polymorphic restriction fragment length polymorphisms (RFLP) of the DNA.[5] Presence of Y-chromosome-specific sequences, identified by the Y-chromosome-specific probe in a tumor would indicate a gestational type of tumor. RFLPs, which are identified by locus-specific mini-satellite probes, are different bands with varying allelic size. Presence of RFLPs which are similar between the tumor and the spouse indicates that the tumor is gestational in origin.

Is this primary ovarian or metastatic to the ovary from a possible uterine choriocarcinoma?

Primary ovarian choriocarcinoma is associated with ovarian pregnancy. For ovarian pregnancy, Spiegelberg created the following criteria: 1) the gestational sac must occupy the normal site of the ovary; 2) the gestational sac must be connected to the uterus by the ovarian ligament; 3) ovarian tissue must be present within the wall of the sac; 4) the ipsilateral fallopian tube including its fimbriated end must be normal in appearance and completely separated from the gestational sac.[12] In gestational ovarian choriocarcinoma, no gestational sac should be present but the tumor should fulfill the rest of the criteria. In the index case, the tumor occupied the normal site of the ovary, the tumor is connected to the uterus by the ovarian ligament, and the fallopian tube is normal.

Gestational choriocarcinoma spreads hematogenously whereas non-gestational choriocarcinoma spreads contiguously to the adjacent organs and abdominal peritoneum, through blood vessels and lymphatics. Like other malignant germ cell tumors, complete surgical staging is necessary in non-gestational choriocarcinoma. Non-gestational choriocarcinoma is generally resistant to chemotherapy. In the gestational type, chemotherapy and adjunctive surgery are mainstays of treatment.

Another problem in this case is the application of the FIGO anatomic staging. Most choriocarcinomas arise in the uterus and lesions elsewhere are often metastatic in nature. In the FIGO anatomic staging where the uterus is the primary organ, gestational trophoblastic tumor involving the adnexa is assigned a Stage II. However, in this case, since there is no uterine focus and no other organs are involved, the appropriate anatomic stage is Stage I.

Like most cancers, prognosis depends on the stage of disease at the time of diagnosis. Unlike other cancers, certain clinical factors significantly affect success of treatment. The combined FIGO-WHO Risk Factor Scoring System (Table1) considers both the extent of disease and the clinical factors that influence prognosis. The index case is categorized as high risk with a numerical score of 12. A high risk choriocarcinoma case means that her tumor is predicted to respond poorly to single agent chemotherapy so that at the outset she should receive multi-agent chemotherapy. The score of 12 was culled from the following prognostic factors: 1) the patient is 37 years old which corresponded to a score = 0, 2) her antecedent pregnancy was a term pregnancy with a score = 2, 3) the pregnancy interval between the last delivery in 1999 and the choriocarcinoma is 7 years and scored 4, 4) the preoperative β-HCG is 268,733 mIU/ml which scored 4, and 5) the size of the largest tumor is 10 cm x 10 cm x 8 cm which is given a score = 2. The total score is 12. Numerical scores 7 or greater are high risk while scores 6 or less are considered low risk.

Although the patient is in Stage 1, the plan was to give multi-agent chemotherapy. The intensive chemotherapy was recommended not only because she is a high risk patient but also due to the histological diagnosis of choriocarcinoma which has a graver prognosis compared to other types of gestational trophoblastic neoplasia. Additionally, there is the possibility, no matter how small, that this case is actually metastatic - in which she is in stage III disease.

Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, and Oncovin (EMA-CO) make up the currently recommended protocol for metastatic high risk disease. This regimen is reputed

Table II. Distribution of patients according to nodal involvement.

Prognostic factor	FIGO-WHO Risk Factor Scoring System Score 0	1	2	4
Age (Years)	<40	>40		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	
Pregnancy interval (months)	< 4	4 - 6	7 - 12	> 12
BHCG (mIU/ml)	< 1,000	1000- < 10,000	10,000- < 100,000	> 100,000
Largest tumor	<3	3- < 5	> 5cm	
Site of metastasis		Spleen, kidney	GI tract	Liver, Brain
# of metastasis		1-4	5-8	>8
Prior chemotherapy			Single agent	2 or more agents

every week (EMA on days 1-3, CO on day 8, EMA on days 15-17, CO on day 22, etc) until β-HCG goes down to normal level of 5 miu/ml.

After the normal β-HCG titer, three (3) consolidation courses are given to complete the treatment. After completion of treatment, the patient enters biochemical remission when her three consecutive weekly serum β-HCGs are normal. Her serum β-HCG is then measured every month for six months, then every two months for the next six months, and every three months on the second year of follow-up. She is monitored every six months thereafter.

No additional surgery is recommended for the index case since the tumor was completely removed. In choriocarcinoma, conservative surgery may suffice especially when preservation of fertility is desired. Salvage surgery may be done for chemo-resistant focus of disease.

Even with advanced disease, the prognosis for choriocarcinoma is better compared to other cancers stage for stage. The tumor responds well to intensive chemotherapy and adjuvant surgery and radiation. Non-metastatic choriocarcinoma has a cure rate of almost close to 100%. Depending on site of involvement, prognosis is in the range of 70-80% for stage II and III disease, and 30-50% for stage IV disease. Women with intact uteri and who have had choriocarcinoma can expect normal pregnancy outcomes.

Summary and Conclusion

In summary, a case of a 37 year old with a two-week history of vaginal spotting and hypogastric pain was initially diagnosed as ectopic pregnancy. Exploratory laparotomy with left salpingo-oophorectomy and evacuation of hemoperitoneum were done. The histopathological report revealed ovarian choriocarcinoma. The clinical presentation and histological findings point to gestational ovarian choriocarcinoma as the more likely diagnosis. Additionally, she has stage I high risk disease. Although gestational ovarian choriocarcinoma offers a better prognosis compared to the non-gestational variant, this patient still needed to undergo intensive chemotherapy with the EMACO protocol. It is unfortunate that this patient refused further treatment.

In patients who present with signs and symptoms of ectopic pregnancy, ovarian choriocarcinoma should be included as a differential diagnosis.

References

1. Corakci A, Ozeren S, Ozkan S, et al. Pure non-gestational choriocarcinoma of ovary. Arch Gynecol Obstet 2005; 271: 176–177.
2. Axe S, Klein V, Woodruff D. Choriocarcinoma of the ovary. Obstet Gynecol 1985; 66 (1): 111-114.
3. Kurman RJ. Blaustein's Pathology of the Female Genital Tract. 5th edition. Springer-Verlag 2002.
4. Koo H, Choi J, Kim K, et al. Pure non-gestational choriocarcinoma of the ovary diagnosed by DNA polymorphism analysis. Pathol Int 2006; 56: 613–616.
5. Fisher R, Newlands E, Jeffreys A, et al. Gestational and non-gestational trophoblastic tumors distinguished by DNA analysis. Cancer 1992; 69 (3): 839-844.
6. Germar-Martinez G. Non-gestational choriocarcinoma. Phil J Obstet Gynecol 1985; 9(3): 205-216.
7. Balat O, Kutlar I, Ozkur A. Primary pure ovarian choriocarcinoma mimicking ectopic pregnancy: a report of fulminant progression Tumori 2004; 90: 136-138.
8. Ozaki Y, Shindoh N, Sumi Y, et al. Choriocarcinoma of the ovary associated with mucinous cystadenoma. Radiation Medicine 2001; 19 (1): 55–59.
9. Lorigan P, Grierson A, Goepel J. Gestational choriocarcinoma of the ovary diagnosed by analysis of tumour DNA. Cancer Letters 1996; 104: 27-30.
10. Shetty S, Lobo F, Shetty M. Post-mortem diagnosis of gestational choriocarcinoma –A case report . JIAFM 2007; 29(4): 59-61.
11. Roghaei M, Rezaei F, Manzuni P. A pure non-gestational choriocarcinoma of the ovary. Journal Res Med Sci 2007; 12 (5): 269-270.
12. Benjamin F, Rorat E. Primary gestational choriocarcinoma of the ovary. Am J Obstet Gynecol 1978; 131 (3): 343-345.
13. Patton G Jr., Goldstein D. Gestational choriocarcinoma of the tube and ovary. Surg Gynecol Obstet 1973; 137: 608-612.
14. Dekel A, Van Iddekinge B, Isaacson C, et al. Primary choriocarcinoma of the fallopian tube. Report of a case with survival and postoperative delivery. Review of the literature. Obstet Gynecol Surv 1986; 41 (3): 142-147.
15. Bazot M, Cortez A, Sananes S, et al. Imaging of pure primary ovarian choriocarcinoma. Am J Roent 2004; 182: 1603-1604.
16. Farman C, Benirschke K, Horner M, et al. Ovarian choriocarcinoma in a rhesus monkey associated with elevated serum chorionic gonadotropin levels. Veterinary Pathology 2005; 42: 226–229.
17. Vance R, Geisinger K. Pure non-gestational choriocarcinoma of the ovary report of a case. Cancer 1985; 56: 2321-2325.

Ovarian Malignancy in Pure Gonadal Dysgenesis (Swyer Syndrome): A Case Report*

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The Case

B.E., a 28 year old, female, single, nulligravid, was referred to the Gynecology Service for co-management of abdominal pain and enlargement.

The patient's past medical, personal and social histories are unremarkable. She is the eldest among siblings of six, with four sisters and a brother. Two sisters have regular menstrual cycles and two other sisters have primary amenorrhea.

The patient was seen by a private gynecologist at age 14 for primary amenorrhea. A transrectal ultrasound was done but she did not return for follow-up.

Two weeks prior to admission, the patient noted abdominal enlargement associated with vague pain. She self-medicated with pain relievers which afforded temporary relief. A week prior to admission, the patient consulted at a local hospital. Acute appendicitis and urinary tract infection were considered. However, complete blood count and urinalysis were normal. The patient was given analgesics. Pain persisted and abdominal girth increased prompting her to seek admission in our hospital under the surgical service. A large abdominal mass was appreciated which was confirmed by ultrasound of the whole abdomen (Appendix 1). She was referred to the Gynecology Service for co-management.

Vital signs were normal. Pertinent physical examination findings revealed the following: Weight = 72kg (158 lbs), Height = 175 cm (5 feet 7 inches), with an arm span of 179 cm.

Pertinent physical examination showed: underdeveloped breasts, Tanner stage 3, absent facial hair and scanty axillary hair. A solid, 25 cm x 20 cm x 20 cm abdominopelvic slightly tender mass of limited mobility was palpated. The patient had scanty pubic hair, normal looking female external genitalia, normal sized clitoris and labia, intact hymen and nulliparous vagina. Speculum examination revealed a small, pink, smooth cervix. On bimanual examination, the uterus and adnexae were not delineated due to the large, solid, tender abdominopelvic mass almost filling the entire abdomen.

