# Neoadjuvant Cisplatin - Ifosfamide followed by Radical Surgery for Bulky Early Stage (IB2-IIB) Cervical Cancer*

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**Background:** Cervical cancer is the most common gynecologic malignancy in the Philippines. Concomitant chemoradiation is the primary mode of the treatment for all stages. Unfortunately, lack of adequate radiotherapy facilities in the country, particularly brachytherapy, has led to innovations in treatment to hopefully address this problem. **Objective:** To determine the efficacy and safety of neoadjuvant Cisplatin-Ifosfamide followed by radical surgery for bulky early stage (IB2-IIB) cervical cancer. **Methods:** This is a phase II study on bulky early stage (IB2-IIB) cervical cancer patients treated with neoadjuvant Cisplatin 100 mg/m$^2$ and Ifosfamide 6.0 gm/m$^2$ plus Uromitexan at 60% of Ifosfamide dose at a 28-day cycle for 2 cycles, followed by radical hysterectomy, bilateral salpingooophorectomy, pelvic lymph node dissection and adjuvant pelvic radiotherapy. Patient demographics, tumor characteristics, chemotherapy toxicities, intra-operative findings, response rates and survival rates were observed and analyzed. **Results:** A total of nine cases (5 cases of stage IB2, 1 case of stage IIA bulky disease and 3 cases of Stage IIB) were included in the study. The mean age of the patients was 42 years (range: 32-52 years). The mean tumor diameter was 6.5 cm (range: 3-10 cm) with the most common tumor histology being squamous cell carcinoma, large cell non-keratinizing (62.5%). After two cycles of neoadjuvant Cisplatin-Ifosfamide, there were 5 cases of partial response, 1 complete response and 1 stable disease giving an overall response rate of 77.78%. There were no grade 3-4 chemotoxicities. Radical surgery was successfully done in 7 cases (77.78%) after 2 cycles of chemotherapy. There was 1 case of bladder injury incurred during radical surgery. There was 1 case of complete pathologic response. Six patients (66.67%) eventually died of persistent progressive disease with a mean survival of 33 weeks while 3 patients (33.33%) are presently alive with no evidence of disease. **Conclusion:** Neoadjuvant cisplatin-Ifosfamide followed by radical surgery for bulky early stage (IB2-IIB) cervical cancer may be a feasible management option.

**Key words:** Cisplatin, Ifosfamide, neoadjuvant chemotherapy, radical surgery

* Won first place in the 2009 Philippine Society of Oncology (PSO) Research Contest

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Cervical cancer is still one of the most common and lethal malignancies in women. Although it is considered as a preventable disease, cervical cancer remains to be a major cause of death in low socioeconomic level population.[1] Majority of patients present with advanced stage of the disease (stage IIB 30%, stage IIIB 40%, stage IV 15%) and most die within a year of diagnosis.[2] At the Cancer Institute of the Philippine General Hospital from 2004-2007, an average of 491 new cases was seen per year, 68 percent of which are in the advanced stages (Stage III and IV). During the last two decades, survival of women in developing countries with cervical cancer remained unchanged. The long-term outlook is grim, with overall five-year survival rates of approximately 40% when conventional treatments are used.[3] In the 2005 Philippine Cancer Facts and Estimates, the median survival rate is 76 months with a 51.5% 5-year survival rate and 44.4% 10-year survival rate for cervical cancer in general.

Concurrent chemoradiation has been the recommended primary treatment of choice for all stages of cervical cancer (1999 US National Cancer Institute Clinical Announcement) resulting in a decrease in overall death rates by 30% - 50%. Surgical treatment in the form of radical hysterectomy with lymph node dissection is an option for good surgical risk patients with early stage disease (Stage IA2–IIA) with non- bulky lesions (≤4.0cm).

Unfortunately, the outcome of the battle against this aggressive malignancy is still unchanged in developing countries where cervical cancer incidence has remained the same for the past four decades. The inadequacies of a national screening program, the financial incapacity of patients and the lack of adequate radiotherapy facilities all compound the woes of gynecologic oncologists in treating patients burdened with cervical cancer. At government hospitals, the radiotherapy facilities are very inadequate to answer the needs of most patients with backlogs reaching unacceptable levels. There are approximately 100 patients waiting for their external pelvic radiotherapy schedules which would approximately start two months from initial consult. In addition, there are approximately 53 patients awaiting their brachytherapy schedule, which would start around three months from consultation. These factors contribute to the development of disease persistence or recurrence.

To address the needs of cervical cancer patients in developing countries, innovative therapeutic modalities have been investigated. One such alternative is neoadjuvant chemotherapy followed by radical surgery. The main objective of preoperative chemotherapy is shrinkage of the primary tumor bulk to achieve radical operability and early eradication and elimination of micrometastases. In a study by Benedetti-Panici et al. in women with advanced cervical cancer given neoadjuvant chemotherapy, a 48% to 100% operability rate is observed with no influence on surgery-related morbidity. Pathologically confirmed complete responses were detected in 9% to 18%, and the incidence of lymph node metastases was much lower than expected for the same stage and tumor size.[3] The five-year survival rates of 83% and 45% for stages IB2-IIB and stage III, respectively, strongly suggest a cure benefit from neoadjuvant chemotherapy when it was followed by radical surgery compared with exclusive radiation therapy alone.[3]

The list of active chemotherapeutic drugs for cervical cancer that can be used in the neoadjuvant setting is limited. Cisplatin is the most active and extensively evaluated single agent chemotherapeutic drug in the treatment of cervical cancer with a response rate of 23%.[4] Ifosfamide, a compound chemically similar to cyclophosphamide, is also an active agent for cervical cancer. It is active in non-irradiated sites of the disease with a response rate of 20-50%.[5] Dibromodulcitol is a halogenated sugar that acts as an alkylating agent with an overall response rate of 15%.[6] Doxorubicin is another drug that can be used as a single agent chemotherapy for cervical cancer with a response rate of 20%. Single-agent chemotherapy generally has lower response rates than combination drug therapy. However, improvement of survival has not been demonstrated.[1]

Since Ifosfamide and Cisplatin have demonstrated synergistic actions in tumor models and since both drugs are active single agents in cervical cancer, studies on its combination as a

neoadjuvant treatment regimen to improve long-term local and distant disease control and survival in patients with advanced cervical cancer have been done. Lara, et al. (1990) reported a partial response rate of 62.5% and a three-year disease-free survival of 54% after neoadjuvant therapy with Ifosfamide and Cisplatin and subsequent radiotherapy in stage IIB squamous cell carcinoma of the cervix without major toxicity. In a study by Cervellino, et al.[5] (1995), the combination of Ifosfamide and Cisplatin was well tolerated and had a 50% overall remission rate with improvement of quality of life for patients with advanced stage cervical carcinoma. Bolis, et al.[7] (1996) reported a 69.6% response rate (64.5% partial response [reduction of tumor size by > 50%] and 5.1% complete pathologic response [disappearance of disease at histological examination]) for a neoadjuvant Cisplatin-Ifosfamide regimen in stage IB – IIB invasive cervical cancer. The overall 24-month survival rate was 80% (93% for responders and 43% for non-responders). A study by De Jonge, et al.[2] (1997) on 62 patients with Stage IIB diseases showed 17 patients with complete response (31%) and 27 patients with partially response (49%), and 11 patients with stable disease (20%), for an overall response rate of 80% after using 2 cycles of a combination regimen of Cisplatin 20 mg/m$^2$ and Ifosfamide 1.2 gm/m$^2$ on Days 1-5 of a 21-day cycle.

Thus, this study was initiated to determine the local applicability of neoadjuvant Cisplatin-Ifosfamide followed by radical surgery to hopefully obviate the need for brachytherapy which is definitely lacking in facilities in the Philippine setting.

## Objectives

### *General Objective*

The objective of this study was to determine the efficacy and safety of neoadjuvant Cisplatin-Ifosfamide, followed by radical surgery on patients with bulky early stage (IB2-IIB) cervical cancer.

### *Specific Objectives*

1. To determine the patient demographics of patients with bulky early stage (IB2-IIB) cervical cancer.
2. To determine the tumor characteristics of patients with bulky early stage (IB2-IIB) cervical cancer.
3. To determine the overall response rate (complete response, partial response and stable disease) to neoadjuvant Cisplatin-Ifosfamide of patients with bulky early stage (IB2-IIB) cervical cancer.
4. To determine the chemotherapy toxicities to neoadjuvant Cisplatin-Ifosfamide of patients with bulky early stage (IB2-IIB) cervical cancer.
5. To determine the surgical complications during radical surgery (radical hysterectomy, bilateral salpingo-oophrectomy, lymph node dissection) after neoadjuvant Cisplatin-Ifosfamide of patients with bulky early stage (IB2-IIB) cervical cancer.
6. To determine the survival rates of patients with bulky early stage (IB2-IIB) cervical cancer after neoadjuvant Cisplatin-Ifosfamide followed by radical surgery.

## Materials and Methods

### *Patient Population*

Patients with bulky (i.e. tumor size > 4 cm) early stage (i.e. stage IB2 – IIB) cervical cancer from May 2000 to November 2002 were included in the study. The following were the inclusion and exclusion criteria:

### *Inclusion Criteria*

1. Age $\geq$ 18 to $\leq$ 60 years old.
2. Histological proven cervical cancer.
3. Patients with bulky (tumor size > 4 cm) early stage (IB2-IIB) cervical cancer. (Appendix A – FIGO Staging for Cervical Cancer)
4. All patients must have measurable or evaluable disease. (Appendix B - Definitions of Disease and Response)

5. Patients must not have received any prior treatment for cervical cancer.
6. ECOG performance status of 0-2. (Appendix C)
7. Life expectancy greater than 12 months
8. Normal organ function, except if abnormal due to tumor involvement.
   a. Adequate bone marrow function as indicated by:
      - Platelets $\geq$ 150,000/mm$^3$
      - Hemoglobin $\geq$ 11 g/dl
      - Absolute Neutrophil Count $\geq$ 1.5 x 10$^3$/mm$^3$
   b. Adequate renal function as indicated by:
      - Serum Creatinine < 2.5 mg/dl
   c. Adequate liver function as indicated by:
      - Total Bilirubin and AST < 2 times upper limit of normal
9. Written informed consent.

*Exclusion Criteria*

1. Patient has received prior treatment (radiotherapy and/or chemotherapy) for cervical cancer.
2. History of cardiac disease, with New York Heart Association Class II or greater with congestive heart failure. (Appendix D)
3. Clinically significant hepatic and/or renal disease.
4. Patient has uncontrolled bacterial, viral, or fungal infection.
5. Patient exhibits confusion or disorientation.
6. Any condition (medical, social, psychological) which would prevent adequate follow up.
7. Any other active primary tumor under treatment, except basal or squamous cell carcinoma of the skin, or carcinoma in situ.
8. Prior biologic response modifiers, or any other investigational drugs.

*Methodology*

This was a phase II study of Ifosfamide in combination with Cisplatin as neoadjuvant treatment prior to radical surgery for patients with bulky early stage cervical cancer.

Neoadjuvant Cisplatin and Ifosfamide were administered as follows:

*Cisplatin was diluted according to package insert guidelines. Each patient received Cisplatin 20mg/m$^2$ as a 1-hour infusion intravenously via a peripheral or central line on days 1-5 of each cycle in a 28-day cycle. No dose reduction was permitted for Cisplatin.*

*Immediately following the end of the Cisplatin infusion, each patient received Ifosfamide 1.2gm/m$^2$ solution in D5W 500 cc as a 30-min infusion via a peripheral or central line on days 1-5 of each cycle in a 28-day cycle. Cisplatin was always administered first before the Ifosfamide.*

*Uromitexan at 20% of the Ifosfamide dose was administered at 0, 4, 8 hours from Ifosfamide infusion on days 1-5 of each cycle in a 28-day cycle.*

The dose limiting toxicities of both chemotherapeutic agents and any adverse reactions were assessed carefully prior to administration of the next cycle. Increasing the length of the cycle was the optimum method for avoiding subsequent occurrence of the toxicities if present.

Active follow up included physical and pelvic examinations, laboratory tests and evaluation of adverse experiences. Patients had appropriate radiological imaging (X-ray, ultrasonography, computerized tomography scan and/or magnetic resonance imaging) to document baseline disease.

Patients were followed up weekly for hematological toxicities. Radiological imaging was repeated after the second cycle of chemotherapy to assess disease status. Patients who achieved complete or partial response, stable disease, or progressive disease after the two cycles were recorded for response rates.