The admitting impression was abdomino-pelvic mass, ovarian malignancy (germ cell tumor) highly considered; Primary amenorrhea.

Tumor markers were requested and results showed an elevated LDH, serum β-HCG and CA-125 (Appendix 2). Simultaneous laboratory investigation of gonadal function was done. Tests revealed an increased follicle stimulating hormone, normal prolactin and normal TSH (Appendix 3) establishing gonadal failure.

* Finalist, 7th SGOP Interesting Case Contest, September 2008.

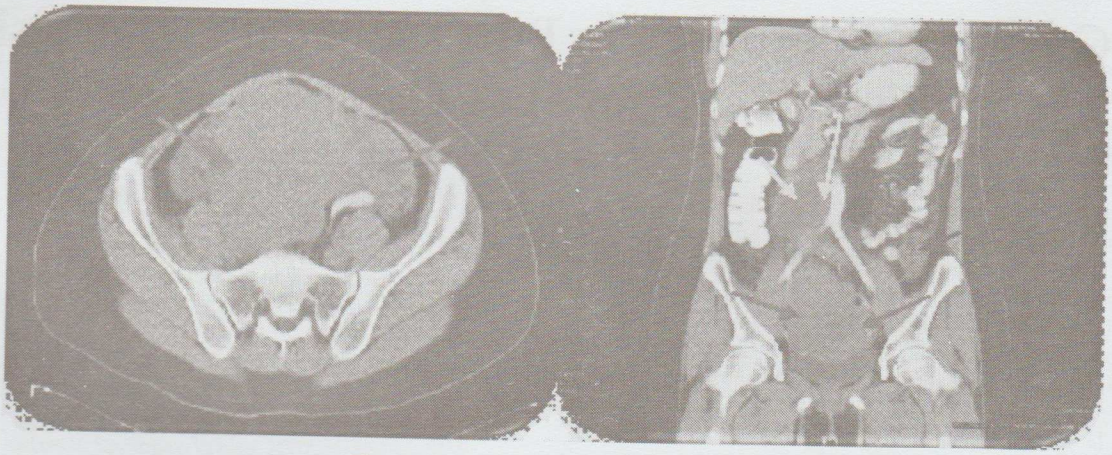


Figure 1. CT scan of the whole abdomen.

CT scan confirmed a pelvic tumor with mesenteric and omental infiltration, tumor encasement of the right ureter with bilateral hydronephrosis, enlarged necrotic right para-aortic lymph node with questionable infiltration of the anterior wall of the inferior vena cava (Figure 1).

A buccal smear was performed and no Barr body was seen. Conditions commonly associated with a single X chromosome are 1) Turner's syndrome, 2) Mosaic XO gonadal dysgenesis, 3) Swyer syndrome. The first was ruled out because the patient was tall with no evidence of webbed neck, shield chest, increased carrying angle at the elbow consistent with Turner's syndrome. The second was likewise ruled out since the patient did not have ambiguous genitalia.

Swyer syndrome was strongly considered because the physical attributes of the patient were compatible with this disease entity namely, primary amenorrhea, immature sexual characteristics, normal female external genitalia, infantile uterus and streak gonads. Chromosomal analysis was subsequently done and the patient showed an XY karyotype consistent with the diagnosis of 46XY pure gonadal dysgenesis or Swyer syndrome.

The patient underwent cystoscopy and bilateral ureteral stenting because of the tumor encasement to the right ureter, followed by exploratory laparotomy. The mass had smooth glistening capsule, lobulated, solid, 30 cm x 30 cm x 28 cm, covered by omentum and loops of small intestines. Superiorly, it was adherent to the transverse colon and both sidewalls. Inferiorly, it was adherent to the urinary bladder and posteriorly to the rectosigmoid. Tumor was noted in the transverse colon, anterior surface of the inferior vena cava and urinary bladder. The uterine corpus was posterior to the mass, infantile in appearance, measuring 3 cm x 2 cm x 2 cm with smooth serosal surface. The contralateral fallopian tube was normal and there was no identifiable ovary with fibrous tissue in its place. On cut section, the enlarged right ovary was solid vascular, with areas of necrosis and cystic spaces (Figure 2).

With a surgical stage of IIIC, the patient underwent resection of ovarian malignancy with hysterectomy and removal of both tubes, omentectomy, extensive dissection for tumor debulking and peritoneal fluid sampling.

Microscopic appearance showed large, round, ovoid polygonal cells that had irregular hyperchromatic nuclei with prominent nucleoli, scanty to absent cytoplasm. Cells were in lobules and nests separated by fibrous septae which were extensively infiltrated by lymphocytes, epithelioid cells and multinucleated giant cells characteristic of dysgerminoma (Figure 3).

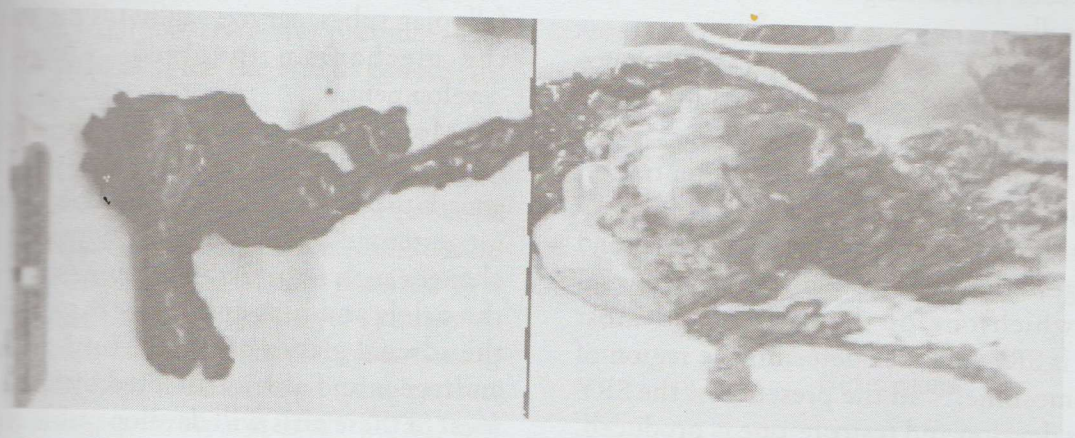


Figure 2. Intraoperative findings showing the uterus on the left and the right ovarian mass on the right.

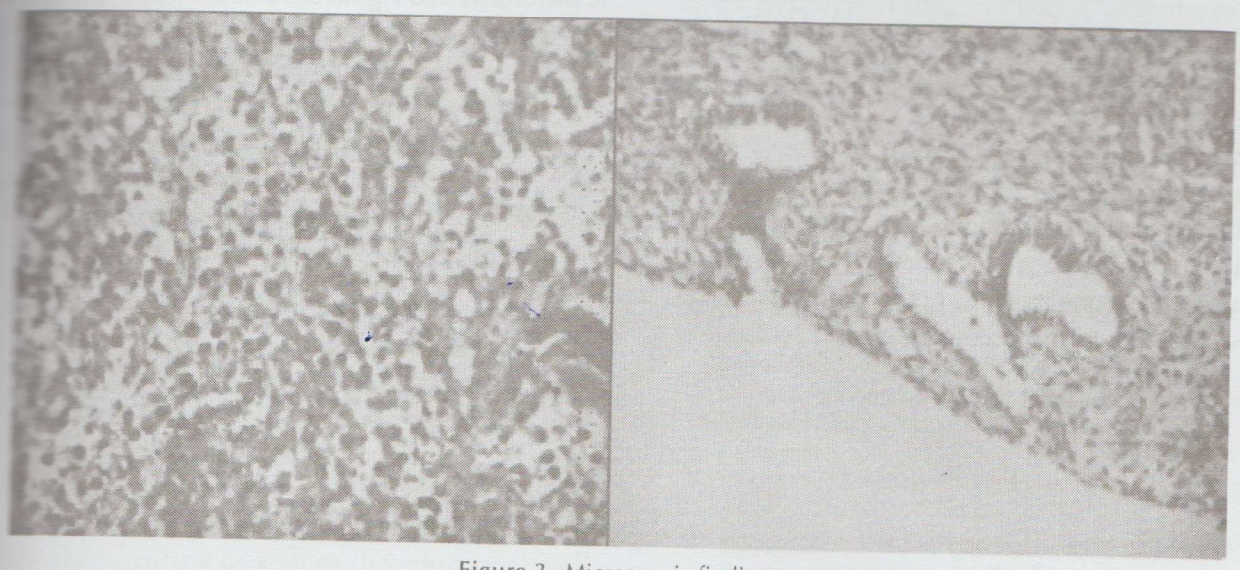


Figure 3. Microscopic findings.

She received chemotherapy in the form of Bleomycin, Etoposide and Cisplatin (BEP) but tolerated only 4 cycles. Repeat CT scan showed disappearance of residual tumors in the transverse colon and more than (50%) diminution in size of tumor in the vena cava. She was subsequently given external beam radiotherapy 50 Gy to the pelvis and 45 Gy to the para-aortic area and is presently without clinical evidence of disease.

Discussion

A rare syndrome characterized by a phenotypic female who is tall, eunuchoid with normal female external genitalia, hypoplastic uterus and fallopian tubes, streak gonads and primary amenorrhea was first described by Swyer in 1955[1]. Chromosome analysis of 46 XY, pure gonadal dysgenesis occurs with a frequency of one in 20,000 births.[2] Less

than five cases presenting similarly have been reported locally.

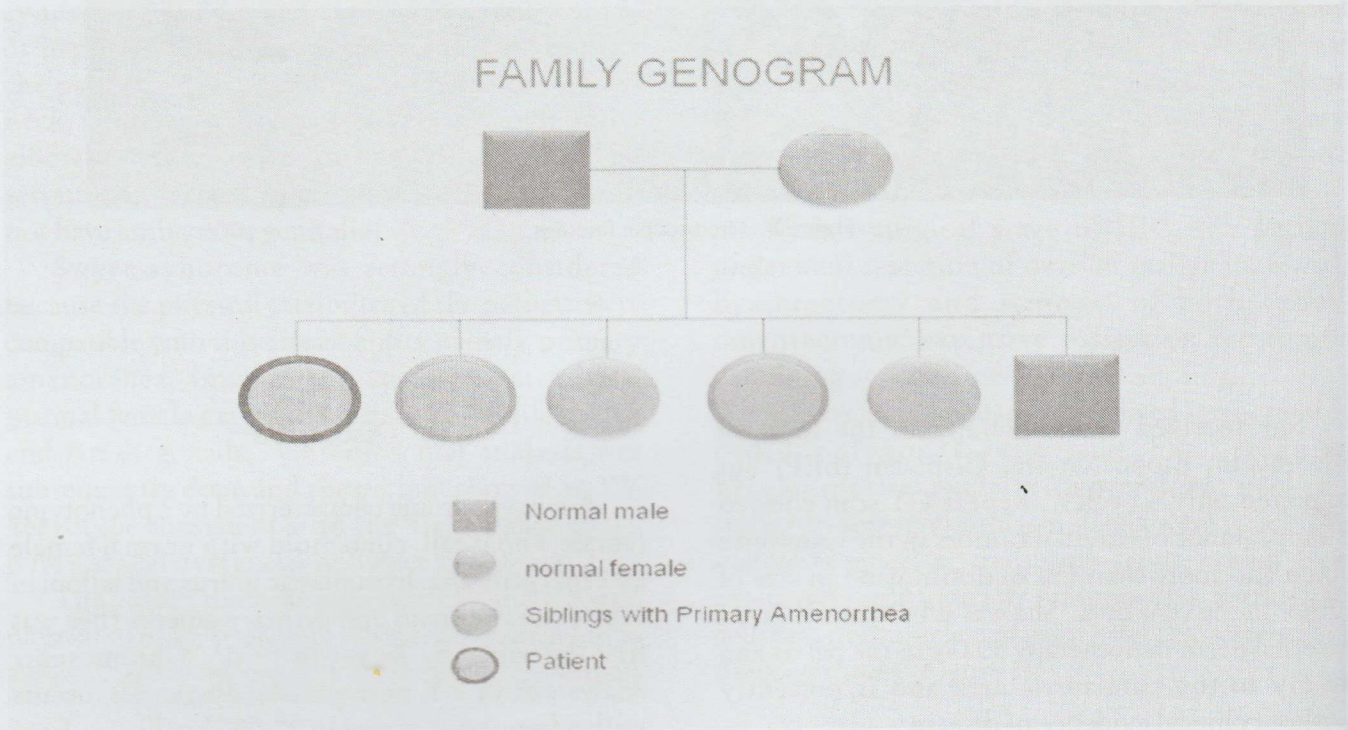
Our patient demonstrated the typical appearance and characteristics of Swyer syndrome. XY karyotype confirmed the diagnosis.

The first known step at sexual differentiation of a normal XY fetus is the development of testes.[3] The early stages of testicular formation in the second month of gestation require the action of several genes, of which one of the earliest and most important is SRY, the "sex determining region of the Y chromosome."[4] In the presence of the SRY gene, testes develop and testosterone is produced. This results in a male external genitalia and an adult phenotype.

Mutations of SRY account for most cases of Swyer syndrome. When this gene is defective, testes fail to develop in an XY (genetically male) fetus. Without testes, no testosterone or anti-mullerian hormone (AMH) are produced. In the absence of testosterone, the external genitalia fails to virilize, resulting in female genitalia.

The wolffian ducts also fail to develop and no internal male organs are formed. Furthermore, without testosterone or AMH, the mullerian ducts develop into normal internal female organs (uterus, fallopian tubes, cervix, vagina). This was probably the mechanism involved in our patient's development.

Most of the secondary sex characteristics do not develop because of the inability of the streak gonads to produce sex hormones (both estrogen and progesterone). This is especially true of estrogenic changes such as breast development, widening of the pelvis and hips and menstrual period. Since the adrenal glands can make limited amounts of androgens and are not affected by this syndrome, most of these girls will develop pubic hair, though it often remains sparse[9]. Evaluation of delayed puberty usually reveals elevation of gonadotropins, as in our index patient indicating that the pituitary is providing the signal for puberty but that gonads are failing to respond. The next step in the evaluation usually includes checking the karyotype and imaging of the pelvis. Evaluation of relatives with primary and secondary amenorrhea is essential since it may occur in phenotypically female siblings. The patient's family genogram shows that two other phenotypically female siblings are afflicted.



Imaging may demonstrate the presence of a uterus but no ovaries since the streak gonads are not usually seen by most imaging studies. Although an XY karyotype can also indicate a girl with complete androgen insensitivity syndrome, the absence of breast development, and the presence of uterus and pubic hair in this patient exclude the possibility. At this point it is usually possible for a physician to make a diagnosis of Swyer syndrome.

Streak gonads with Y chromosome-containing cells have a high likelihood of developing cancer. The risk of dysgerminoma is high (30%)[1] and gonadectomy is recommended.

Streak gonads are usually removed within a year or so of diagnosis since the cancer can begin during infancy.[10] If cancer develops, resection of primary lesion and proper surgical staging, chemotherapy and irradiation can be done.[12] Once gonads are removed, estrogen and progesterone may be given to prevent osteoporosis.

This patient underwent extensive surgery for dysgerminoma followed by adjuvant chemotherapy and radiotherapy. Her two phenotypically female siblings with primary amenorrhea likewise have XY karyotype and have been advised gonadectomy.

A woman with a uterus with no ovaries may be able to become pregnant by implantation of another woman's fertilized egg or embryo transfer.[11]

Medical and surgical management are not enough in patients with gonadal dysgenesis. Making a correct determination of gender is both for treatment purposes as well as the emotional well-being of the person.[13] In this aspect, the index patient was fortunate since at the time of the diagnosis she was already an adult. She was strongly identified with the female gender, being phenotypically female, and she was perfectly comfortable.

In patients with primary amenorrhrea or secondary amenorrhrea associated with dysgerminoma, early appropriate recognition, investigation and management should be done.

Appendix

Appendix 1. Ultrasound result: Complex mass arising from the pelvis extending to the lower abdomen. Consider gynecologic origin.

Appendix 2. LDH: 886 U/L (Normal values: 100-190 U/L) Serum β-HcG: 35.38 mIU/ml (Normal values: 0.5-2.90 mIU/ml) CA-125: 127.1 U/ml (Normal values: 0-35U/ml)

Appendix 3. FSH: 114.6 mIU/ml (3.5-12.5 mIU/ml Follicular Phase) (4.7-21.5 mIU/ml Ovulation Phase) (1.7-7.7 mIU/ml Luteal Phase) (26-135 mIU/ml Post Menopause) Prolactin: 10.76 ng/mL (Premenopausal: 3.34-26.72 ng/mL) TSH: 0.89 uIU/ml (0.34-5.6uIU/ml)

References

1. Swyer GM. Male pseudohermaphroditism: a hitherto undescribed form. Br Med J 1955; 2: 417-420.
2. Robinson A, Linden MG. Ambiguous genitalia and hermaphroditism. In: Clinical Genetics Handbook. 2nd edn. Boston: Blackwell Scientific, 1993:305-315.
3. Sultana R, Myerson D, Disteche CM. In situ hybridization analysis of the Y chromosome in gonadoblastoma. Genes Chromosom Cancer 1995; 13: 257-259.
4. Sternbarg WH, Barcaly DL, Kloefer HW. Familial XY gonadal dysgenesis. N Engl J Med 1968; 278: 695-700.
5. Barlett DJ, Grant JK, Pugh MA, Aherne W. A familial feminizing syndrome. A family showing intersex characteristics with XY chromosomes in three female members. J Obstet Gynaecol Br Commonw 1968; 75:119-210.
6. Boczowska K, Piapkowski B. Familial occurrence of gonadal tumors in women with 46, XY karyotype. Endokrynlo Pol 1978; 29: 527-535.
7. German J, Sampson JL, Chaganti RS, et al. Genetically determined sex reversal in 46, XY humans. Science 1978; 202: 53-56.
8. Thomas JC, Gonadal dysgenesis and chromosomal constitution 2007; 10:34.
9. Lucena, Pakarine, Sistonen, Chapelle. Mutation in the follicle stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. Pub med, genetic disorders and gynecology. 05:23, 4 August 2007.
10. Atienza MD. Familial complete androgen insensitivity syndrome. Phil J Obstet Gynecol 2002; (1): 14-24.
11. Behtash N, Zarchi MK. Dysgerminoma in three patients with Swyer syndrome. World J Surg Oncol 2007; 5: 71.
12. Migeon C, Wisniewski A. Ambiguous genitalia in the newborn. June 22, 2005.
13. Gimelli, Dimasi, Battista, Zuffardi. Identification and molecular modeling of a novel familial mutation in the SRY gene implicated in the pure gonadal dysgenesis. Human Genet 2007; 15(1): 76-80.
14. Sarafoglou K, Ostrer H, Familial sex reversal: A review. J Clin Endocrinol Metabol 85 (2): 483-493.
15. Cherfas J. Sex and single gene. Science 1991; 252: 782
16. Cohen MM, Shaw MW. Two XY siblings with gonadal dysgenesis and a female phenotype. New Eng J Med 1965; 272: 1083-1088.

17. Jawaheer D, Juo S-HH, Le Caignec C, David A, et al. Mapping a gene for 46, XY gonadal dysgenesis by linkage analysis. Clin Genet 2003; 63: 530-535.
18. Guyton and Hall. Reproductive and hormonal functions of the male. Textbook of Medical Physiology. Chapter 80, pp. 1014-1015.
19. Katz, Lentz, Lobo, Gerhenson. Comprehensive Gynecology. 5th Edition pp. 581, 937-942.

Non-Puerperal Uterine Inversion with Adenosarcoma in a Nulligravid: A Case Report*

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Non-puerperal uterine inversion is an extremely rare entity, which many gynecologists would never come across in their lifetime. Association of uterine inversion with malignancies such as endometrial carcinoma or sarcoma makes the case even rarer. It is encountered as an obstetric emergency and a diagnostic challenge in gynecology. Non-puerperal inversion usually results from a tumor implanted on the fundus of the uterus. Treatment depends on the associated pathology and the stage of the inversion.

This report focuses on a 40 year old nulligravid presenting with a prolapsed introital mass and severe hypogastric pain. A vaginal myomectomy followed by abdominal hysterectomy was performed. Histopathology report revealed an adenosarcoma of the uterine corpus.

Key words: inversion, non-puerperal, uterus

A fundal uterine mass has the capacity to cause uterine inversion provided it is large and heavy so that it gravitationally pulls the uterine fundus along with it to appear outside the cervix and into the vagina; the end result being a prolapsed mass lying outside the introitus with the inverted uterus. In a series of 233 cases studied by McCullagh, 85.8 percent were puerperal and 16.35 percent or one-sixth of all cases of inversion were non-puerperal, 20 percent of which were malignant, making it a rare problem.[1] This case report shall illustrate this rare condition, discuss the mechanism which led to uterine inversion, the associated signs and symptoms and treatment options.