Cytokines, although discouraged prophylactically, were allowed under specific circumstances in this study. Patients would need cytokine support in cases of prolonged neutropenia

(grade 4 neutropenia lasting > 7 days, or failure of white blood cell count to recover by 22 days from Day 17 of treatment), or the occurrence of febrile neutropenia in a prior cycle of treatment.

All patients were premedicated with 5HT3 antagonists (anti-emetics) prior to receiving Cisplatin and were properly hydrated as per local institution protocol for Cisplatin infusion.

Approximately two weeks from the second cycle of Cisplatin-Ifosfamide, assuming there is no disease progression, patients underwent a Wertheim's type II or III radical hysterectomy (RH), bilateral salpingo-oophorectomy (BSO) and pelvic and para-aortic lymph node dissections (LND). Intra-operative findings, surgical morbidities and surgico-pathologic factors were recorded.

All patients were followed up for a minimum of three years for disease-free interval and over-all survival.

*Sample Size*

The study being a phase II trial did not warrant any sample size calculation.

*Statistical 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 progression in months was also calculated.

The primary endpoint was objective response rate as determined by physical examination, radiological assessment, and surgical histopathologic factors.

Secondary endpoints included progression-free survival and overall survival. Kaplan- Meier estimates and curves were used to present progression-free survival and overall survival.

Safety was assessed by examination of adverse events, clinical laboratory data, and vital signs. Adverse events, use of cytokines and changes in the laboratory parameters were also summarized and noted.

## Results

*Patient Characteristics*

Between May 2000 and November 2002, nine patients were included in the study (Tables 1 & 2). The patients had a mean age of 42 years with an age range of 32 – 52 years. Squamous cell carcinoma, large cell non-keratinizing was seen in 6 cases (62.5%) with a mean tumor diameter of 6.5 cms (range: 3-10 cm). There was a total of five cases of stage IB2 (55.56%), one stage IIA bulky disease (11.11%) and three stage IIB diseases (33.33%).

*Clinical Response and Toxicity to Neoadjuvant Chemotherapy*

All patients received a total of two cycles of neoadjuvant Cisplatin-Ifosfamide. After two cycles of chemotherapy, there were five cases of partial response (55.56%), one complete response (11.11%) and one stable disease (11.11%) giving an overall response rate of 77.78%. There were no reported grade 3-4 toxicities.

*Surgical Intervention*

Radical surgery (RHBSO-LND) was successfully done in 6 cases (66.67%) after two cycles of chemotherapy. There was one case of bladder injury incurred during radical surgery. There was one case of complete pathologic response (11.11%).

*Response After Treatment*

Six (66.67%) patients eventually died of persistent progressive disease with a mean survival of 33 weeks. However, 3 of the 6 patients (50%) who expired did not complete the 3 treatment modalities (i.e. neoadjuvant chemotherapy, radical surgery and adjuvant pelvic external beam radiotherapy). There are three patients (33.33%) who are presently alive with no evidence of disease. Three surviving patients comprise half (50%) of the 6 patients who actually completed all 3 treatment modalities.

## Discussion

Although the advent of concomitant chemoradiation for cervical cancer has decreased overall death rate significantly, the current standard of treatment for cervical cancer is still suboptimally delivered in patients residing in developing countries. One of the treatment options to address the lack of radiotherapy facilities, specifically brachytherapy units, is the use of neoadjuvant chemotherapy followed by radical surgery and external radiation for cervical cancer. In this study, the authors report the results of a treatment modality incorporating neoadjuvant chemotherapy followed by radical surgery for early stage cervical carcinoma with tumor diameters of more than 4.0 cm (i.e. bulky disease).

A study by Bolis, et al.[7] on neoadjuvant Cisplatin-Ifosfamide regimen for stage IB – IIB invasive cervical cancer reported a 69.6% response rate (64.5% partial response and 5.1% complete pathologic response). De Jonge, et al.[2] showed a complete response of 31%, a partial response of 49%, and a stable disease of 20%), for an overall response rate of 80%, after using two cycles of a combination regimen of Cisplatin 20 mg/m$^2$ and Ifosfamide 1.2 gm/m$^2$ on Days 1-5 of a 21-day cycle on patients with a stage IIB disease. In this study, all patients received two cycles of neoadjuvant Cisplatin-Ifosfamide with no grade 3-4 toxicities. After two cycles of chemotherapy, there were five cases of partial response (55.56%), one complete response (11.11%) and one stable disease (11.11%), giving an overall response rate of 77.78%.

Neoadjuvant chemotherapy prior to a radical surgery is a promising treatment modality for patients with early stage cervical cancer. Studies have shown that neoadjuvant chemotherapy with radical surgery is more effective than radiotherapy alone. Chemotherapy-induced tumor shrinkage rendered radical excision possible in a high percentage of cases. Longer overall and progression-free survival rates were observed in the chemosurgery arm as compared with radiotherapy alone.[3] Previous studies have shown that the operability rate after neoadjuvant chemotherapy in advanced cervical cancer was between 60% - 70% and surgery was performed in 95% of cases.[8] The response to chemotherapy is not the sole indicator in the determination of the degree of operability. We must take into account the crucial role of the surgeons and their aggressiveness to operate or not. In this study, radical surgery was made possible after two cycles of Cisplatin-Ifosfamide in 66.67% of cases.

Studies have shown that there is an increased survival rate for patients who had chemotherapy followed by radical surgery than those without surgery or radiotherapy alone. The five-year disease-free rate is 72.2% - 85.3% for the patients who had surgery after neoadjuvant chemotherapy as compared with 25.0% - 31.3% survival rate for those who had radiotherapy.[8] Bolis, et al.[7] showed an overall 24-month survival rate of 80% (93% for responders and 43% for non-responders) when they used neoadjuvant Cisplatin-Ifosfamide prior to surgery for stage IB – IIB invasive cervical cancer. In this study, three out of nine patients (33.33%) remained alive without evidence of disease. However, focusing on just the patients who completed all three treatment modalities (i.e. neoadjuvant chemotherapy, radical surgery and adjuvant pelvic external beam radiotherapy), three out of six patients (50%) account for the three surviving patients.

Nevertheless, it is still unfortunate that majority of the patients (66.67%) in this phase II study died of the disease after a mean survival of 33 weeks. However, three of the six patients (50%) who expired did not actually complete the three treatment modalities which may explain eventual progression of disease. It is apparent that affordability of treatment, not only the lack of radiotherapy facilities, is also a major factor in the battle against cervical cancer.

In conclusion, neoadjuvant Cisplatin-Ifosfamide followed by radical surgery and adjuvant external beam radiotherapy is a feasible management option for bulky early stage (IB2-IIB) cervical cancer, especially in regions where there are no or sparse brachytherapy facilities. Only a randomized controlled trial comparing neoadjuvant chemotherapy followed by radical surgery and adjuvant external beam radiotherapy versus upfront

concomitant chemoradiation for bulky early stage (IB2-IIB) cervical cancer can determine its true efficacy and safety.

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**Appendix A.** Figo staging of cervical cancer.

| | |
|---|---|
| STAGE 0 | Carcinoma in situ; Cervical intraepithelial neoplasia grade III |
| STAGE I | The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded). |
| Stage IA | Invasive carcinoma that can be diagnosed only by microscopy. All macroscopically visible lesions - even with superficial invasion - are allotted Stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not more than 7.0 mm. Depth of invasion should not be more than 5.0 mm related to the base of the epithelium of the original tissue - superficial or glandular. The involvement of the vascular spaces - venous or lymphatic - should not change the stage allotment. |
| Stage IA1 | Measured stromal invasion of not more than 3.0 mm in depth and extension of not more than 7.0 mm |
| Stage IA2 | Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm with an extension of not more than 7.0mm |
| Stage IB | Clinically visible lesions limited to the cervix uteri, or subclinical cancers greater than Stage IA |
| Stage IB1 | Clinically visible lesions not larger than 4.0 cm |
| Stage IB2 | Clinically visible lesions larger than 4.0 cm |
| STAGE II | The carcinoma extends beyond the cervix but has not extended to the pelvic wall. The carcinoma involves the vagina but not as far as the lower third. |
| Stage IIA | No obvious parametrial involvement |
| Stage IIB | Obvious parametrial involvement |
| STAGE III | The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to other causes. |
| Stage IIIA | No extension to the pelvic wall |
| Stage 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 clinically involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allotted to Stage IV. |
| Stage IVA | Spread of growth to adjacent organs |
| Stage IVB | Spread to distant organs |

**Appendix B.** Definitions 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 bone 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 lesion 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 first evidence of progression

**Survival**

From the time of start of 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 analyses of evaluable patients, intent-to-treat analyses 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 study drug (partial or complete dose) will be evaluable for safety.

**Appendix C.** 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 diabled; No self-care |
| 5 | Dead |

RECOMMENDATIONS

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

**Appendix D.** New York Heart Association Classification.

| | |
|---|---|
| CLASS I | Patients in whom angina is provoked by strenuous exertion. Patients with cardiac disease but 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 sligh limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, 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 any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest |

# Tumor Ploidy in Mucinous Ovarian Tumors*

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**Background:** Epithelial ovarian cancer remains the second most common gynecologic cancer and the leading cause of death from gynecologic malignancy. Survival is influenced primarily by extent of disease at the time of diagnosis. Prognostic factors that are well-established fail to account fully for the biologic behavior of ovarian carcinoma. It is of interest therefore to identify new prognostic factors which are more objective, quantifiable and reproducible. DNA ploidy has been shown to be an independent prognostic factor in epithelial ovarian malignancies. The general objective of the study was to determine the ploidy characteristics of epithelial ovarian cancers particularly the mucinous type and to associate these with different clinico-pathologic variables. **Methods:** Forty eight patients with a final histopathology of mucinous type of epithelial ovarian cancer were included. DNA ploidy was determined using flow cytometry of paraffin embedded blocks at another institution. **Results:** DNA ploidy was obtained in all of the 48 paraffin-embedded blocks. Aneuploidy was established in 4 (8.33%) tumors. Two from 24 mucinous cystadenocarcinoma (8.33%) and 2 from 24 mucinous tumor of low malignant potential (8.33%) showed an aneuploid DNA profile. The average age for those with DNA aneuploid was 48.5 years old. Twenty two (91.66 %) mucinous tumor of low malignant potential were diploid. Likewise, the remaining (91.66%) cases of mucinous cystadenocarcinoma were also diploid. **Conclusion:** Results confirmed that aneuploidy is present in older patients. Results also showed that the incidence of aneuploidy is similar for both tumors of low malignant potential and for mucinous cystadenocarcinoma. No further association yet can be given pending the recommended continuation of this study. It is recommended upon continuation of this study to reach a larger population size by including the other histologic types of epithelial ovarian cancers and that patient survival be included in the analysis to prove the prognostic value of DNA ploidy in the local setting.

**Key words:** epithelial ovarian cancer, mucinous tumors of the ovary, tumor ploidy, flow cytometry

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Epithelial ovarian cancer remains the second most common gynecologic cancer and the leading cause of death from gynecologic malignancy.[1] In the Philippines, the ovary is the fifth leading site of cancer among females.[2] Survival is influenced primarily by extent of disease at the time of diagnosis. About two thirds of patients present with advanced disease despite the paucity of symptoms. Early detection is difficult because of lack of appropriate tumor markers and clinical symptoms.[3] The International Federation of Gynecology and Obstetrics (FIGO) stages I and II account for 20-40% of all cases of epithelial ovarian cancer. The five-year survival rates range from 60% to 95% for stage I and from 35% to 70% for stage II. The differences in survival may be explained by the presence of heterogeneity of women in the classic series because of the inclusion of tumors of low malignant potential and inclusion of stage III patients after incomplete surgical staging.[4] Prognostic factors that are well-established such as FIGO stage, histologic type, grade of differentiation, amount of residual tumor, age, and performance status are insufficient for predicting prognosis of the individual patient diagnosed with ovarian cancer.[5] These factors fail to account fully for the biologic behavior of ovarian carcinoma. The morphologic spectrum of ovarian mucinous tumors is well known, but the features that predict aggressive behavior are still controversial.[19] Over the last decade, along with the increase in interest in identifying new prognostic factors, investigations dealt with more objective, quantifiable and reproducible prognostic variables.

DNA ploidy has been shown to be an independent prognostic factor in epithelial ovarian malignancies.[6] Recently, attention has focused on borderline lesions to determine if flow cytometry plays a role in separating potentially aggressive tumors from those which pursue a more innocuous course. All other atypical mucinous tumors, when confined to the ovary and optimally sampled, had an excellent prognosis. DNA ploidy analysis may prove useful in determining the risk of progression, especially in stage 1 invasive mucinous carcinomas.

This finding of Gaweski, et al. is also consistent with the findings of previous investigators. In his study, flow cytometric analysis was done from paraffin-embedded tumor blocks of 87 patients. The goal was to define high risk patients with early-stage disease who might benefit from adjuvant therapy. The finding is noteworthy since the dilemma in treatment regarding adjuvant therapy and aggressiveness is highly debated for this group (stage I and II). In another study, flow cytometric DNA quantification was the main independent prognostic factor of relapse and survival in women with Stage I – II epithelial ovarian cancers.[4] Clinical management of patients with these diseases may be aided by studying their tumors for these objective markers of biological aggressiveness.

Ploidy is usually assessed by a technique called flow cytometry. This can be used to measure the number of cells in the S-phase of the mitotic cycle. This latter measurement is, however, best considered under the heading of "proliferation indices" and only the use of flow cytometry for ploidy determination is usually employed. Ploidy and proliferative activity are the two properties commonly measured by DNA content flow cytometric study. These two properties were used as biologic predictors of aggressive behavior in a variety of ovarian carcinomas. Both abnormalities are associated with poor outcome in all stages of ovarian cancer.

Ploidy can also be evaluated by the currently less commonly used technique of static image cytometry in which the DNA content of Feulgen-stained nuclei in histological sections of touch preparations is measured via an image analysis system. Although there is a good correlation between ploidy results obtained from flow and static image cytometry, the static image technique allows for the identification of small subpopulations of aneuploid tumor cells that may be missed on flow cytometry; static cytometry also has the advantage that tissue morphology is retained. It is possible that static image cytometry will be more widely utilized in the future but most reported studies of ploidy in gynecological tumors have been based upon flow cytometric data.[6,7,8]

Flow cytometry is a relatively simple and rapid technique for the measurement of cellular DNA content which can be used on both fresh and archival tissue and allows for tumors to be classified, in general terms, as either diploid or aneuploid. In essence, either cells are dissociated from tumors by mechanical or enzymatic techniques or recovered from paraffin blocks, stained with a fluorochrome dye that binds specifically and stoichiometrically with nucleic acids and then passed through a flow cytometer in a liquid suspension medium as a laminar flow jet. Flow cytometers measure and record fluorescence and light scatter in the cells and the fluorescence of the stained cells is converted into a digital electronic signal: the results are shown as a histogram in which the number of stained cells is plotted as a function of the intensity of the fluorescence. If the main peak of the DNA histogram centers around the 2C region and the overall DNA distribution is comparable to that of normal somatic cells, the tumor is classified as diploid. Populations of cells with a DNA content dissimilar to that of normal cells are classified as aneuploid and these may be hypodiploid, hyperdiploid or tetraploid. The DNA index (DI) is calculated by dividing the modal DNA content of the tumor cells in G0/G1 phases of the mitotic cycle: diploid cells will therefore have a DI of 1 while aneuploid cells will have a DI of less than 1, more than 1 or, if tetraploid, 2.

The technique is not, however, without its pitfalls and difficulties and can detect DNA aneuploidy only if a significant proportion of the tumor cells have lost or duplicated several chromosomes. Other variables that have to be taken into consideration are the method of extraction and staining of the nuclei, delays in tissue fixation, intra- and inter-laboratory variability, the minimum number and proportion of tumor cells analyzed, the choice of the reference cell population, the program for debris correction and, very importantly, tumor heterogeneity.[9] The general objective of the study was to determine the ploidy characteristics of mucinous tumors of the ovary. The specific objectives were to determine the association of age and aneuploidy, the association of tumor size and aneuploidy and the association of stage and aneuploidy.

## Materials and Methods

*Patient Population*

The eligibility criteria for the patients included final histopathology of mucinous ovarian cancer and the availability of representative samples for flow cytometry. The exclusion criteria included previous treatment with chemo- or radiotherapy and other previous or concomitant malignant disease.

The study required 323 patients based on the incidence of aneuploidy in epithelial ovarian cancers of 70%, margin of error of 0.05 and confidence level of 95%. All tissues originated from patients who were surgically staged between 2004 and 2009. However, due to limited budget, the study population consisted only of 48 paraffin blocks from 48 cases of mucinous type of ovarian tumors. 24 belonged to the histopathologic type mucinous cystadenocarcinoma of low malignant potential (LMP) and the remaining half were mucinous cystadenocarcinoma. Even with those limitations, the researchers wanted to test the possibility of doing the study in the local setting considering that DNA ploidy testing through flow cytometry is a new independent prognostic factor in epithelial ovarian malignancies[3], thus guiding the clinicians in the postoperative management.

*Data Collection*

The list and registry of epithelial ovarian cancer cases from 2004 to 2009 were obtained and reviewed from the surgico-pathologic census and weekly ward reports of the Department of Obstetrics and Gynecology. A total of 48 cases of mucinous tumors of the ovary were included. There were 24 cases with mucinous cystadenocarcinoma of low malignant potential and 24 cases with mucinous cystadenocarcinoma. Tumor type was documented with the World Health Organization classification.[16] Clinical data were obtained from the Medical Records Section, files from the Cancer Institute and

files from the Surgical Pathology Census of the Department of Obstetrics and Gynecology. Clinical data were retrospectively analyzed and recorded. The patient characteristics retrieved were age, tumor size, intraoperative and final stage according to the International Federation of Gynecology and Obstetrics. [10] Histopathologic reports, archieval paraffin blocks and corresponding slides were retrieved from the Surgical Pathology Section. These were sent to the Histopathology/Immunology Section of another institution for review and tumor ploidy test using flow cytometry.

### DNA Ploidy by Flow Cytometry and Analysis

Briefly, a monodispersed cell suspension is prepared from physical and chemical disruption of 5 strips of 50 micron section from paraffin embedded tissue, previously microdissected for tumor cell enrichment. The resulting cell suspension is incubated simultaneously with RNAse to remove RNA and Propidium iodide for DNA staining. The tissue sections are deparaffinized using three cycles of xylene incubation and rehydrated with decreasing strengths of ethanol and final incubation in distilled water. The rehydrated sections are enzymatically digested with pepsin incubation at 37°C for 45 minutes after mechanical disaggregation with a glass pestle. The sample is resuspended in RPMI, filtered using a membrane filter and stained with Bauer's stain solution at 37°C for 20 minutes. Room temperature Bauer's salt solution is added and the sample is vortezed and stored at 4°C until flow cytometric analysis.

Flow cytometric analysis of the cell suspension is performed with an excitation wavelength of 342nm-514nm and the resultant emission is measured at 610 nm. DNA histograms are generated which are then analyzed for diploid and aneuploid peaks. Criteria for aneuploidy would include the following:

1. Two or more distinct G0/G1 peaks with the second peak having a DNA index of 0.95 to 1.05.
2. Single G0/G1 peak with right sided shoulder.
3. G2M peak over 10% of the total population.

## Results

The average age of patients was 39.05. The range was from 13 to 72 years of age. The most common symptoms are abdominal mass (100%) and increase in abdominal girth (100%). Other signs and symptoms experienced were as follows in decreasing order of incidence: anorexia and abdominal pain (31.25%), weight loss (14.6%), ascites (12.25%), and edema (6.25%). Most of the cases had an intraoperative and final stage of 1A (79.1%). The remaining had a final stage of 1C (10.4%), IIIA (2.1%), IIIB (4.2%) IIIC (6.25%). The largest tumor size was 60cm in its widest diameter and the smallest was 12cm.

DNA ploidy was obtained in all of the 48 paraffin-embedded blocks of mucinous tumors of the ovary analyzed in the present study (Table 1). Aneuploidy was established in four (8.33%) tumors - two from 24 mucinous cystadenocarcinoma (8.33%) and two from 24 mucinous tumor of low malignant potential (8.33%). All four showed a multiploid aneuploid DNA profile. The average age for those with DNA aneuploidy was 48.5. (Table 2). Twenty-two (91.66%) mucinous tumor of low malignant potential were diploid as well as the remaining 22 (91.66%) cases of mucinous cystadenocarcinoma. The mean age for those with DNA diploid was 39.05. Aneuploidy was found on the widest diameter of the primary tumor which ranged from 11cm to 40cm.

## Discussion

This is a study in which flow cytometric DNA analysis has been carried out on epithelial tumors of the ovary in this tertiary institution. In this study, the DNA ploidy pattern was investigated in 48 primary mucinous tumors of the ovary. Though a small study population, the results have shown that patients with aneuploid tumors were older than those with diploid tumors. This finding was of no surprise, because ovarian cancer is most common in menopausal women over 45 years of age. [11] Findings were also similar to that of the studies of Zangwill and Klemi, wherein patients with ovarian

Table 1. DNA ploidy classification.

| Histopathologic Type | DNA Ploidy Distribution DIPLOID | ANEUPLOID |
|---|---|---|
| Mucinous cystadenocarcinoma | 22 | 2 |
| Mucinous Tumor of Low Malignant Potential | 22 | 2 |
| STAGE | | |
| I | 38 | 4 |
| II | N.A. | N.A. |
| III | 6 | 0 |
| IV | N.A. | N.A. |

Table 2. Clinicopathologic variables.

| | | |
|---|---|---|
| AGE (mean), years | 39.05 | 48.5 |
| Gravidity (mean) | 2 | 5 |
| Parity (mean) | 2 | 5 |
| Tumor Size (largest diameter), Centimeters | | |
| ≤ 10 | 0 | 0 |
| 11 - 20 | 5 | 1 |
| > 20 | 39 | 3 |

cancers with aneuploidy were older than those patients with diploid DNA.[8,12]

The results also showed that the incidence of aneuploidy were similar for both mucinous cystadenocarcinoma and mucinous tumor of low malignant potential (8.33%). This finding was not consistent with the study of Harlow, wherein the author concluded that only less than a third of patients with mucinous tumors of low malignant potential had aneuploidy.[5] Patients with aneuploid type of mucinous tumor of low malignant potential had a poor survival rate than did those with their diploid counterparts and should be treated like a low grade epithelial ovarian cancer as mentioned in the study made by Ehen, et al.[20]

According to Trope, nearly 80% of patients with advanced ovarian carcinoma are aneuploid and that aneuploidy was more frequent in tumors with poorly differentiated histologic type or nuclear atypia. This finding however was not shown in this study since the study population was only confined mostly with Stage 1A (79.1 %).

With the limited population, aneuploidy cannot be associated yet with the variables on tumor size with aneuploidy. Several studies state that tumor aneuploidy has been seen to correlate with a poor prognosis of ovarian cancer both in advanced[13,14] and early stage disease.[6,15] It is therefore recommended that continuation of the study be done to correlate the DNA ploidy findings with patient survival to further confirm these findings in the local setting.

## Summary and Conclusion

The results of the study on tumor ploidy of mucinous tumors of the ovary were presented. The DNA ploidy was determined without knowing the final outcome in terms of the overall survival of the patients. Results confirmed that aneuploidy is present in older patients. Results also showed that the incidence of aneuploidy is similar for both tumors of low malignant potential and for mucinous cystadenocarcinoma. No further association yet can be given pending the recommended continuation of this study. It is recommended that this study be continued to reach a larger population size. It is also recommended that survival be included in the analysis to prove the prognostic value of DNA ploidy in the local setting.

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# Accuracy of Ultrasound in Pre-Operative Assessment of Patients with Early Stage Non-Bulky Cervical Carcinoma: A Preliminary Report

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**Objective:** To determine the accuracy of ultrasound in predicting poor prognostic factors in patients with early stage non-bulky cervical carcinoma who will undergo radical hysterectomy. The specific objectives are to determine the specificity, sensitivity, positive predictive value and negative predictive value and likelihood ratios of sonographic examination in pre-operative assessment of the following poor prognostic factors of cervical carcinoma: tumor size, parametrial involvement, cervical stromal invasion and lymph node involvement. **Materials and Methods:** Patients with stage IB1 and non-bulky IIA cervical cancer for radical hysterectomy (RH), bilateral salpingo-oophorectomy (BSO), pelvic lymph node dissection (BLND) and para-aortic lymph node sampling (PALS) from January 27, 2009 to July 14, 2009 were included in the study. Poor prognostic factors of cervical carcinoma determined through pre-operative pelvic examination and sonographic examination were compared to the final histopathologic result. **Results:** A total of 13 patients were included in the study. The mean age was 50 years old with a range of 32-57 years. Histologic types were squamous cell carcinoma (n = 12), adenocarcinoma (n = 1), and transitional carcinoma (n = 1). Majority of the patients were clinical stage IB1 (n = 12). There was one case of clinical non-bulky stage IIA. All patients underwent radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. One patient did not undergo para-aortic lymphadenectomy because of intraoperative blood loss. Assessment of tumor size greater than or equal to 2 cm by pelvic examination showed a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 71.4%, 83.3%, 83.3%, 71.4%, and 81.25%, respectively. False negative and false positive rates were 28.6% and 16.7%, respectively.