The Case

This is the case of A.M., a 40 year old, nulligravid, single, from Manila, who was admitted for the first time in our institution on March 15, 2008 with a chief complaint of prolapsed introital mass. The patient is obese, diabetic, non-smoker, non-alcoholic beverage drinker, with no history of sexual contact. Menarche was at age 12 with subsequent menses occurring at regular monthly

* Finalist, 7th SGOP Interesting Case Contest, September 2008.

intervals lasting for 7 days, consuming 3 to 4 pads per day. Her last menstrual period was on January 24, 2008. She had a history of prolonged and profuse menses at 24 year old for which diagnostic dilatation and curettage was done, which revealed dysfunctional uterine bleeding. Medroxyprogesterone acetate 10mg once a day for 10 days was prescribed.

Present condition started 1 year and 5 months prior to admission, when the patient started to have prolonged and profuse menses lasting for 1 month from the usual 1 week, consuming 5-6 fully soaked diapers per day from the usual of 4 pads per day. No other signs and symptoms were noted like difficulty in urination or abdominal enlargement. She consulted a gynecologist who advised that a transvaginal ultrasound be done. Transvaginal ultrasound revealed a normal sized uterus with thickened endometrium (2.2cm), no uterine or adnexal mass seen. Complete blood count was normal. She self-medicated with iron and tranexamic acid. She was advised to have a pelvic examination done but refused. Diagnostic dilatation and curettage was likewise advised but she did not comply.

Nine months prior to admission, the patient's menses normalized to 2 pads per day lasting for 1 week. A follow-up transvaginal ultrasound revealed a proliferative phase endometrium. Still, no pelvic mass was seen. She informed her gynecologist about the result. A pelvic examination was advised but again the patient did not comply.

Six months prior to admission, the prolonged and profuse menses recurred. Transvaginal ultrasound revealed a thickened endometrium. She had a phone call consult with another gynecologist. Dilatation and curettage was advised but the patient refused. She self-medicated with Medroxyprogesterone acetate 10 mg OD for 10 days which stopped the vaginal bleeding.

Three months prior to admission, the patient again had prolonged and profuse menses consuming approximately 1 diaper per hour, moderately soaked lasting for 2 weeks, then subsiding to vaginal spotting. She started to have incomplete emptying of the bladder. No ultrasound nor consult were done.

One month prior to admission, still with vaginal spotting and incomplete emptying of the bladder, she started to feel a soft introital mass, approximately 5 cms, bulging from the vagina, which was reducible and aggravated by straining.

On the day of admission, still with incomplete emptying of the bladder, she tried to bear down after voiding. Immediately, a mass prolapsed from the vagina resulting to severe, excrutiating pain and minimal bleeding. She was rushed to our institution and was subsequently admitted.

On admission, the patient was conscious, coherent, screaming because of the excrutiating pain and stretcher-borne. Vital signs were stable. Complete blood count revealed hemoglobin of 99 g/L and hemotocrit of 0.31. Pelvic examination under anesthesia revealed an 8 cm x 12 cm x 15 cm reddish brown hemorrhagic mass at the introitus (Figure 1). Impression was a prolapsed myoma. Vaginal myomectomy was planned. A tourniquet was applied at the pedicle of the myoma (Figure 2). Vasoconstrictor was injected around the area to be incised (Figure 3). The myoma was cut using electrocautery (Figure 4) but in the course of the procedure, what was suspected to be the pedicle of the submucous mass turned out to be an inverted uterine fundus (Figure 5). Using an abdominal approach, the vaginocervical ring was incised posteriorly and carried up to the posterior wall of the uterus until it can be repositioned after which abdominal hysterectomy and right salpingooophorectomy was accomplished (Figures 6 & 7). Intraoperative findings revealed a 16 cm x 12 cm x 17 cm soft, well-circumscribed prolapsed reddish brown hemorrhagic mass protruding out of the introitus. The mass was noted to be bilobed, the largest portion measuring approximately 7cm x 4.5 cm x 3 cm (Figure 8). No palpable pelvic lymph nodes were noted. Two units of whole blood were transfused intra-operatively.

Postoperatively, the patient was started on intravenous antibiotics and round the clock pain medications. Repeat CBC revealed a hemoglobin of 115 g/L and hematocrit of 0.36. Medications for diabetes mellitus were started the following day.

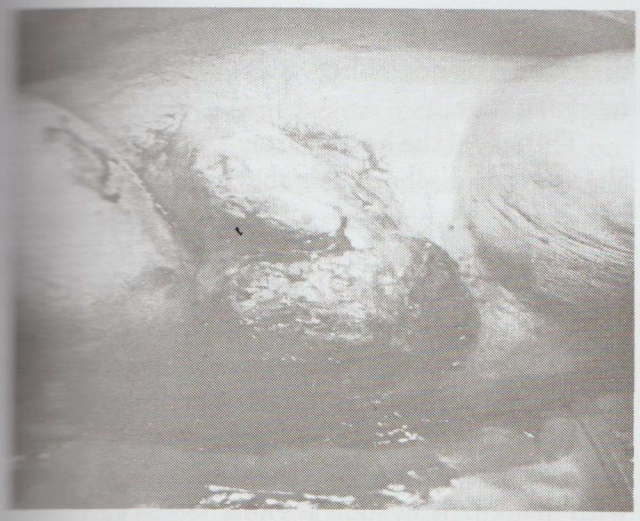

Figure 1. Pelvic examination under anesthesia revealed an 8 cm x 12 cm x 15 cm reddish brown hemorrhagic mass at the introitus.

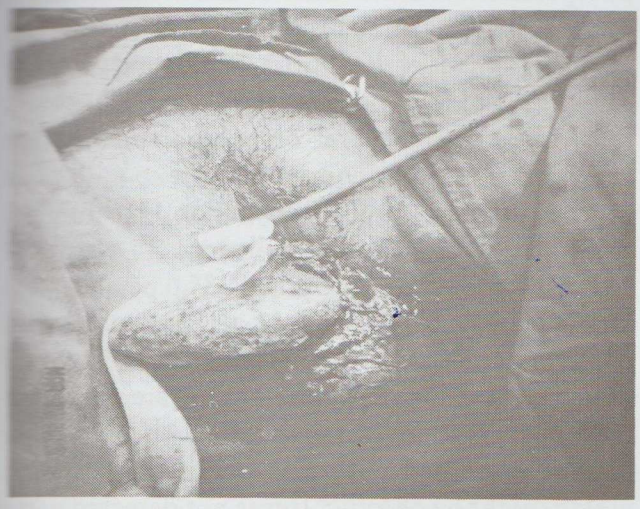

Figure 2. A tourniquet was applied at the pedicle of the myoma.

Figure 3. Vasoconstrictor apllied around the area to be incised.

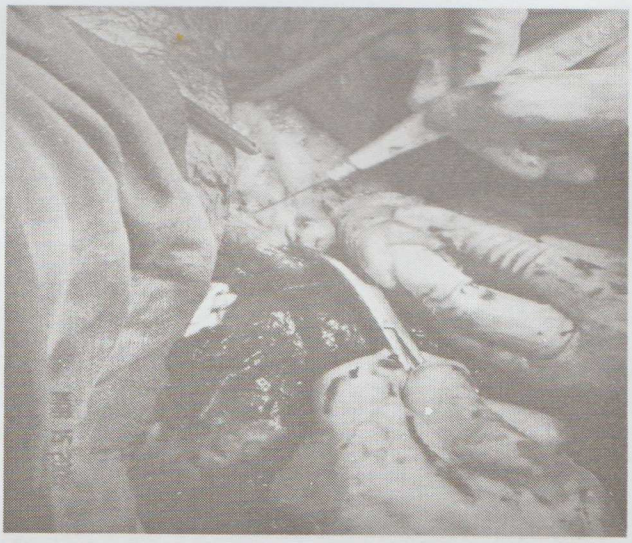

Figure 4. The myoma was cut using electrocautery.

Figure 5. The uterine fundus which was suspected to be the pedicle of the submucous mass.

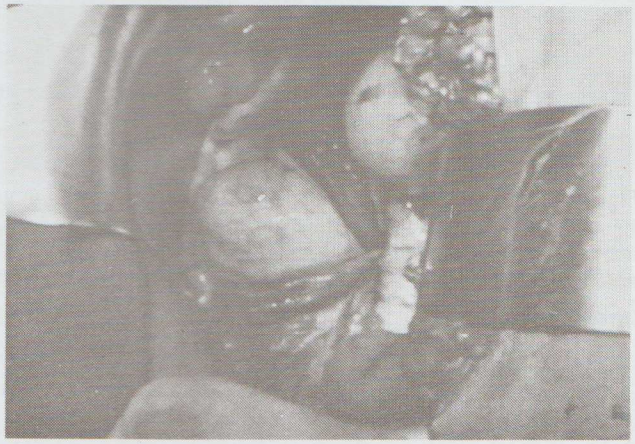

Figure 6. Intra-abdominal view of the inverted submucous mass, fallopian tubes and round ligaments.

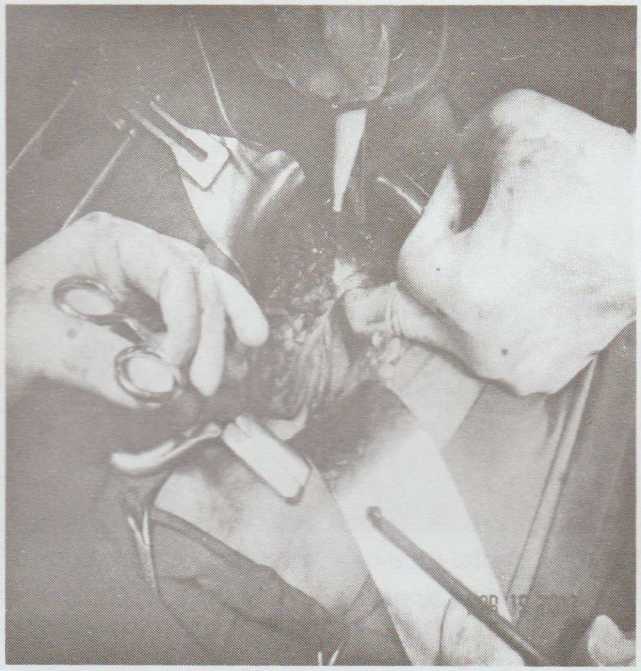

Figure 7. Repositioning of the inverted uterus.

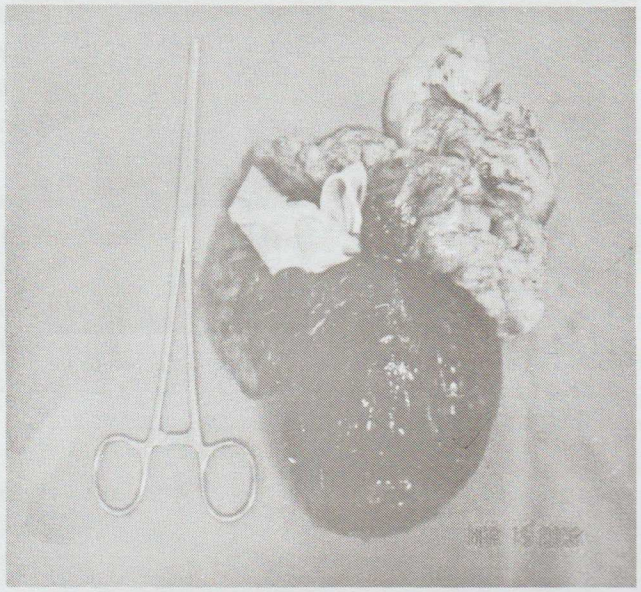

Figure 8. Intraoperative findings revealed a 16 cm x 12 cm x 17 cm soft, well-circumscribed prolapsed reddish brown hemorrhagic mass protruding out of the introitus. The mass was noted to be bilobed, the largest portion measuring approximately 7 cm x 4.5 cm x 3 cm.

Final histopathology report revealed Adenosarcoma, homologous, uterine corpus, with foci suspicious for lymphovascular space invasion; Chronic cervicitis with squamous metaplasia; No diagnostic abnormality recognized, ovary and fallopian tube.

The rest of the hospital stay was unremarkable. She was then discharged on the third post-operative day.

Discussion

Inversion of the uterus is a rare and extremely challenging clinical dilemma. It is well-described as an obstetric emergency and a diagnostic challenge in gynecology. Association of uterine inversion with malignancies such as endometrial carcinoma or sarcoma is even rarer.

Inversion of the uterus may be puerperal or non-puerperal. Most of the cases of uterine inversion is puerperal in nature, brought about mainly by mismanagement of the third stage of labor, by either excessive cord traction, fundal pressure or both. As it is, cases of puerperal or postpartum uterine inversion is not very common, more so with cases of non-puerperal uterine inversion or those not associated with labor and delivery. In a series of 233 cases studied by McCullagh, 85.5 percent were puerperal and 16.35 percent or one-sixth of all cases of inversion were non-puerperal, 20 percent of which were malignant, making it a rare problem.[1] Non-puerperal inversion is often chronic. Our patient presented with non-puerperal inversion which might be chronic. It was not detected early on due to the patient's poor compliance to follow-up.

The mechanism behind uterine inversion is well understood in obstetric cases. However, in cases of nonpuerperal inversion, the mechanism is not well understood. The three proposed main factors involved in tumor-associated inversion are:

1) a sudden emptying of the uterus previously distended from a tumor
2) the thinning of the uterine walls due to the intrauterine tumor
3) dilatation of the cervix

Another possible factor is a distended myometrium that becomes irritated, leading to

contractions which can further dilate the cervix and assist in the expulsion of the tumor. Other possible etiologic factors include the weight of the intrauterine mass, the manual traction on the tumor or increased intraabdominal pressure due to coughing, straining or sneezing. In the case of our patient, the weakening of the uterine wall at the point of the tumor's implantation at the uterine fundus, coupled with the weight of the said mass and straining, led to uterine inversion associated with the prolapsed mass. To date, there is no recorded incidence rate of uterine inversion specifically in a nulligravid. The mechanism of uterine inversion is, however, the same as in multigravids.

Classification of genital inversion has been described as[2]:

Stage 1: Inversion of the uterus is intrauterine or incomplete. The fundus remains within the cavity

Stage2: Complete inversion of the uterine fundus through the fibromuscular cervix

Stage 3: Total inversion, whereby the fundus protrudes through the vulva

Stage 4: The vagina is also involved with complete inversion through the vulva along with an inverted uterus.

For cases of inversion caused by tumors, according to Thorn, et al. 25% are partial and 75% are total. Of 83 cases due to intrauterine tumors, a fibroid tumor was the cause in the vast majority of cases, 4 being sarcoma and 1 from cancer.[3] Uterine inversion is suspected when a tumor is palpable in the vagina but the uterine fundus is not palpable on bimanual examination.

There was difficulty in the performance of the vaginal examination in this case since a huge mass was prolapsing out of the introitus and the patient was in extreme pain. Our patient presented with stage 3 inversion which is total inversion whereby the fundus protrudes through the vulva.

Adenosarcoma is initially reported by Clement and Scully in 1974 as a biphasic tumor composed of benign epithelial elements and a sarcomatous stroma.[4] It is a polypoid endometrial neoplasm that grows into the cavity and can enlarge the uterus. Adenosarcoma is a rarely observed variant of mixed mullerian tumors, consisting of neoplastic glands with benign appearance and a sarcomatous stroma. Kerner and Lictig reported that an early sign of a uterine adenosarcoma is its protrusion as a prominent cervical polyp. This has been observed in 7 adenosarcoma cases in women between the ages of 14 and 63 years. These cases were diagnosed as cervical polyps formerly with the protrusion of the tumor from the external ostium.[5] The mesenchymal component of an adenosarcoma generally is a homologous sarcoma such as stromal sarcoma or fibrosarcoma. This definition pertains to the one seen in our patient which on histopathology revealed a homologous adenosarcoma.

Clement and colleagues evaluated 100 women between the ages of 14 and 89 years with uterine adenosarcomas.[5] Most of these cases had abnormal vaginal bleeding as a symptom, like in our case.

Several factors can increase or decrease the risk of developing a uterine sarcoma. Obesity is a strong risk factor for endometrial cancer. Women who are obese or having a body mass index of more than 30 are two to threefold at increased risk due to increased circulating estrogen levels that result from conversion of androstenedione to estrone in the adipose tissue. Middle-aged and older women are more likely than younger women to develop uterine sarcomas. African American women are more likely than whites or Asians to develop sarcomas. Hormonal factor is also a consideration. Uterine carcinosarcomas develop more frequently in women who have risk factors for endometrial cancer, such as obesity, estrogen replacement therapy, infertility, diabetes, late onset of menstruation or late onset of menopause or treatment with tamoxifen. Nulliparity is associated with a twofold increased risk in endometrial cancer. Diabetes increases the risk by 2.8 fold and have been found to be an independent risk factor. Prior pelvic radiation therapy increases the risk for uterine sarcoma accounting for less than one third of this cancer and is diagnosed 5 to 25 years after exposure. Our patient had several risk factors identified including

age, nulligravid, obesity and diabetes. However, she had no history of previous pelvic radiation.

Our patient presented with vaginal bleeding which is the most common presenting symptom in uterine inversion. Other signs and symptoms are vaginal discharge, lower abdominal pain, non-specific urinary symptoms and a palpable pelvic mass described as a mass in the vagina or of something protruding or coming down the introitus. She likewise had incomplete emptying of the bladder and a mass at the introitus.

Pelvic examination in each of the cases reported in literature revealed a large uterus and a polypoid mass protruding from the external ostium of the cervix. Recurrent polyps were observed in 5 cases. Adenosarcoma recurs in 25-40 percent of patients and occasionally follows an aggressive course. Recurrence is generally in the pelvis or vagina, but distant metastases occur in 5 percent of patients. Invasion of capillary–lymphatic spaces in the myometrium portends an unfavorable outcome. The postoperative interval to recurrence was 5 years in about a third of the cases. Our patient experienced chronic abnormal uterine bleeding with no associated abdominal pain. Unfortunately, there was no pelvic examination done on the early course of the disease which could have detected a polypoid mass coming from the uterus.

Abnormal vaginal bleeding is the most frequent symptom of endometrial pathologies. It warrants an endometrial sampling to confirm the cause. Transvaginal ultrasound is an adjunct to the diagnosis of endometrial pathologies. MRI has been shown to be a useful diagnostic tool since it can examine the characteristic image of uterine inversion. Endometrial biopsy was not done in our patient for early diagnosis due to poor follow-up. The last transvaginal ultrasound done in our patient was 6 months prior to admission which revealed a thickened endometrium with no uterine and adnexal masses seen. If the patient had an endometrial biopsy done, the disease would have been detected at an earlier time providing more options for management.

The system used to stage endometrial cancer is called the FIGO system. It classifies the cancer from stages I to IV, with some of these stages being further subdivided. The FIGO endometrial cancer staging system is also used for uterine sarcoma. Our patient is stage IC, with cancer limited to the uterus with invasion of the myometrium and no endocervical involvement. The 5-year survival rate for women with stage I disease, which is confined to the corpus, is approximately 50% versus 0 to 20% for the remaining stages.

The prognosis depends on the initial diagnosis and the stage of disease. For women with sarcomas, some investigators consider tumor size to be the most important prognostic factor. Women with tumors greater than 5.0 cm in maximum diameter have a poor prognosis. However, in a Gynecologic Oncology Group study, the mitotic index was the only factor significantly related to progression-free interval. In a study by Norris HJ, et al. tumors with fewer than 5 mitoses per 10 high power field (HPF) rarely metastasize. In a follow-up study from Armed Forces Institute of Pathology, O'Connor and Norris evaluated 73 smooth muscle tumors of the uterus with 5 to 9 mitotic figures per 10 HPF but lacking cytologic atypia. They concluded that the metastatic rate was too low. [6]

In a similar study done by Kempson and Bari, mitotic count is important but they stated that prognosis is poor if more than 5 mitoses per 10 HPF are identified. Their experience with tumors containing 5 to 9 mitoses per 10 HPF indicates that the tumors usually behave aggressively and will metastasize. The degree of mitotic activity was a good index of the degree of clinical malignancy. Our patient presented with 2 to 6 mitotic figures in 10 HPF, revealing it to have low metastatic potential.

Successful treatment of uterine prolapse is ultimately enhanced by prompt recognition. Delay in treatment causes dense constriction ring formation, progressive edema, hemorrhage and tissue necrosis. If these things occur, uterine repositioning by vaginal manipulation will be unsuccessful, such as in the case of our patient.

The appropriate treatment depends on the preoperative diagnosis, but abdominal or vaginal hysterectomy with bilateral salpingo-oophorectomy is recommended for benign causes if childbearing

is not an issue. When a uterine malignancy is associated with uterine inversion, abdominal hysterectomy with appropriate staging biopsies is usually indicated. Some authors suggest transvaginal excision of the tumor mass before abdominal hysterectomy.