* Won third place in the 2009 Philippine Society of Oncology (PSO) Research Contest.
* With permission for publication from the Philippine Society of Oncology.

Assessment of tumor size greater than or equal to 2 cm by sonography showed a sensitivity, specificity, PPV, NPV, and accuracy of 85.7%, 33.3%, 60%, 66.7%, and 72.22%, respectively. False negative and false positive rates were 14.3% and 66.7%, respectively. Only one patient had parametrial involvement by histology. This was not detected by pelvic examination. Ultrasound identified two patients as having parametrial involvement, however only one was confirmed by histology. Sensitivity, specificity, PPV, NPV, accuracy was 100%, 91.6%, 50%, 100%, and 92.86% respectively. False negative and false positive rates were 0 and 8.4%, respectively. Stromal invasion of greater than one third by ultrasound had a sensitivity, specificity, PPV, NPV, false negative rate, false positive rate, and accuracy of 100%, 50%, 70%, 100%, 0%, 50%, and 81.25%, respectively. Only one patient had pelvic lymph node involvement by ultrasound which was confirmed by histology.

**Conclusion**: Ultrasound can be used to detect preoperative poor prognostic factors in patients undergoing radical hysterectomy for early cervical cancer, however false positivity is high. Pre-operative ultrasound can be used to advise the patient of a possibility of adjuvant treatment after surgery however final histopathology will determine this. Although chemoradiation can be used as primary treatment for early cervical cancer, poor prognostic factors seen in preoperative ultrasound should not deter the surgeon from proceeding with surgery.

**Key words**: non-bulky cervical carcinoma

Cervical cancer ranks second in the leading causes of cancer deaths of Filipino women and is the top gynecologic cancer in the Philippines.[1] Relentless efforts are being made for its prevention, early detection, and successful treatment.

Early stage cervical cancer has high survival rates of 80.1% - 94.5% and can be treated by either surgery or concurrent chemoradiation.[2] Radical hysterectomy with lymph node dissection is done for early stage cervical cancer. Chemoradiation entails a combination of external beam radiation therapy concurrent with weekly Cisplatin followed by brachytherapy.[3-7] Various studies have proven that both surgery and radiotherapy offer similar overall and disease-free survival rates.[8]

In the Philippines where there is a lack of radiotherapy facilities accessible to indigent patients, surgery has the advantage of eradication of the primary tumor in one sitting. Chemoradiotherapy on the other hand, requires the patient to go to the radiotherapy center daily and to her oncologist weekly for radiosensitizing chemotherapy. This becomes difficult for patients with limited funds who need to spend for treatment, as well as transportation expenses. This is apparent in our setting in which 44.8% of newly diagnosed cervical cancer patients are lost to follow-up mainly because of financial reasons.[9] Thus, surgery is a very attractive management for operable patients (stage IB1 to non-bulky IIA) to eliminate the limitations of radiotherapy.

Several surgico-pathologic prognostic factors have been identified in the radical hysterectomy specimen associated with tumor recurrence. These include tumor size of > 2 cm, greater than one third cervical stromal invasion, positive lines of resection, lymph node metastasis, lymphovascular space invasion, endomyometrial invasion and

abdominal metastasis. If these factors are found, postoperative adjuvant treatment in the form of concurrent chemoradiation is deemed necessary.[10]

The combination of surgery and radiotherapy, however, has the worst morbidity especially urological complications.[8] In the presence of poor prognostic factors pre-operatively, a surgeon may decide to institute chemoradiation rather than pursue surgical intervention. Or if surgery is still contemplated, the surgeon may advise the patient of the need for postoperative adjuvant therapy. Thus, it is prudent to determine poor prognostic factors in patients who are candidates for surgery. The International Federation of Gynecology and Obstetrics (FIGO) has limited clinical staging to findings from physical examination, colposcopy, chest radiography, intravenous pyelography, cystoscopy, proctosigmoidoscopy, barium enema, and skeletal survey. This stems from the belief that staging methods should be universally available so that staging can serve as a standardized means of communication between institutions and around the world.

However, clinical staging has its inaccuracies. Surgical staging has shown that FIGO clinical staging results in understaging of up to 20 – 30% in stage IB, up to 23% in stage IIB, and nearly 40% in stage IIIB. It also produces overstaging of approximately 64% in stage IIIB.[11] These inaccuracies primarily involve assessment of the parametria, pelvic sidewalls, and pelvic and paraaortic lymph nodes.

Clinical staging also fails to evaluate the cranio-caudal measurement of the cervical tumor, cervical stromal invasion and endomyometrial invasion, which as mentioned, represent poor prognostic factors necessitating adjuvant concurrent chemoradiation in patients who have undergone radical surgery as the primary mode of treatment.

Determination of tumor size, stromal infiltration and other prognostic factors are

**Table 1.** FIGO staging of cervical cancer.

| | |
|---|---|
| Stage I | Carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded. |
| Stage IA | Invasive cancer diagnosed only by microscopy. All macroscopically visible lesions even with superficial invasion are stage Ib cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm* and no wider than 7mm. |
| Stage IA1 | Stromal invasion is no greater than 3 mm in depth and no wider than 7 mm in horizontal spread. |
| Stage IA2 | Stromal invasion >3 mm but 5 mm in depth and with horizontal spread of 7 mm. |
| Stage IB | Clinically visible lesions confined to the cervix or microscopic lesions greater than stage IA2. |
| Stage IB1 | Clinically visible lesions no greater than 4 cm in greatest dimension. |
| Stage IB2 | Clinically visible lesions > 4 cm in greatest dimension. |
| Stage II | Tumor extends beyond the cervix but has not extended onto the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third. |
| Stage IIA | No obvious parametrial involvement. Involvement of up to the upper two-thirds of the vagina. |
| Stage IIA1 | Clinically visible lesions no greater than 4 cm in greatest dimension. |
| Stage IIA2 | Clinically visible lesions > 4 cm in greatest dimension. |
| Stage IIB | Obvious parametrial involvement, but not onto the pelvic sidewall. |
| Stage III | Tumor extends to the pelvic sidewall and/or involves the lower third of the vagina and/or causes hydronephrosis or non-functioning kidney. On rectal examination, there is no cancer free space between the tumor and the pelvic sidewall. |
| Stage IIIA | No extension to the pelvic sidewall but involvement of the lower third of the vagina. |
| Stage IIIB | Extension to the pelvic sidewall or hydronephrosis or non-functioning kidney. |
| Stage IV | Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum. |
| Stage IVA | Spread of the tumor onto adjacent pelvic organs. Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis. |
| Stage IVB | Spread to distant organs. |

important in treatment individualization, especially for young patients who are planning fertility-sparing procedures or are candidates for ovarian preservation. The absence of poor prognostic factors allows them to undergo these procedures for future childbearing and delay of menopause.

Numerous studies have shown that CT and MRI can aid in the evaluation of these prognostic factors. Cross sectional imaging in the form of MRI can accurately demonstrate tumor size, degree of stromal invasion, and involvement of the lower uterine segment, vagina, parametria, pelvic sidewall, bladder, and rectum.[12] The use of PET/CT scan also has a high sensitivity and specificity for metastases especially in the paraaortic nodes.[13] Cost of these modern imaging techniques limit their use especially in the low-resource setting such as in the Philippines.

Ultrasound is an imaging modality which serves as a primary diagnostic tool for the obstetrician-gynecologist. It is widely available, cost-effective, and does not emit ionizing radiation. Transvaginal and transabdominal ultrasound by the obstetrician-gynecologic sonologist is included in the baseline diagnostic work-up of all patients who undergo radical hysterectomy for cervical cancer in our institution in place of CT scan or MRI. Its use was previously limited to the determination of other gynecologic pathologies present in the patient. However, with increasing expertise of sonologists, ultrasound may be able to detect size, tumor invasion and lymph node metastasis in cervical cancer.

Ultrasound has been used effectively in predicting myometrial invasion and cervical involvement in patients with endometrial cancer who are for surgery. Several international and local studies have shown sensitivity and specificity ranging from 76.47% to 100% and 75% to 100%, respectively, in detecting deep myometrial involvement.[14-16] Its use in determining cervical involvement in endometrial cancer has a sensitivity and specificity range of 66.67% - 85.71% and 95.4% - 100%, respectively. It was the goal of this study to determine if ultrasonography can be clinically useful in pre-operative evaluation of early stage cervical cancer patients.

*Objectives*

The general objective of this study was to determine accuracy of ultrasound in predicting poor prognostic factors in patients with early stage non-bulky cervical carcinoma who will undergo radical hysterectomy. The specific objectives were to determine the specificity, sensitivity, positive predictive value, negative predictive value and likelihood ratios of sonographic examination in pre-operative assessment of the following poor prognostic factors of cervical carcinoma: tumor size, parametrial involvement, cervical stromal invasion and lymph node involvement.

## Materials and Methods

Patients with stage IB1 and non-bulky IIA cervical cancer for radical hysterectomy (RH), bilateral salpingo-oophorectomy (BSO), pelvic lymph node dissection (BLND) and para-aortic lymph node sampling (PALS) from January 27, 2009 to July 14, 2009 were included in the study. Demographic data such as age, gravidity, parity and body mass index were taken.

Diagnosis of cancer was based on biopsy with a histologic report of cervical cancer. Patients who underwent cold-knife conization or loop electrocautery excision procedure and/or radiotherapy and chemotherapy were excluded from the study. Pelvic examination for clinical staging was performed by a senior gynecologic oncology fellow and confirmed by a consultant.

Patients underwent transvaginal and transabdominal ultrasound performed by two expert sonologists using the MINDRAY DC-6 machine with a 7.5 MHz transvaginal probe and 5 MHz transabdominal probe. Both sonologists were aware of the clinical stage. Spearman coefficient was computed and it showed no significant difference between the measurements taken by the ultrasonographers. The uterine cervix was scanned transvaginally to measure tumor size, stromal invasion and parametrial involvement. Pelvic and paraaortic areas were scanned using the transabdominal probe.

Cervical neoplasia appeared as an irregular mass that was less echogenic than the adjacent healthy cervical tissue. The hyperechogenic endocervical mucosa appeared altered, interrupted or absent. Size of the tumor was measured by obtaining the anteroposterior, craniocaudal and transverse diameters. The greatest diameter obtained was considered to represent the tumor size sonographically.

Invasion of the parametria was identified by irregular extension of hypoechogenic prominences into the parametrial fat. The lateral extension of the tumor would obliterate the parametrial vessels and depending on the amount of obliteration or the sizes of the vessels obliterated, a free parametria could be differentiated from a nodular parametria in which the latter would obliterate small more medial vessels. Parametria involved until the pelvic side wall would obliterate all parametrial vessels, including the larger, more lateral vessels.

Degree of cervical stromal invasion of the tumor was measured by dividing the stroma into inner, middle and outer thirds with the endocervical as the reference point. Location of the tumor was noted. Anterior to the endocervical canal and posterior to endocervical canal was the anterior and posterior lip, respectively.

Pelvic and para-aortic lymphadenopathies were assessed as well-circumscribed hypoechoic solid masses often seen beside the great pelvic and para-aortic vessels, respectively.

Radical hysterectomy and lymphadenectomy was performed 0-23 days after the ultrasound. Preoperative pelvic examination under anesthesia was done by the surgeons who were senior gynecologic oncology fellows. Tumor size and parametrial involvement were assessed. Measurements for tumor size were taken in two dimensions (width and height). The greater diameter measured would be considered to represent tumor size. Presence or absence of parametrial involvement was determined by recto-vaginal examination. Intraoperative findings would be recorded.