Four different surgical approaches have been described for the management of uterine inversion, 2 vaginal and 2 abdominal approaches. An initial attempt to reposition the fundus by vaginal manipulation, or Johnson procedure, should be done. This is accomplished by placing the operator's fist on the uterine fundus, gradually pushing it back into the pelvis through the dilated cervix. If the initial attempt fails, laparotomy is imperative. The surgical approach of choice is the procedure described by Huntington in 1928. This procedure relies on traction on the round ligaments, thus, restoring the uterus to its normal anatomy. If this is not successful, the procedure described by Haultain in 1901 is recommended. It involves a surgical incision of the cervical ring posteriorly through an abdominal approach, repositioning of the uterus and subsequent repair of the cervical incision.[8] For our patient, the huge prolapsed mass was removed vaginally prior to uterine repositioning. Using an abdominal approach, the vaginocervical ring was incised posteriorly and carried up to the posterior wall of the uterus until it can be reinverted after which abdominal hysterectomy was accomplished.

A vaginal approach, although less popular, is also an option. Two types have been described. The first one is the Kustner procedure which involves entering the space of Douglas vaginally and splitting the posterior aspect of the uterus and the cervix. Anatomic repositioning can be achieved by upward pressure, with subsequent suturing to the uterine incision to retain anatomy or proceeding with a vaginal hysterectomy. The Spinelli procedure is similar to the Kustner however, the uterine incision is made on the anterior aspect of the uterus after the bladder is dissected off upwards.[9]

The precise role of radiotherapy as an adjuvant treatment of uterine sarcomas remains controversial. Several authors showed that it may reduce local pelvic recurrence, but none had demonstrated long term improvement in survival rate. In a current study by Salazar and Dunne, postoperative adjuvant pelvic irradiation seemed to delay, but not prevent, local recurrence without any significant impact on survival. Adjuvant chemotherapy improved the prognosis of patients with early stage uterine sarcoma. In the Gynecologic Oncology Group randomized trial, adjuvant single-agent doxorubicin has a response rate of 25%. It was one of the first drugs identified with good activity against endometrial cancer. Other drugs on trial were cisplatin, paclitaxel, and ifosfamide but none of them showed a higher response rate than doxorubicin.[10] The plan for our patient is a single-agent doxorubicin for 6 courses.

As for the follow-up care, routine surveillance intervals are done every 3-4 months for the first 2 years, since 85 percent of recurrences occur in the first 2 years after diagnosis. Intervals are every 6 months for the next 3 years and annually thereafter. Each visit should include a pelvic examination, Pap smear, and a lymph node survey. Chest x-ray may be done annually or if symptoms arise. Elevated CA-125 usually indicates an extrauterine disease. Most recurrences are discovered during evaluation of symptomatic patients. The majority of recurrences in early-stage disease are at the vaginal cuff and pelvis.

Summary and Conclusion

In summary, we have presented a 40 year old, nulligravid who came in due to prolapsed introital mass with a history of abnormal vaginal bleeding and incomplete emptying of the bladder. Initial impression was that of a prolapsed submucous myoma but further examination revealed that this was complicated by uterine inversion. Vaginal myomectomy followed by uterine repositioning and abdominal hysterectomy with right salpingoophorectomy were done.

Non-puerperal uterine inversion is a very unusual condition that most gynecologists will never encounter. It can be mistaken as just a simple case of prolapsed vaginal mass, myoma or a case or

procidentia. In this instance, a high index of suspicion is required. Adenosarcoma is a rare cause of uterine inversion. Survival depends on the stage of the disease at the time of diagnosis. An endometrial biopsy leads to early detection of the disease and prompt definitive treatment. A low mitotic index predicts a better prognosis. Therefore, prompt evaluation of patients suspected of having these kind of tumors will increase the survival rate and improve the quality of life.

References

1. Mc Cullagh WMH. Inversion of the uterus: A report of three cases and an analyses of 233 recently recorded cases. J Obstet Gynaecol Br Emp 1925; 32: 280-297.
2. Eftekhar N. Non-puerperal uterine inversion in a virgin woman. Iranian J Reprod Med 2007; 5(3): 135-236.
3. Thorn W. Zuo inverso uteri Samml. Klin. Votrr, leipzigg, No. 625-627 gynaekologic 1911; 229.
4. Abu J, et al. Adenosarcoma of an endometrial polyp in a 27 year old nulligravida: a case report. J Reprod Med 2007; 52(4): 326-328.
5. Tinar S, et al. Adenosarcoma of the uterus: a case report. Med Gen Med 2004; 6(10): 51.
6. Kapp D, Shin J, Chan J, et al. Prognostic factors and survival of 1396 patients with uterine leiomyosarcomas. Cancer 2008; 112(4): 820-830.
7. Novak E, Anderson DF. Sarcoma of the Uterus. Am J Obstet Gynecol 1937; 740-761.
8. Hankins G, et al. Operative Obstetrics. Connecticut: Appleton and Lange, 1995; 273-281.
9. Rocconi R, et al. Postmenopausal uterine inversion associated with endometrial polyps. Obstet Gynecol 2003; 102(3): 521-523.
10. Kohorn EI, Schwartz PE, et al. Adjuvant therapy in mixed mullerian tumors of the uterus. Gynecol Oncol 1986; 23(2): 212-221.
11. Safdarian A, et al. Non-puerperal uterine inversion: A case report. Acta Medica Iranica 2003; 41(1): 312-314.
12. Ashraf-Ganjooie T. Non-puerperal uterine inversion: A case report. Arch Iran Med 2005; 8(1): 63-66.

The FIGO Staging

Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium (as adapted from the International Journal of Gynecology and Obstetrics 2009; 105: 103-104)

Table 1. Carcinoma of the vulva.

Stage I	Tumor confined to the vulva
IA	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm*, no nodal metastasis
IB	Lesions ≥ 2 cm in size or with stromal invasion > 1.0 mm*, confined to the vulva or perineum, with negative nodes
Stage II	Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes
Stage III	Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes
IIIA	(i) With 1 lymph node metastasis (≥ 5 mm), or
	(ii) 1–2 lymph node metastasis(es) (< 5 mm)
IIIB	(i) With 2 or more lymph node metastases (≥ 5 mm), or
	(ii) 3 or more lymph node metastases (< 5 mm)
IIIC	With positive nodes with extracapsular spread
Stage IV	Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures
IVA	Tumor invades any of the following:
	(i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or
	(ii) fixed or ulcerated inguino-femoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

* The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Table 2. Carcinoma of the cervix uteri.

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≥ 7 mm
IA1	Measured stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0 mm
IA2	Measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not > 7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*
IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IB2	Clinically visible lesion > 4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IIA2	Clinically visible lesion > 4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney**
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

* All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not > 7.00 mm. Depth of invasion should not be > 5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~ 1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.

** On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Table 3. Carcinoma of the endometrium.

Stage I*	Tumor confined to the corpus uteri
IA*	No or less than half myometrial invasion
IB*	Invasion equal to or more than half of the myometrium
Stage II*	Tumor invades cervical stroma, but does not extend beyond the uterus**
Stage III*	Local and/or regional spread of the tumor
IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexae #
IIIB*	Vaginal and/or parametrial involvement #
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes #
IIIC1*	Positive pelvic nodes
IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV*	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA*	Tumor invasion of bladder and/or bowel mucosa
IVB*	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

* Either G1, G2, or G3
** Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II
# Positive cytology has to be reported separately without changing the stage.

FIGO staging for uterine sarcomas (As adapted from the International Journal of Gynecology and Obstetrics 2009; 104: 179)

Staging for uterine sarcomas (leiomyosarcomas, endometrial stromal sarcomas, adenosarcomas, and carcinosarcomas)

Table 4. (1) Leiomyosarcomas.

Stage	Definition
I	Tumor limited to uterus
IA	< 5 cm
IB	> 5 cm
II	Tumor extends to the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen).
IIIA	One site
IIIB	> one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

Table 4. (2) Endometrial stromal sarcomas (ESS) and adenosarcomas*

Stage	Definition
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends to the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	> one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

Table 4. (3) Carcinosarcomas.

Carcinosarcomas should be staged as carcinomas of the endometrium.

* Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

Current FIGO Staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia

(As adapted from the International Journal of Gynecology and Obstetrics 2009; 105: 3-4)

Table 5. Carcinoma of the vagina: FIGO nomenclature.

Stage I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
Stage III	The carcinoma has extended to the pelvic wall
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to Stage IV.
IVa	Tumor invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis
IVb	Spread to distant organs

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Table 6. Carcinoma of the fallopian tube: FIGO nomenclature (Singapore, 1991)

Stage 0	Carcinoma in situ (limited to tubal mucosa)
Stage I	Growth limited to the fallopian tubes
Ia	Growth is limited to one tube, with extension into the submucosa and/or muscularis, but not penetrating the serosal surface; no ascites
Ib	Growth is limited to both tubes, with extension into the submucosa and/or muscularis, but not penetrating the serosal surface; no ascites
Ic	Tumor either Stage Ia or Ib, but with tumor extension through or onto the tubal serosa, or with ascites present containing malignant cells, or with positive peritoneal washings
Stage II	Growth involving one or both fallopian tubes with pelvic extension
IIa	Extension and/or metastasis to the uterus and/or ovaries
IIb	Extension to other pelvic tissues
IIc	Tumor either Stage IIa or IIb and with ascites present containing malignant cells or with positive peritoneal washings
Stage III	Tumor involves one or both fallopian tubes, with peritoneal implants outside the pelvis and/or positive regional lymph nodes. Superficial liver metastasis equals Stage III. Tumor appears limited to the true pelvis, but with histologically-proven malignant extension to the small bowel or omentum
IIIa	Tumor is grossly limited to the true pelvis, with negative nodes, but with histologically-confirmed microscopic seeding of abdominal peritoneal surfaces
IIIb	Tumor involving one or both tubes, with histologically-confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Lymph nodes are negative
IIIc	Abdominal implants > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
Stage IV	Growth involving one or both fallopian tubes with distant metastases. If pleural effusion is present, there must be positive cytology to be Stage IV. Parenchymal liver metastases equals Stage IV

Table 7. Carcinoma of the ovary: FIGO nomenclature (Rio de Janeiro 1988).

Stage I	Growth limited to the ovaries
Ia	Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact
Ib	Growth limited to both ovaries; no ascites present containing malignant cells. No tumor on the external surfaces; capsules intact
Ica	Tumor either Stage Ia or Ib, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
IIa	Extension and/or metastases to the uterus and/or tubes
IIb	Extension to other pelvic tissues
IIca	Tumor either Stage IIa or IIb, but with tumor on surface of one or both ovaries, or with capsule(s) ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings
Stage III	Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive regional lymph nodes. Superficial liver metastases equals Stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum
IIIa	Tumor grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologic proven extension to small bowel or mesentery
IIIb	Tumor of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative
IIIc	Peritoneal metastasis beyond the pelvis > 2 cm in diameter and/or positive regional lymph nodes
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV

[1] In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage Ic or IIc, it would be of value to know if rupture of the capsule was spontaneous, or caused by the surgeon; and if the source of malignant cells detected was peritoneal washings, or ascites.

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Table 8. Gestational trophoblastic neoplasia.

GTN: FIGO staging and classification (Washington,2000a)

FIGO Anatomical Staging	
Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

Modified WHO Prognostic Scoring System as Adapted by FIGO

Scores	0	1	2	4
Age	< 40	≥ 40	–	–
Antecedent pregnancy	mole	abortion	term	–
Interval months from index pregnancy	< 4	4-6	7-12	> 12
Pretreatment serum hCG (iu/l)	$< 10^3$	10^3 - 10^4	10^4 - 10^5	$> 10^5$
Largest tumor size (including uterus)	< 3	3 - 4 cm	> 5 cm	–
Site of metastases	lung	spleen, kidney	gastrointestinal	liver, brain
Number of metastases	–	1 - 4	5 - 8	> 8
Previous failed chemotherapy	–	–	single drug	2 or more drugs

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To stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, e.g. Stage II:4, Stage IV:9. This stage and score will be allotted for each patient.

Management of Asymptomatic Women with Epithelial Ovarian Cancer with Rising Serum CA-125 Levels

Rafael S. Tomacruz, MD and Christine Joy G. Garcia, MD

Ovarian cancer is the fourth most frequent cause of death in women and is the most lethal of all gynecologic cancers.[1] Based on SEER data from 1976 to 2006, ovarian cancer ranks 7th in incidence, covering 14.82 percent of all cases of cancer in women. Despite comprehensive treatment strategies for advanced stages, 75 to 80 percent of these cancers recur within two years after initial diagnosis.[1] Due to the high probability of disease progression and relapse, regular surveillance measures should be strictly advised and implemented. The success of re-treatment for disease recurrence depends on prompt recognition and early detection.

During follow-up visits, patients are queried on signs and symptoms that may suggest recurrence. Physicians likewise perform complete physical and pelvic examinations on these women. However, most often than not, these strategies are insufficient in detecting early stages of relapse since small deposits of tumor generally produces no symptoms nor abnormal physical examination findings. Physicians have turned to laboratory tests and diagnostic imaging modalities to supplement the clinical evaluation of women on follow-up for ovarian cancer. However, these adjunctive examinations have inherent limitations in women with minimal peritoneal disease. Moreover, some imaging modalities such as the computed tomography (CT) scan or magnetic resonance imaging (MRI) test carry prohibitive costs, especially in the setting of third-world countries. Currently, the serum tumor marker, cancer antigen 125 (CA-125), is the most accurate and cost-effective tumor marker in monitoring therapeutic response and in detecting recurrent disease.

Determination of CA-125 levels has been the recommended laboratory surveillance tool in women with epithelial ovarian cancer during and after completion of combination chemotherapy. CA-125 values that plateau or rise during initial treatment usually signify chemotherapy drug resistance, while rising levels after treatment can accurately predict recurrence in most patients. Another advantage of measuring CA-125 levels post-treatment is the observation that CA-125 levels can rise months before women experience signs or symptoms of recurrence. An increasing CA-125 concentration predates clinical or radiological evidence of relapse in approximately 70 percent of patients with ovarian cancer by a median of 4 months (Van der Burg, 1990; Tuxen, 1995; Rustin, 1996).[2,3] Although women with recurrent ovarian cancer usually respond to re-treatment with systemic chemotherapy, the intent is rarely curative and there is very little evidence that early re-treatment (prior to signs or symptoms and/or radiological evidence) improves overall survival. Thus, the biggest dilemma of oncologists handling situations like these is whether they should wait for definite proof of recurrence or start re-treatment based solely on rising levels of CA-125. This review discusses this scenario of asymptomatic patients presenting with rising CA-125 levels during

follow-up. The Phase III trial of Rustin and van der Burg, which was presented during the last ASCO meeting on May 2009, will likewise be presented.

Case Report

R.B. is a 56-year old nulligravid who underwent exploratory laparotomy for abdominal enlargement. Pre-operative CA-125 value was 2,500 U/mL. She had ascites of 5 liters. Bilateral ovaries were enlarged, solid and hemorrhagic. There were tumor implants on the parietal and visceral peritoneum, including the surfaces of the liver, subdiaphragmatic areas, and cul-de-sac. Extrafascial hysterectomy, bilateral salpingo-oophorectomy and tumor debulking were performed. Greatest residual tumor was approximately 5 cm at the cul-de-sac area, densely adherent to the rectum. Histopathological report showed Papillary Serous Adenocarcinoma and she was classified as Stage IIIC. She subsequently received 6 courses of Carboplatin-Paclitaxel (CT). CA-125 levels were as follows: Prior to 1st CT was 875 U/mL, after the 3rd cycle of CT was 150 U/mL, and post-6th CT was 15 U/mL. She tolerated the treatments well and asymptomatic with no clinical evidence of disease after systemic chemotherapy. She was advised regular office follow-up with surveillance using CA-125 every 3 months. Ultrasound and/or CT scan evaluations were likewise advised at certain intervals.

The following table is a summary of the patient's follow-up:

Controversial Issues

In women with advanced ovarian carcinoma who have achieved complete remission after first-line platinum-based chemotherapy, surveillance of disease status usually rests on regular gynecologic examinations and serial CA-125 monitoring. Rising CA-125 concentrations in the background of an asymptomatic patient with no radiological evidence of relapse brings about major diagnostic and therapeutic decisions:

1. What are the criteria for determining disease recurrence?
2. Can we diagnose disease recurrence based on rising CA-125 levels only?
3. Should we initiate immediate therapy or should we continue monitoring the patient and initiate treatment only when clinical or radiographic confirmation is achieved?

Parameter	3rd month post-CT	6th month post-CT	8th month post-CT	10th month post-CT
Signs/Symptoms	None	None	None	Anorexia, weight loss, abdominal fullness
CA-125 value	8 U/mL	18 U/mL	42 U/mL	105 U/mL
Radiological evaluation	---	---	Abd'l UTS: No evidence of recurrence	CT scan: Fluid at cul-de-sac, liver masses ~ 2 cm, cul-de-sac mass ~ 4 cm, and carcinomatosis
Treatment	None	None	None	Topotecan chemotherapy initiated

Definition of CA-125 Progression in Ovarian Cancer

CA-125 levels that fall to normal at the end of treatment do not always indicate a woman is free from disease. In fact, Rubin and associates noted that around 50 percent of women with normal CA-125 after primary therapy had persistent disease documented at second look surgery.[4] During the administration of chemotherapy, failure of CA-125 values to fall to normal levels after three cycles has been correlated with persistent disease at second look surgery.

It is generally accepted that a rising CA-125 value is an early indicator of disease recurrence in women previously treated with chemotherapy for epithelial ovarian cancer. An increasing CA-125 value predates clinical evidence of relapse in approximately 70 percent of women by a median of 4 months. Rustin and associates in the North Thames Ovary Trial defined disease progression as an increase of CA-125 levels more than 2 times the upper limit of normal.[2] When this criterion was used, the sensitivity and specificity was 85.9% and 91.3%, respectively. When doubling of CA-125 values from its nadir levels was used to define disease progression, sensitivity and specificity increased to 94% and 100%, respectively.

Disease progression can also be suggested by progressive, low-level increases in CA-125 values within the normal range. Wilder and associates observed that 3 progressively rising CA-125 values within the normal range was associated with tumor recurrence.[5] The mean time from the third value to clinical confirmation of the recurrence was 189 days (range of 8-518 days). They suggested that in this scenario, immediate investigation to identify and document the recurrence is paramount for initiating prompt re-treatment. Santillan and associates in Johns Hopkins, on the other hand, enumerated significant predictors of recurrence.[6] A relative increase in CA-125 values from baseline nadir levels of 100% had an odds ratio of 23.7. Moreover, an absolute increase in CA-125 value of 5 U/mL had an odds ratio of 8.4, while an absolute increase of 10 U/ml from baseline nadir levels had an odds ratio of 71.2.

The most widely accepted definition of disease progression at the present was proposed by the Gynaecologic Cancer Intergroup (GCIG), taking into consideration both clinical and CA-125 criteria.[7] The RECIST (Response Evaluation Criteria in Solid Tumors) definition of clinical evaluation specifies either the presence of new lesions or a 20% increase in the sum of the largest diameters of previously seen lesions through imaging modalities. The CA-125 definition of progression, on the other hand, takes into account three specific groups of patients, depending on their pretreatment CA-125 values. The first group consists of patients with elevated CA-125 values pretreatment whose values normalize after chemotherapy. Progression in this group is diagnosed when CA-125 increases to 2 times the upper limit of normal (ULN) on two occasions. The second group consists of patients with elevated CA-125 values pretreatment but never normalizes after chemotherapy. Progression in this group is diagnosed when CA-125 increases to 2 times the nadir on two occasions. The last group consists of patients whose CA-125 values were in the normal range pretreatment and remained normal throughout. Progression in this group is diagnosed when CA-125 increases to 2 times the upper limit of normal (ULN) on two occasions (similar to the first group).

The Pro's and Con's of Evaluating Disease Status Using CA-125 Levels

Early treatment of tumor recurrence and its potential sequelae (e.g., ascites, intestinal obstruction) underscores the importance of serially measuring CA-125 levels and confirming clinical disease by radiographic modalities. However, whether treatment based on these diagnostic examinations will increase the overall survival has still not been established. It is generally believed that the cure rate for salvage therapy is so low that some oncologists suggest that the probability of complete response is essentially zero. Management

of recurrent ovarian cancer is purely palliative. However, the impact of treatment probably lies in an improvement of progression-free survival and quality of life of women with disease relapse.

With these in mind, the issue on whether or not to actually monitor these patients using serial CA-125 measurements continues to hound clinicians on its actual benefit. An advantage of serial measurements of CA-125 is the reassurance it provides patients and doctors when these values are within normal limits. Mayerhofer and associates evaluated women with gynecologic cancers and their knowledge of tumor markers.[8] Most women indicated that it was important to monitor tumor markers (85%) and that they felt reassured and relieved when their markers were within normal (72%). However, it also has to be reiterated to them by their physicians that around 50 percent of early recurrences may be associated with normal CA-125 levels. Another potential advantage of using CA-125 measurements is that it is a simple evaluation tool that can obviate the need for expensive, time consuming, and often false negative radiographic investigations.

However, measurement of CA-125 also has its disadvantages. It can induce a rare phenomenon called CA-125 psychosis. This results when patients experience severe anxiety, fearing the possibility of relapse, more treatments, and even death. This anxiety is often related to the amount of knowledge patients have about their disease.