The formalinized surgical specimen was examined by one pathologist. The uterus was bisected along the anteroposterior axis. Measurements of tumor dimensions were made along the longitudinal and radial axes. The greatest diameter recorded represented the surgico-pathologic tumor size. Location of the tumor was also noted. Degree of stromal invasion was quantified as the ratio of tumor with the full thickness of the cervical wall and confirmed histologically. Presence of parametrial and lymph node involvement was also confirmed histologically.

Data were gathered and entered into a data registry form. Tables were constructed comparing tumor size and parametrial involvement by internal examination and surgico-pathologic findings. Pre-operative sonography and surgico-pathologic findings of tumor size, parametrial involvement, stromal invasion and lymph node involvement were also compared. Accuracy, sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios of internal examination (when applicable) and ultrasound were calculated by standard statistical formulas.

## Results

A total of 17 patients were recruited, 13 of which were included in the study. Of the 4 patients excluded from the study, one had abandoned hysterectomy because of invasion of the prevesical space, one had pre-operative pelvic lymphadenopathies on CT scan for which the patient opted for concurrent chemoradiation, and the other two were still awaiting funds for surgery at the time of this study.

The mean age was 50 years old with a range of 32-57 years. The mean gravidity was 5 (range 0-15) and mean parity was 4 (range 1-12). Histologic types were squamous cell carcinoma (n = 11), adenocarcinoma (n = 1), and transitional carcinoma (n = 1). Majority of the patients were clinical stage IB1 (n = 12). There was one case of clinical non-bulky stage IIA. Average body surface area was 22.5, range 17.7 to 28.2 (Table 2). All patients underwent radical hysterectomy, bilateral salpingo-

oophorectomy, pelvic lymphadenectomy. One patient did not undergo para-aortic lymphadenectomy because of intraoperative blood loss.

Table 2. Patient demographics.

| Patient Characteristics (n=13) | |
|---|---|
| Age (mean, range) | 50, 32-57 |
| Gravidity (mean, range) | 5, 0-15 |
| Parity (mean, range) | 4, 1-12 |
| Histology | |
| Squamous cell carcinoma | 11 |
| Adenocarcinoma | 1 |
| Transitional carcinoma | 1 |
| Stage | |
| IB1 | 12 |
| IIA | 1 |
| BMI (mean, range) | 22.5,17.7-28.2 |
| Adjuvant chemoradiation | |
| Necessary | 7 |
| Unnecessary | 6 |

Assessment of tumor size greater than or equal to 2 cm by internal examination showed a sensitivity of 71.4%, specificity of 83.3%, positive predictive value of 83.3%, negative predictive value of 71.4%. False negative was 28.6% and false positive was 16.7%. Accuracy of internal examination to detect tumor size ≥ 2 cm was 81.25% (Table 3).

Assessment of tumor size greater than or equal to 2 cm by sonography showed a sensitivity of 85.7%, specificity of 33.3%, positive predictive value of 60%, negative predictive value of 66.7%. False negative was 14.3%, while false positive was 66.7%. Accuracy of internal examination to detect tumor size ≥ 2 cm was 72.22%. (Table 4)

Only one patient had parametrial involvement by histology. This was not detected by internal examination. Thus, computation for specificity and sensitivity could not be done (Table 5).

Table 3. Determination of tumor size: Pelvic examination versus surgico-pathologic.

| | Histology | | Total |
|---|---|---|---|
| Pelvic exam | ≥ 2 cm | < 2 cm | |
| ≥ 2 cm | 5 | 1 | 6 |
| < 2 cm | 2 | 5 | 7 |
| Total | 7 | 6 | 13 |

| | | | | |
|---|---|---|---|---|
| Sensitivity | 71.4 % | (95% CI 0.2907-0.9633) | False negative | 28.6 % |
| Specificity | 83.3 % | (95% CI 0.3588-0.9958) | False positive | 16.7 % |
| Positive predictive value | 83.3 % | (95% CI 0.3588-0.9958) | Likelihood ratio+ | 4.27 |
| Negative predictive value | 71.4% | (95% CI 0.2907-0.9633) | Likelihood ratio- | 0.34 |
| | | | Accuracy | 81.25% |

Table 4. Determination of tumor size: Ultrasound versus surgico-pathologic.

| | Histology | | Total |
|---|---|---|---|
| Pelvic exam | ≥ 2 cm | < 2 cm | |
| ≥ 2 cm | 6 | 4 | 10 |
| < 2 cm | 1 | 2 | 3 |
| Total | 7 | 6 | 13 |

| | | | | |
|---|---|---|---|---|
| Sensitivity | 85.7 % | (95% CI 0.4210-0.9964) | False negative | 14.3% |
| Specificity | 33.3% | (95% CI 0.4328-0.7773) | False positive | 66.7 % |
| Positive predictive value | 60% | (95% CI 0.2625-0.8784) | Likelihood ratio+ | 1.28 |
| Negative predictive value | 66.7% | (95% CI 0.9430-0.9916) | Likelihood ratio- | 0.43 |
| | | | Accuracy | 72.22% |

Table 5. Determination of parametrial involvement: Internal examination versus surgico-pathologic.

| | Histology | | Total |
|---|---|---|---|
| IE | (+) parametria | (-) parametria | |
| (+) parametria | 0 | 0 | 0 |
| (-) parametria | 1 | 12 | 13 |
| Total | 1 | 12 | 13 |

| | | | |
|---|---|---|---|
| Sensitivity | NA | False negative | NA |
| Specificity | 100% | False positive | 0 |
| Positive predictive value | NA | Likelihood ratio+ | NA |
| Negative predictive value | 92.3% | Likelihood ratio- | NA |

Ultrasound identified two patients as having parametrial involvement, however only one was confirmed by histology. Sensitivity was 100%, specificity was 91.6%, positive predictive value was 50% and negative predictive value was 100%. False negative was 0, and false positive was 8.4%. Accuracy of ultrasound to detect parametrial involvement was 92.86% (Table 6).

Stromal invasion of greater than one third by ultrasound had a sensitivity of 100%, specificity of 50%, PPV 70%, NPV 100%, false negative 0, false positive of 50%. Accuracy was 81.29% (Table 7).

Only one patient had pelvic lymph node involvement by ultrasound which was confirmed by histology. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 100% (Table 8).

Of the 13 patients who underwent radical hysterectomy, seven underwent or will still undergo adjuvant chemoradiation for poor prognostic factors. The rest of the patients did not require adjuvant therapy after surgery. Concurrent chemoradiation will also be given to the patient whose radical hysterectomy was abandoned due to invasion of the prevesical space. This is invasion was not detected pre-operatively by ultrasound.

## Discussion

A student of gynecology is first and foremost trained in the art and science of the pelvic examination. No other gynecologic pathology best utilizes this skill than cervical malignancy. Cervical and vaginal cancers remain as the two gynecologic malignancies which are staged clinically, while others (endometrial, ovarian, fallopian tube and vulvar cancers) are surgico-pathologically staged. Pelvic examination is the primary basis for the stage of cervical cancer and also what the gynecologist believes is operable and non-operable disease. While the goal of staging is to provide a unified terminology that is able to provide appropriate prognosis to patients and enhance the exchange of

**Table 6.** Determination of parametrial involvement: ultrasound versus surgico-pathologic.

| | Histology | | Total |
|---|---|---|---|
| IE | (+) parametria | (-) parametria | |
| (+) parametria | 1 | 1 | 2 |
| (-) parametria | 0 | 11 | 11 |
| Total | 1 | 12 | 13 |

| | | | | |
|---|---|---|---|---|
| Sensitivity | 100% | (95% CI 0.0250-1.0) | False negative | 0 |
| Specificity | 91.6% | (95% CI 0.6151-0.9976) | False positive | 8.4% |
| Positive predictive value | 50% | (95% CI 0.01258-0.9874) | Likelihood ratio+ | 11.9% |
| Negative predictive value | 100% | (95% CI 0.7152-1.0) | Likelihood ratio- | 0 |
| | | | Accuracy | 92.86% |

**Table 7.** Determination of stromal invasion: ultrasound versus surgico-pathologic.

| | Histology | | Total |
|---|---|---|---|
| Ultrasound | >1/3 | <1/3 | |
| >1/3 | 7 | 3 | 10 |
| <1/3 | 0 | 3 | 3 |
| Total | 7 | 6 | 13 |

| | | | | |
|---|---|---|---|---|
| Sensitivity | 100% | (95% CI 0.5903-1.0) | False negative | 0 |
| Specificity | 50% | (95% CI 0.1181-0.8819) | False positive | 50% |
| Positive predictive value | 70% | (95% CI 0.3476-0.9332) | Likelihood ratio+ | 2 |
| Negative predictive value | 100% | (95% CI 0.2924-1.0) | Likelihood ratio- | 0 |
| | | | Accuracy | 81.25% |

**Table 8.** Determination of lymph node involvement: ultrasound versus surgico-pathologic.

| | Histology | | Total |
|---|---|---|---|
| Ultrasound | (+) lymph node | (-) lymph node | |
| (+) lymph node | 1 | 0 | 1 |
| (-) lymph node | 0 | 12 | 12 |
| Total | 1 | 12 | 13 |

| | | | | |
|---|---|---|---|---|
| Sensitivity | 100% | (95% CI 0.0250-1.0) | False negative | 0 |
| Specificity | 100% | (95% CI 0.7352-1.0) | False positive | 0 |
| Positive predictive value | 100% | (95% CI 0.0250-1.0) | Likelihood ratio+ | NA |
| Negative predictive value | 100% | (95% CI 0.7352-1.0) | Likelihood ratio- | 0 |
| | | | Accuracy | 100% |

information among health professionals, clinical staging of cervical cancer has its limitations. Its main drawback is its inability to measure tumor in the cranio-caudal dimension, as internal examination can usually just determine the anteroposterior and transverse dimension. Thus, actual tumor size can be underestimated.

Tumor size is an important predictor of prognosis. A prospective study conducted by the Gynecologic Oncology Group included 645 patients who underwent radical hysterectomy and pelvic lymphadenectomy for stage IB squamous cell carcinoma of the cervix.[17] Their study showed that with respect to tumor size, disease free interval were 94.8%, 88.1% and 67.8% for occult, less than or equal to 3 cm, and greater than 3 cm, respectively. Local data also reflect these figures. In a local review by Sotto which included 627 patients with stage IB cervical cancer who underwent radical hysterectomy, the three year survival rate was 87.8% for lesions <2cm and 58.5% for lesions greater than 2cm.[18] Incidence of recurrence was six times higher for lesions greater than 2cm at 36.8%, compared to small stage IB lesions which were less than or equal to 2cm at 6.1%. A later study conducted by Pagkatipunan, et al. involving 136 cervical cancer patients who underwent radical hysterectomy showed that the mean survival time for patients with tumor diameters of <2 cm, 2-2.9cm, 3-3.9cm, 4-4.9cm and ≥ 5cm was 68.0, 54.6, 51.2, 29.0 and 25.1 months, respectively.[19] These studies underscore the importance of tumor diameter in the prognosis of these patients.

Increased risk recurrence with larger tumor size may be related to a higher incidence of lymph node metastasis. In stage IB cervical cancer, tumor size of ≤ 1cm, 2-3cm, 4-5cm, ≥ 6cm have 18.1%, 22.1%, 35.5% and 50% lymph node metastasis, respectively.[20] In a study by Jardiolin, et al. it is has been shown that even in the absence of lymph node metastasis, tumors > 2cm have a 5-6 times higher incidence of recurrence than smaller lesions. This points out that tumor size in itself is a poor prognostic factor.[21]

In our study, ultrasound had a higher sensitivity than pelvic examination (85% versus 71%) in detecting tumor size of ≥ 2cm. Ultrasound appears to have the advantage of being able to measure the cranio-caudal dimension which is limited in internal examination. However, specificity of tumor size is greater in internal examination than in ultrasound (83% versus 33%), such that the false positive rate of ultrasound is 66.7%. This shows a tendency of the sonographer to overestimate the size of the tumor mass.

On literature review, there appears to be no studies comparing transvaginal ultrasound with clinical staging. In this study, the transvaginal approach was utilized in all the patients. Sonographers in this institution generally use the transvaginal probe in diagnosing gynecologic lesions, and use the transrectal approach in selected cases. Accuracy of transrectal ultrasound in staging invasive carcinoma of the cervix has been reported to be 83%, as compared to clinical staging accuracy of 78%.[22] In another study, accuracy of transrectal ultrasound in staging of early cervical cancer was 75% compared to 85% for clinical examination under anesthesia.[23] The result of the latter study is similar to this study wherein in terms of size of tumor of early stage cervical cancer, internal examination was more accurate than ultrasonography (81.25% versus 72.22%). A possible explanation in the limitation of ultrasound is the lack of contrast resolution between the normal and abnormal neoplastic tissue. In the study of Yang, et al. involving 38 women, cervical carcinomas appeared hypoechoic in 60% of cases and isoechoic in 40% of cases.[23] Accurately delineating normal and malignant cervical tissue would therefore be difficult.