Early Treatment Based on CA-125 Levels Alone vs Delayed Treatment Based on Clinical Confirmation

With the knowledge that rising CA-125 levels precedes clinical or radiographic evidence of recurrence, should we start early treatment based solely on this CA-125 elevation? Or should we wait for clinical confirmation of disease relapse before initiating treatment? These issues were forefront when Rustin and van der Burg collaborated on a randomized control trial on treatment versus observation of recurrent ovarian carcinoma with rising CA-125 concentrations. The results of this trial were recently reported during the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO).[9]

The objective of the study was to investigate the benefit of early chemotherapy for relapsed ovarian cancer based on rising CA-125 levels alone versus delayed chemotherapy based on conventional clinical indicators. Women with ovarian cancer in complete remission after first-line platinum-based chemotherapy and a normal CA-125 were enrolled and CA-125 measurements were done every 3 months. Women with a CA-125 level that was more than 2 times the upper limit of normal were randomized to either early or delayed treatment.

There were 1,442 registered patients enrolled from May 1996 to August 2005. After excluding patients for various reasons, 529 women (37%) were subsequently randomized. Sixty-seven percent (67%) of patients were previously Stage III/IV and 53% had serous carcinoma as the histologic type (17% endometrioid, 7% mucinous, 6% clear cell). The median survival of all registered patients was 70.8 months (95% CI = 64.1-78.0).

There was no significant differences between both arms with regards age, FIGO stage, WHO performance scores, and histology of the tumor. Distribution of second-line chemotherapy is shown in Table 1.

Table 1. Second-line chemotherapy between the 2 arms.

Regimen administered	Early N (%)	Delayed N (%)
Single agent platinum	78 (29)	67 (25)
Combination platinum (no taxane)	40 (15)	33 (13)
Platinum + taxane based	91 (34)	101 (38)
Taxane without platinum	15 (6)	9 (3)
Other	28 (11)	15 (6)
Unknown treatment	2 (1)	8 (3)
No treatment given	11 (4)	24 (9)
Not yet given (no clinical relapse)	0	7 (3)
Total	265	264

Overall survival between the 2 arms is shown in Figure 1. There is no significant difference in overall survival between women who underwent early treatment based on rising CA-125 levels and those whose treatment was delayed until clinical conventional indicators were confirmed. The Hazard Ratio was 1.0 (95% CI 0.82-1.22) and a p value = 0.98.

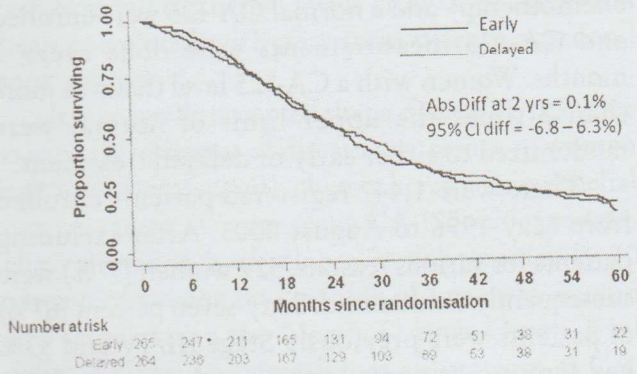

Figure 1. Overall survival.

Sixty-eight percent (68%) of women on the early treatment arm and 56 percent on the delayed treatment arm received third-line treatment (p=0.0021). Table 2 shows the status of women after receiving second-line treatment.

Table 2. Status of women after second-line treatment.

	Early (N=265)	Delayed (N=264)
Alive, no third-line treatment	9%	12%
Alive, after third-line treatment	16%	14%
Died, after third-line treatment	52%	41%
Died, no third-line treatment	23%	33%

The median time from randomization to third-line treatment or death was 12.5 months for the early treatment arm versus 17.1 months for the delayed treatment arm (HR=0.69 with 95% CI 0.58-0.83 and p=0.0001).

A quality of life questionnaire (EORTC QLQ-C30) was collected every three months from registration and prior to each cycle of chemotherapy until the end of third-line treatment. Primary outcome measures were: 1. Time until first Global Health related deterioration or death; 2. Overall time with "good" Global Health Score (GHS) during first two years after randomization. Global health deterioration is a >10% decrease from pre-randomization score. A "good" GHS score is improved or <10% decrease from pre-randomization score. Figure 2 shows the time from randomization to first deterioration in GHS or death.

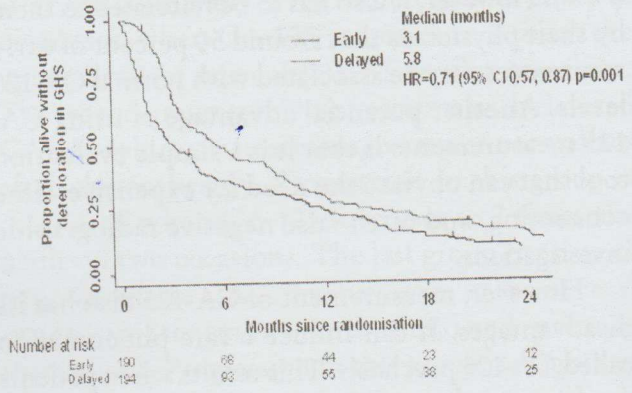

Figure 2. Time from randomization to deterioration of GHS or death.

Figure 3 shows the overall time spent with good GHS. The median overall time for the early treatment arm and delayed treatment arm is 7.1 and 9.2 months, respectively.

Rustin and van der Burg concluded that second-line chemotherapy started approximately 4.8 months earlier in the early treatment arm based on rising CA-125 levels and third-line chemotherapy started 4.6 months earlier. However, early treatment based solely on CA-125 elevation did not improve overall survival and does not improve quality of life for these patients.

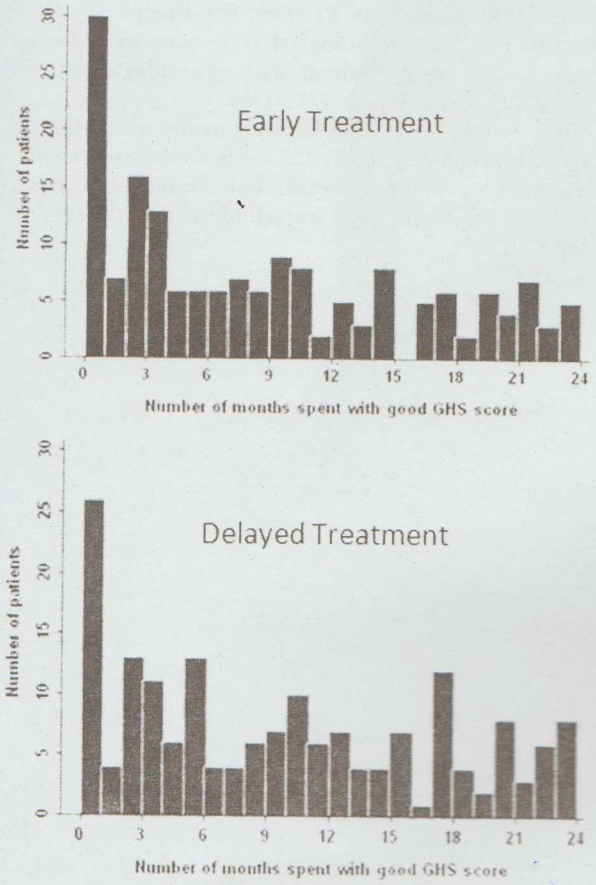

Figure 3. Overall time spent with good GHS.

Conclusions

The management of asymptomatic women with epithelial ovarian cancer after combination chemotherapy with rising serum CA-125 levels continues to be a challenge to practicing oncologists. Based on the latest Phase III trial of early treatment based on rising CA-125 levels versus delayed treatment based on conventional clinical indicators, women can be reassured that there is no benefit from early detection of disease recurrence by routine, serial monitoring of CA-125 levels.[9] Despite the elevation of CA-125, chemotherapy can be delayed until signs or symptoms of tumor recurrence are present. Women should be offered informed choices during their follow-up: 1. No routine CA-125 measurements but assurance of rapid access to this test when signs or symptoms of relapse occur, or 2. Regular CA-125 measurements, usually every 3 months after completion of initial chemotherapy.

Discussion of treatment options for recurrent ovarian cancer is beyond the scope of this article. There is still no "standard of care" for managing women with disease relapse. Though chemotherapy seems to be the most logical choice for salvage treatment, surgery might play a bigger role in the future. With the advancement in maximal cytoreductive techniques, gynecologic oncologists may utilize these procedures prior to administering second-line chemotherapy with, hopefully, some improvement in overall survival. Investigators are also turning to novel targeted therapies as an adjunct to chemotherapy for this group of women. The trend in managing recurrent epithelial ovarian cancer is towards multimodality therapies aimed at not only increasing overall and progression-free survival, but also improving the quality of life for these patients. Until there is definite evidence that these modalities will work, there is no proof that treating these patients aggressively and early based on rising levels of CA-125 will increase survival. Understanding this scenario can convince patients to change their expectations and to choose to delay treatment until clinical signs or symptoms occur or when there is radiographic confirmation of disease relapse.

References

1. Cannistra SA. Cancer of the ovary. N Engl J Med 2004; 351: 2519-2529.
2. Rustin GJ, Nelstrop AE, Tuxen MK, Lambert HE. Defining progression of ovarian carcinoma during follow-up according to CA-125: A North Thames Ovary Group Study. Ann Oncol 1996; 7: 361-364.
3. Van der Burg ME, Lammes FB, Verweil J. The role of Ca125 in the early diagnosis of progressive disease in ovarian cancer. Ann Oncol 1990; 1: 301-302.
4. Rubin SC and Sutton GP. Ovarian Cancer. 2nd ed., Philadelphia, PA: Lippincott, Williams and Wilkins, 2001.
5. Wilder JL, Pavlik E, Straughn JM, et al. Clinical implications of a rising CA125 within the normal range in patients with epithelial ovarian cancer: a preliminary investigation. Gynecol Oncol 2003; 89: 233-235.

6. Santillan A, Garg R, Zahurak ML, et al. Risk of epithelial ovarian cancer recurrence in patients with rising serum CA125 levels within the normal range. J Clin Oncol 2005; 23: 9338-9343.
7. Therasse P, Arbuck SG, et al. New guidelines to evaluate the response to treatment in solid tumors. EORTC, NCI of the US, NCI of Canada. J Natl Cancer Inst 2000; 92: 205-216.
8. Mayerhofer K, Bodner K, et al. Knowledge of tumor markers and the psychological consequences of tumor marker sampling in patients with gynecologic cancers. Anticancer Res 2000; 20: 1281-1284.
9. Rustin G and van der Burg M. Early treatment of relapsed ovarian cancer based on CA-125 levels alone versus delayed treatment based on conventional clinical indicators. Presented during the 2009 Annual Meeting of the ASCO, May 31, 2009.