Transrectal ultrasound was found to be comparable to MRI in detecting early stage cervical cancer. The accuracy of detecting tumor was 93.7% for transrectal ultrasound and 83.2% by MRI ($P \leq 0.006$). In small tumors ($\leq 1cm^3$), accuracy of tumor detection by transrectal ultrasound was 90.5% and 81.1% by MRI ($P \leq 0.049$). These results support that ultrasound is a viable diagnostic tool in a low-resource setting like the Philippines for early cervical cancer where MRI may not be readily available and accessible.[24]

None of the patients included in this study had parametrial involvement by pelvic examination. Parametrial involvement would clinically stage the patient to at least a stage IIB, and thus would no longer be a candidate for radical hysterectomy in this institution. Sensitivity and specificity of internal examination for parametrial involvement could not be computed in this study.

On the other hand, ultrasound identified 2 out of 13 patients as having parametrial involvement. Histologic confirmation was found in only one of these patients. Sensitivity of ultrasound was 100% and specificity was 91.6%. In a study by Aoki, et al. sensitivity, specificity, positive predictive value, negative predictive value and predictive accuracy of transrectal ultrasonography and rectal examination were 100% and 25%, 90% and 93%, 50% and 25%, 100% and 93% and 91% and 87%, respectively.[25] This study claims that transrectal ultrasound provides a better assessment of the parametrium, in contrast to transvaginal scanning which produces a sharp image at focal ranges of 1.5-7 cm. Despite disparity of technique, the results of Aoki's study are comparable to the results of this study. The false positive result obtained in both studies could be secondary to presence of old or occult inflammation or to a sclerotic change in the blood vessels of the parametrium. Studies have shown that parametrial involvement and positive lines of resection are independent risk factors for recurrence necessitating adjuvant treatment.[26,27] Although accuracy of ultrasound for parametrial invasion in this study was 92.6%, more subjects are required to make this significant.

Stromal invasion considered as a poor prognostic factor as well. There is a significant relationship between depth of stromal invasion, lymph node spread and risk of recurrence. Stromal invasion of less than 1/3 was shown to have no lymph node metastasis, where as 1/3-<2/3 invasion showed 6.7%, 2/3-<3/3 showed 27.3%, and full thickness invasion showed 32.7% pelvic node metastasis, respectively.[21] The uterine cervix has a thick fibromuscular stroma. Patients with good prognosis have more fibers especially reticular fibers, more mast cells and plasma cells in the stroma surrounding the cervical cancer. There appears to be higher concentration of glycosaminoglycans and a higher hydroxyproline/collagenase ratio for patients with good prognosis rather than for patients with poorer prognosis. The stromal reaction appears to have an important part of the host's defense against cervical cancer invasion.

In this study, ultrasound was able to detect all cases of more than 1/3 stromal invasion, however specificity was only 50%. This shows that ultrasound may overestimate actual stromal invasion present in the patient. This may be due to the lack of contrast seen in ultrasound to distinguish normal from neoplastic cervical tissue. Thus, although ultrasound can detect stromal invasion which is a poor prognostic factor, surgico-pathologic analysis is required to be definitive about its extent.

One case of lymph node metastasis was detected preoperatively by ultrasound and confirmed by histopathology, giving a sensitivity and specificity of 100%. Most studies will say that ultrasound has poor sensitivity in detecting lymph node metastasis while specificity is good. Although these data appear to be impressive, more patients are needed for this to be significant. However, detection of lymph nodes on ultrasound will alert the physician that he may be dealing with advanced disease which will not be demonstrated by physical examination.

We had one case of abandoned radical hysterectomy due to invasion of the prevesical space. This was not detected through physical examination or by ultrasound. Bladder involvement is demonstrated by disruption of the endopelvic fascia which was not demonstrated in this case. Perhaps it is the retroverted uterus seen in this patient which prevented the complete evaluation of the pubocervical fascia. Detection of bladder involvement or invasion of the prevesical space, especially if minimal, could be an inherent limitation of ultrasonography. For these cases, a magnetic resonance imaging would be the more ideal diagnostic modality to diagnose this. Thus our study suggests abandonment of radical hysterectomy can not be predetermined by ultrasonography. Until more data are collected, surgeons in our

institution will have to depend on internal examination under anesthesia and findings on laparotomy.

## Conclusion

Ultrasound can be used to detect preoperative poor prognostic factors in patients undergoing radical hysterectomy for early cervical cancer, however false positivity is high. Pre-operative ultrasound can be used to advise the patient of a possibility of adjuvant treatment after surgery however final histopathology will determine this. Although chemoradiation can be used as primary treatment for early cervical cancer, poor prognostic factors seen in preoperative ultrasound should not deter the surgeon from proceeding with surgery.

## Limitation of the Study

The main limitation of this study is the small number of patients included in the study. Only 10-15% of new patients of cervical cancer seen in the Cancer Institute is early stage and is still operable. Of these, some may not be able to undergo the surgery because of financial constraints. Thus the study is highly dependent on the number of early stage cervical cancer patients who consult in our institution and how many of them are able to proceed with the surgery. Another limitation is that internal examination will be performed by different individuals. However, all internal examinations will be performed by senior fellows confirmed by a consultant. It will be assumed that competency level in doing an internal examination is comparable.

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# When Prevention is Definitely Better Than Cure... Risk-Reducing Surgeries for Women Carrying a Gene Mutation for a Hereditary Cancer Syndrome*

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A 38-year old G3P1 (1011) was diagnosed with Invasive Ductal Carcinoma of the right breast on her 23rd week of gestation. The malignancy was estrogen and progesterone receptor assay and HER2/neu negative. She subsequently had 5 cycles of Cyclophosphamide-Doxorubicin chemotherapy beginning at 25 weeks gestation, repeat cesarean section with bilateral salpingo-oophorectomy at 36 weeks gestation 4 more courses of chemotherapy with Docetaxel starting 1 month postpartum, modified radical mastectomy, and radiotherapy. With a strong family history of breast and ovarian cancers, she underwent genetic testing for the BRCA gene mutation. She was positive for deleterious mutations of BRCA1 and BRCA2. She subsequently underwent "risk-reducing" simple mastectomy of the contralateral breast 2 years postpartum. Three sisters between the ages of 40 and 50 were likewise discovered to have a variety of BRCA gene mutations, one of whom also developed breast cancer. All sisters subsequently had risk-reducing mastectomies and salpingo-oophorectomies.

The American Society of Clinical Oncology (ASCO) recommends genetic testing for cancer predisposition when the individual has a personal or family history suggestive of a cancer susceptibility syndrome. The benefits of genetic testing include a more precise estimation of cancer risks for the individual and her family members, and the identification of those individuals who could participate in risk-reducing surgeries in an effort to virtually eliminate the probability of developing a particular inherited malignancy. Risk-reducing bilateral simple mastectomy can be performed for high-risk women who have been documented to carry the BRCA gene mutation. On the other hand, risk-reducing contralateral simple mastectomy is recommended for women with breast cancer who previously underwent modified radical mastectomy (MRM). Consequently, risk-reducing bilateral salpingo-oophorectomy is strongly recommended in women with BRCA gene mutations because of the high mortality rate associated with ovarian cancer and the lack of effective screening and preventive approaches for this malignancy.

**Key words**: hereditary cancer syndrome, risk-reducing surgeries

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Since the 1980's, breast cancer ranks first among the top leading cancers of women in the Philippines. However, it ranks a close second to lung cancer if both sexes are considered. There are 26 out of 100 females and 1 out of 105 males diagnosed with breast cancer annually. In 2004, the International Agency for Research on Cancer named the Philippines to have the highest prevalence of breast cancer in Asia. The UP-DOH Report (cited in The Manila Bulletin on January 2004) reported that breast cancer cases in the Philippines exceeded lung cancer by 685 cases for both sexes.[1]

The units of information in every cell of our body are called "genes". These come in pairs, one coming from each parent. During development, these genes determine what kind of tissues to become, when to divide and make more cells, and tell our bodies how to repair damages from toxins, sun exposure, dietary factors, hormones, or other influences. When changes or mutations occur in the genes, some of these cells can go "out of control" and may thus predispose the development of cancer later in life.[2]

Over the last decade, there has been an increased awareness of the hereditary predisposition to a wide range of diseases including cancer, heart disease, and diabetes. These are all complex multigene disorders, but the identification of specific genes associated with a predisposition to these conditions has allowed clinicians to more accurately assess the risk of developing these conditions and thus prescribe preventive interventions.[3] Hereditary syndromes that are associated with breast and ovarian cancers have systematically been reported. Genetic testing has made possible the documentation of these syndromes and has facilitated counseling of affected individuals and families as to its prognosis, future implications on the succeeding generations, surveillance and management. The hereditary breast–ovarian cancer syndrome is characterized by the clustering of large numbers of breast cancer alone or breast and ovarian cancer in a single family. Approximately 5-10 percent of breast cancer is familial, and majority of these patients have mutations in the *BRCA*1 and/or *BRCA*2 genes.[4] The concept of prophylactic or risk-reducing surgery has been gaining wide acceptance in women possessing the deleterious mutation of the *BRCA* gene.

In this case report, a woman with hereditary breast cancer will be presented. Management options for surveillance and risk-reducing surgeries will be discussed.

## The Case

YT is a 38-year old G3P1 (1011), S/P low transverse section (LTCS) I for dysfunctional labor, a diagnosed case of breast cancer, on her 36 weeks age of gestation (AOG), admitted for an elective repeat cesarean section.

She is a known asthmatic, last attack was 1 month prior to admission (PTA), maintained on Seretide 500 mcg 1 puff BID. She had an appendectomy in 1988 and nasal polypectomy and Caldwell-Luc operation in 2003.

Family history is positive for hypertension and diabetes (mother, father). History of cancer and genetic history are as follows (please see Pedigree Charts), Liver CA (paternal uncle), Ovarian CA (paternal aunt); Dermatofibrosarcoma, right deltoid (maternal aunt), Lung CA (maternal grandfather and maternal first cousin); Breast CA (paternal grandmother, aunt, and first cousin; maternal aunt and first cousin; mother and sister).

Personal, social, and menstrual histories were non-contributory.

She is a G3P1 (1011), 1st pregnancy delivered via 1° LTCS for dysfunctional labor (arrest of descent), a live term birth in Baltimore, Maryland, USA (1999). The 2nd pregnancy was a spontaneous abortion with a completion curettage done in 2002.

For the present pregnancy, confirmation was by urine bHCG test done at 5 weeks AOG, with subsequent regular intake of multivitamins. Initial CBC, urinalysis, 50-gram Oral Glucose Challenge Test (OGCT) and HBsAg were within normal limits.

At 16 weeks AOG, she noted a 1cm x 1cm firm, movable, non-tender mass at the lateral aspect of her right breast, not accompanied by nipple discharge, or breast dimpling. Ultrasound of the

breast was done showing hypoechoic nodules measuring 1.4cm x 1.2cm and 0.9cm x 0.7cm. Initial impression was fibroadenoma. She was advised close observation.

At 23 weeks AOG, she noticed an increase in the size of the breast mass, now measuring approximately 4 cm, still without any associated symptoms. A repeat ultrasound of the breast was done revealing solid masses in the right breast measuring 4-5cm, with a 2-3cm right axillary lymph node. A referral to a surgical oncologist was done and an incision biopsy with frozen section was performed. Results showed invasive ductal carcinoma. Estrogen and Progesterone Receptor (ER/PR) assays and HER2/neu of the biopsy specimen showed negative results (triple negative). The definitive plan at that time was to administer chemotherapy for four cycles, cesarean section when fetus is viable, then MRM a month after the CS. She subsequently underwent 5 cycles of Cyclophosphamide – Doxorubicin starting at 25 weeks AOG at the Cardinal Santos Medical Center. She tolerated the treatments without any untoward incidents.

The first ultrasound done at 8 weeks AOG for fetal viability revealed good cardiac activity and at 14 weeks AOG showed a normal fetus, with a small myoma at the posterior lower segment. A congenital anomaly scan done at 27 weeks AOG showed the presence of an atrioventricular septal defect (AVSD). A 4D ultrasound done at 29 weeks AOG still showed the AVSD. In light of the possible congenital heart defect, the plan to deliver at 32-34 weeks AOG was deferred. The revised plan for her was to administer a fifth cycle of chemotherapy and deliver at 36 weeks AOG, when the chance for fetal survival is higher.

Biometry done at 36 weeks AOG revealed a live intrauterine pregnancy with an estimated fetal weight of 1958 gm, amniotic fluid level of 12.5 cm, placenta posterior, high lying grade II. Biophysical profile was likewise done showing a score of 8/8, with an elevated resistance index on velocimetry.

On physical examination, she was conscious and coherent with stable vital signs. She had pink palpebral conjunctivae, anicteric sclera with no cervical lymphadenopathy. Heart and lung findings were essentially normal. On breast examination, there was a nodular mass at the lateral and outer aspect of the right breast measuring approximately 2cm x 2cm with no palpable axillary lymph nodes. The left breast was unremarkable. On abdominal examination, the fundic height was 29 cm, FHT of 154 bpm, cephalic. On internal examination, her cervix was closed and uneffaced, corpus enlarged to approximately 34 weeks AOG.

Our admitting impression was: Pregnancy Uterine, 36 weeks AOG, cephalic, not in labor; G3P1 (1011); S/P LTCS I for Dysfunctional Labor and (1999); Invasive Ductal Carcinoma, Right Breast, S/P Incision Biopsy, S/P Cyclophosphamide-Doxorubicin V; intrauterine growth restriction with Congenital AVSD; Bronchial Asthma, not in Acute Exacerbation.

She underwent LTCS II followed by Bilateral Salpingooophorectomy under epidural anesthesia and delivered a live preterm female weighing 1840 gm, with an APGAR score of 8 becoming 9, birth length of 42 cm, and a pediatric aging of 35 weeks, small for gestational age (SGA).

Her postoperative course was unremarkable and she was discharged on the fifth hospital day. Her baby was later diagnosed with Trisomy 21 (by karyotyping) with Atrioventricular Septal Defect (AVSD), not in failure. She remained in the Neonatal Intensive Care Unit for 1 week and was discharged in fair health.

Because of the size of the breast mass at delivery, she subsequently had chemotherapy with Docetaxel (Taxotere) for 4 courses, starting 1 month postpartum. She tolerated these chemotherapeutic treatments well.

Three months postpartum, she underwent modified radical mastectomy on the right with histopathological results showing residual invasive ductal carcinoma in lymphatic vessels, multifocal, poorly differentiated; 5 out of 24 axillary lymph nodes positive for metastases.

She subsequently underwent Radiotherapy (Linear Accelerator) to the right chest wall and right supraclavicular fossa/axilla for 3 months.

She was asymptomatic thereafter and metastatic surveillance using CT scans of the abdomen and

chest 10 months postpartum revealed normal results (no findings suggestive of tumor recurrence). Mammogram of the left breast also showed normal findings.

*Update on YT's Status*

YT unfortunately developed brain and bone metastases 1 year and 5 months after the initial diagnosis of breast cancer. She underwent a craniotomy with excision of a 4cm x 5cm tumor at the left frontal lobe. Histopathological results confirmed metastases from a primary breast carcinoma. She subsequently underwent Whole Brain Radiotherapy (WBRT) and chemotherapy consisting of Paclitaxel-Gemcitabine for four courses and intravenous Alendronate treatments. She tolerated the treatments well and there is no evidence of disease until the present.

Genetic testing for *BRCA* mutations was done 2 years postpartum. She was discovered to be positive for both *BRCA*1 and *BRCA*2 gene mutations. She thus underwent "risk-reducing" Simple Mastectomy of the Left Breast in July 2007.

In December 2008 and June 2009, as part of her metastatic screening work-up, CT scan of the head, chest, and abdomen showed no evidence of tumor recurrence.

*Update on YT's Baby*

The AVSD of YT's baby (AT) was confirmed by 2D echocardiography at birth. No other congenital anomaly was discovered. On consultation with several pediatric cardiologists and thoracovascular surgeons, it was recommended that she undergo closure of the AVSD prior to 6 months of age. This would prevent the development of pulmonary hypertension, a condition that would drastically lessen her chance of surviving past the second decade of life.

AT underwent closure of the AVSD using an endocushion and Gortex patch at a Pediatric Cardiothoracic Center in the United States on her 6$^{th}$ month of life. She was at the NICU for 2 weeks and was subsequently discharged improved. She is presently 4 years of age, off any heart medications, and undergoing regular physical, occupational, and speech therapy. Her neurodevelopment is at par with children of the same age with Down syndrome.

## Discussion

Breast cancer is the most common malignancy diagnosed during pregnancy, affecting women in their mid-30's. It occurs in approximately 1 in 3,000 to 3 in 10,000 pregnant or postpartum women. Pregnancy-associated breast cancer (PABC) refers to cancers that are diagnosed during pregnancy or within 1 year postpartum. This is often perceived as a situation that potentially puts the life of the mother in conflict with that of her fetus. The presence of a discrete mass may be difficult to detect secondary to the natural engorgement of the breasts in the pregnant state. This difficulty in detection may contribute to a delay in its diagnosis. The average reported delay in the diagnosis of PABC is 5 to 15 months from the onset of symptoms.[5] Women with breast cancer during pregnancy tend to have more advanced disease characterized by large tumors, frequent lymph node involvement, and metastases. Although pregnancy on its own does not directly affect the course of breast cancer, the hormonal milieu of pregnancy may theoretically accelerate its growth, especially those positive for ER/PR assays. Conversely, there is no direct evidence that breast cancer per se worsens the perinatal outcome for pregnant women.[6-9]

There was a delay in the diagnosis of breast cancer in the patient due to the belief that the mass initially palpated was benign in nature, possibly a fibroadenoma. However, its rapid growth after only a month alerted her to the possibility that this was no longer a benign mass. As characterized earlier her breast mass was noted to be larger, and with the presence of axillary lymph nodes, suggestive of a more advanced disease stage.

In general, the goal is to treat the cancer and allow the pregnancy to proceed. However, the treatment of breast cancer may indirectly cause maternal and fetal complications. These may be in

uniform of spontaneous abortions, or if live births do occur, fetal malformations with rates between 7.9% - 17% secondary to the teratogenic effects of anti-neoplastic agents, especially when given during the first trimester, the period of organogenesis.[6-9]

For the majority of surgically-resectable tumors, modified radical mastectomy with axillary lymph node dissection can be usually performed, regardless of gestational age. In the study done by Berry, et al. at the University of Texas MD Anderson Cancer Center, first trimester surgery performed in 14 women resulted in no spontaneous abortions. Second- or third- trimester surgery performed in10 women likewise had no evidence of fetal compromise or preterm labor. For advanced breast carcinoma, treatments are usually individualized. Since radiation therapy is contraindicated during pregnancy, neoadjuvant chemotherapy has been used successfully without apparent harm to the mother or fetus.[6,8]

Our patient was diagnosed with advanced breast cancer during pregnancy. She received neoadjuvant combination chemotherapy during the third trimester. Though chemotherapy is relatively safe if administered after the first trimester, it was worth monitoring its effects on the fetus since Doxorubicin has known cardiotoxic complications. Though a fetal heart defect was detected during a congenital anomaly scan, this was attributed not to Doxorubicin, but as part of a congenital defect from a chromosomal condition (Down syndrome).

*Hereditary Cancer Syndromes*

Hereditary cancers occur when a person has both copies of the gene that has been altered or has mutated. The first mutation is inherited from either the father or the mother, and is present in all cells of the body. Mutation of the other gene pair is needed in order to develop one or more types of cancer. Genes associated with these hereditary cancer syndromes are all transmitted in a Mendelian autosomal dominant fashion, but expressed in a recessive manner. Maternal and paternal family histories, therefore, contribute equally to the patient's risk.[2,3,10]

General features of families with inherited cancer syndrome are as follows: 1) multiple family members diagnosed with the same type of cancer; 2) cancers tend to occur at an earlier age, usually below 50 years of age; 3) bilateral cancer in paired organs; 4) multiple primary tumors in the same individual; 5) presence of a rare type of cancer in one or more members of the family (e.g., male breast cancer); 6) evidence of autosomal dominant transmission of cancer susceptibility.[2, 3, 11,12]

If a hereditary cancer syndrome is suspected, a detailed family history must be obtained and confirmed, if possible through reviews of medical records or direct interviews with the index patient and her family. This is displayed as a pedigree, showing three or more generations. The pedigree should include both the affected and non-affected relatives.

Approximately 10 percent of ovarian cancers, 10–12 percent of colorectal cancers, and 5 percent of endometrial cancers result from hereditary predisposition.[16]

There are several types of hereditary syndromes that are associated with breast and ovarian cancer. Among these, the two most commonly reported are Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer or HNPCC).

It is very evident that our patient's family possesses a hereditary cancer syndrome (pedigrees). Five members developed cancer before they were 50 years of age (patient, her sister, and 2 first cousins with breast cancer and another first cousin with lung cancer); three members of the patient's direct family had breast cancer (patient, mom and sister); the patient had an aunt (not in pedigree but a first cousin of her father) with both breast and ovarian cancer. A maternal aunt had a rare form of soft tissue sarcoma (Dermatofibrosarcoma) of the right deltoid. She had a first cousin who died of lung cancer at a very young age. This may be considered a rare type of cancer considering that he was a non-smoker and his death occurred at a very young age, not typical for those who have lung cancer. However, just glancing through the patient's pedigree through three generations, we can readily surmise that her

family does indeed possess some form of hereditary cancer syndrome.

*Hereditary Breast and Ovarian Cancer Syndrome*

Only 7 percent to 10 percent of breast and ovarian cancers occur in women with a hereditary cancer syndrome. In this subset of women, approximately 40 percent are found to have *BRCA1* and/or *BRCA2* mutation.[12]

Significant characteristics or risk factors suggestive of Hereditary Breast and Ovarian Cancer Syndrome (HBOC) aside from the general features of hereditary cancer syndrome are as follows: presence of a known mutation in a breast cancer susceptibility gene in any member of the family; a diagnosis of bilateral breast cancer, especially when the initial unilateral cancer is diagnosed at less than 50 years of age; history of breast and ovarian cancer; and Ashkenazi Jewish ancestry.[2, 10-12]

In our patient, aside from her being diagnosed with breast cancer at an age less than 40 (36 y/o), she also had two first cousins (one from the maternal and one from the paternal sides) who were diagnosed with Invasive Ductal Carcinoma of the breast before they were 40 years of age. She had 5 family members diagnosed with breast cancer after the age of 40 and a paternal aunt who died of ovarian cancer in the 7th decade of life.

*Lynch Syndrome*

Hereditary Non-Polyposis Colorectal Cancer (HNPCC), also known as Lynch Syndrome, is an inherited disease that is autosomal dominant. It is divided into Lynch Syndrome Type I (familial colon cancer) and Lynch Syndrome Type II (other cancers of the gastrointestinal tract or the reproductive system). Patients with either syndrome are said to have genetic susceptibility to many types of malignancies, most common are colorectal and endometrial cancers.[3]

Individuals with HNPCC have 40-60% lifetime risk for colon cancer, 30-50% lifetime risk of endometrial cancer, and 5-10% risk for ovarian carcinoma. The average age at diagnosis of endometrial cancer is 46 years. Endometrial and ovarian cancers are common extracolonic tumors in this syndrome. However, few studies have investigated whether genetic changes occur in histologically normal endometrial and ovarian epithelia from HNPCC family members. These cancers are due to mutations in the mismatch repair genes *MSH2, MSH1*, and possibly *MSH6*. Women with these mutations also carry an increased risk of other cancers, such as upper gastrointestinal, pancreatic, upper urinary tract, and brain.[2, 13-15]

*Genetic Testing*

Alterations or mutations in cancer genes make some women more susceptible to developing breast, or any other cancer. Every year, more than 192,000 American women learn that they have breast cancer. Approximately 5-10 percent of these women have a hereditary form of the disease.[11]

The American Society of Clinical Oncology (ASCO) recommends genetic testing for cancer predisposition when the individual has a personal or family history suggestive of a cancer susceptibility syndrome.[2] Although genetic testing is not mandatory, identification of genetic predisposition for cancer not only benefits the patient herself but her extended family. It clarifies the decision-making process for both patient and physician regarding cancer surveillance and prevention and prophylactic surgery. However, families should be reminded that the finding of a genetic mutation only predicts an elevated risk for a cancer to develop, and does not guarantee that the cancer will actually develop. Similarly, a negative genetic test result does not guarantee that the individual will not develop cancer, but instead, share the general population's risk.[16, 10]

The involvement of genetic counselors in the process of genetic testing is highly valuable in helping patients and families work through such issues. For YT's family, these counselors provided all the technical and medical information and their implications on the presence of the *BRCA* gene mutations. They were responsible for sifting through the entire three generations of all the

cancers present and encouraged genetic testing to those family members that needed them. They were essential in the decision-making process regarding the risk-reducing surgeries that the patient and her sisters underwent.

*BRCA1 and BRCA2 Mutation*

Eighty to 90 percent of all cases of hereditary breast and ovarian cancer syndrome (HBOC) are caused by mutations in "breast cancer 1 gene" or *BRCA*1 and "breast cancer 2 gene" or *BRCA*2. These are tumor suppressor genes that recognize and repair damaged DNA. Mutations in the *BRCA*1 on chromosome 17 carry a 50-85% lifetime risk of developing breast cancer, a 40-60% risk for a second breast cancer, and a 15-40% lifetime risk of developing ovarian cancer. *BRCA*2 genetic mutations on chromosome 13, on the other hand, have a 6.0-7.5% lifetime risk of developing breast cancer in men, 50-85% in women, and approximately 14-27% risk of developing ovarian cancer. These genes are responsible for most familial breast and ovarian cancers.[3,15,17]

The presence of *BRCA*1 or *BRCA*2 was also found to be highest in families with a history of multiple cases of breast and ovarian cancer. Both men and women, who inherit an altered *BRCA* gene, whether or not they get cancer themselves, may or may not pass the alteration unto their sons and daughters. The presence of *BRCA* gene mutations is not an absolute guarantee that a cancer will develop. It mainly provides information about a person's risk of developing cancer. And neither does a negative *BRCA* gene mutation reduce an individual's risk for breast cancer to that of the general population. It only means that one is not at risk for developing the hereditary breast cancer related to the *BRCA* mutations.

The discovery of these cancer genes has increased public awareness of its existence and possible sequelae. In families where there is a strong history of breast and/or ovarian cancer, individuals who have not developed any cancer may want to ascertain their risk of having one and identify ways to manage this risk. For the past decade, this concern has led individual family members (and even whole families) seeking genetic counseling or testing. Though identifying family members possessing the gene mutation may cause unwarranted stress and anxiety (with the fear that they may acquire a form of cancer during their lifetime), the consolation is that they can receive appropriate counseling regarding prevention and surveillance. In the past couple of years, the concept of "prophylactic" surgeries (nowadays better referred to as "risk-reducing" surgeries) has become popular and logical options for those possessing the gene mutation, after a thorough and complete evaluation of each individual's profile and risk status.

It is fortunate that *BRCA* testings and their results were available to the patient and her family. When breast cancer was detected in our patient and her sister, her mother decided to seek counseling from a geneticist in the United States. When her mother tested positive for the *BRCA*2 gene mutation, the family was advised to have the same genetic testing for all offsprings. Since the specific loci was already found in the mother's genes, each daughter didn't have to undergo the entire gene screening and all were only tested for *BRCA*2 at that specific loci. The unaffected eldest sister tested negative for the *BRCA*2 mutation. The unaffected third sister tested positive for the same deleterious mutation of *BRCA*2. Although our patient and her affected sister also tested positive for the same BRCA 2 mutation, it was also discovered that both had a deleterious mutation of *BRCA*1. In the light of these findings, the unaffected, *BRCA*2 negative eldest sister had to be tested for that particular *BRCA*1 mutation. As anticipated, she was discovered to have the *BRCA*1 gene mutation. Could it be assumed that the *BRCA*1 gene mutation could have come from the paternal side of the family?

The patient's father was advised to undergo *BRCA*1 testing to complete the family genetic profile but he initially refused. The genetic screening center wanted to confirm if the *BRCA*1 gene mutation could have come from the paternal side. Since the patient's father refused, they instead focused their attention to his family pedigree and discovered that his mother and one sister also had

breast cancer and another sister had ovarian cancer. Thus, they inferred from this profile that his side of the family could also be afflicted with the hereditary breast and ovarian cancer syndrome. They could also indirectly conclude that the *BRCA*1 gene mutation could have come from the father if any affected family member tested positive for that mutation. Unfortunately, his mother and sister with ovarian cancer have already died and the remaining sister with breast cancer also refused to undergo the genetic testing.

Around late 2007, a paternal first cousin (daughter of the father's brother) was diagnosed to have breast cancer at the age of 37. After counseling, she consented to the *BRCA* testing and it was confirmed that she had the *BRCA*1 gene mutation. With this finding, the patient's father consented to the gene screening and he was later confirmed to also carry the *BRCA*1 gene mutation. The family's genetic profile was now complete and hereditary breast and ovarian cancer syndrome was confirmed.

*Related Hormones and the HER2/neu gene*

Estrogen receptors (ER) are cellular proteins that bind estrogens with a high affinity and specificity. They are a necessary component for estrogen-mediated cellular activity. The presence of progesterone receptors (PR) demonstrates an active ER mechanism for the induction of PR expression. Immunohistochemical staining permits the detection and localization of ER/PR within sections from formalin-fixed, paraffin-embedded tissues.[18] Clinical utilities for the measurement of ER/PR include patient prognosis and patient response to adjuvant endocrine therapy. Individuals with receptor-positive tumors generally have a better prognosis, as indicated by a longer interval to disease recurrence and a longer overall survival, than patients with receptor-negative tumors. It is observed that ER/PR positive tumors are generally seen in well- and moderately-differentiated tumors as opposed to poorly-differentiated cancers predominating in ER/PR negative tumors. Studies have shown that $>50\%$ of breast cancer patients with receptor-positive tumors will respond to hormonal treatment (Tamoxifen), whereas $<15\%$ of patients with receptor-negative tumors will have a response.[19,25]

Approximately 15-20% of breast cancers express the HER2/neu gene. This gene, a member of the ErbB protein family, is a protein that gives higher aggressiveness in breast cancers. Overexpression of HER2/neu receptors has been correlated with increased disease recurrence and worse prognosis.[20] Clinically, the presence of HER2/neu receptors in tumors alerts the physician for the need to administer the monoclonal antibody Trastuzumab (Herceptin) to prevent tumor recurrence and improve overall prognosis. Trastuzumab is only effective in breast cancer where the HER2/neu receptor is overexpressed. It works by binding to the HER2/neu receptor and thus increasing levels of p27, a protein that halts cell proliferation.

The our patient had a "triple negative" result with regards ER/PR and HER2/neu receptor assays. One of the reasons why a hysterectomy was not performed during the bilateral salpingo-oophorectomy was the fact that she would not be given Tamoxifen as adjuvant hormonal therapy because of the absence of estrogen and progesterone receptors. The negativity of these hormonal and HER2/neu receptor assays clearly indicates the aggressive nature of the breast cancer she possessed, and this was reflected in its recurrence after initial comprehensive treatment. The poorly-differentiated nature of her tumor also validated the ER/PR negativity and confirmed the aggressive nature of the cancer.

*Cancer Prevention*

Management of individuals with potential cancer risk falls into four categories: screening and close surveillance, risk avoidance, chemoprevention, and prophylactic surgeries.

Screening and surveillance involve monitoring to detect cancer as early as possible or when it is in its "pre-cancerous" state, when the chances for cure are greatest. Currently, management strategies in high-risk women for HBOC include intense follow up of her breasts (clinical breast examination every 6 months, and/or alternating mammogram with

MRI at 6-month intervals starting at 25 years of age), as well as gynecologic screening (biannual transvaginal ultrasound and serum CA-125).[2,10,15]

Adherence to these surveillance measures though appears to be influenced by levels of anxiety, intrusive thoughts about cancer, psychological distress, education, employment, and age.

One of the strategies for risk avoidance is through modification of an individual's diet and nutrition. A randomized clinical trial of the Women's Intervention Nutrition Study (WINS) showed a 42% reduction in breast cancer recurrence in women who have estrogen receptor-negative disease, and a 24% reduction in women who had estrogen receptor-positive disease just by decreasing fat intake. However, it is unclear whether this significant reduction is associated with the low fat diet or the weight loss achieved. Moreover, it is still to be proven whether we can extrapolate the advantages of this diet modification to women at risk of breast cancer.[10]

Chemoprevention involves taking medicines, vitamins, or other substances to reduce the risk of cancer. Tamoxifen given to postmenopausal women for breast cancer showed a 50% risk reduction of contralateral breast cancer, and a 42% risk reduction in *BRCA*1 and *BRCA*2 gene mutation carriers, respectively. The Study of Tamoxifen and Raloxifene (STAR) Trial showed that Raloxifene, a Selective Estrogen Receptor Modulator (SERM) utilized for the prevention and treatment of osteoporosis, is as effective as Tamoxifen in reducing the incidence of breast cancer in postmenopausal women with positive estrogen receptor disease.[4,10]

*Risk-Reducing Surgeries*

The detection of mutations of *BRCA*1 and *BRCA*2 in women with personal or family history of breast and/or ovarian cancer has led to the concept of prophylactic surgeries in an effort to virtually eliminate the probability of developing a particular inherited malignancy. Though radical in concept as it was perceived with its introduction, it is slowly gaining wide acceptance in the medical community. Though the term "prophylactic" has initially been a widely-used terminology for certain procedures, it has slowly lost favor due to the fact that there is no guarantee that a cancer will actually develop. In other words, how sure are we that we can "prevent" a cancer that may not actually occur? Therefore, the widely-accepted term now is "risk-reducing" procedures. These procedures are not usually recommended if there is only clinical suspicion of hereditary syndromes but are generally offered to individuals who actually carry the inherited gene mutations.

*Risk-Reducing Mastectomy*

Risk-reducing bilateral simple mastectomy, also known as prophylactic bilateral mastectomy, is performed in high-risk women who have been documented to carry the *BRCA* gene mutation. On the other hand, risk-reducing contralateral simple mastectomy is recommended for women with breast cancer who previously underwent modified radical mastectomy. Researchers have found out that risk-reducing mastectomy in women with *BRCA*1 and *BRCA*2 gene mutations had a lifetime breast cancer risks of 31% and 45%, respectively, compared to those who chose not to have the prophylactic mastectomy, with an overall lifetime risk of 80%.[12] Bilateral risk-reducing mastectomy leads to 90% reduction in the development of breast cancer in moderate- and high-risk women.[10,21]

These procedures, though significantly decreasing the risk of breast cancer, do not completely eliminate it. Because breast tissue is not solely confined to the chest wall but rather is distributed widely all over the entire anterolateral chest wall and axilla, above the collarbone, and as far down as the abdomen, no mastectomy can remove all mammary tissue. Although breast tissues over the chest wall are removed during the risk-reducing mastectomy, breast cancer can still develop in the small amount of remaining tissue.

Drawbacks of risk-reducing mastectomy include surgical complications such as hemorrhage and infection, aesthetic disfigurement, sexual problems, and psychological trauma. Prophylactic mastectomy may have psychological effects on women's self

image, as well as on their sexual and reproductive function. Though these disadvantages are major factors in a woman's reluctance to have the procedure, this can be alleviated with the option of performing breast reconstruction.

Reconstructive surgery may be performed at the time of mastectomy (immediate reconstruction) or at a later date (delayed reconstruction). It includes the use of breast expanders or implants (silicone or saline), the patient's own tissue (autologous tissue reconstruction using flaps) or a combination of tissue reconstruction and implants.

*Risk-Reducing Salpingooophorectomy*

Risk-reducing bilateral salpingo-oophorectomy, on the other hand, is strongly recommended in women with *BRCA* gene mutations because of the high mortality rate associated with ovarian cancer for which there is lack of effective screening and preventive approaches. A meta-analysis of risk reducing salpingo-oophorectomy in BRCA 1 or BRCA 2 gene mutation carriers was published in the Journal of the National Cancer Institute in February 2009, inclusive of 10 studies with a total of 9170 subjects. Based on their data, the performance of RRSO on women with the BRCA 1 or BRCA 2 mutations has greatly reduced the risk for both breast, and ovarian/fallopian tube carcinomas by 50% and 80%, respectively.[28] Despite the official position of the American College of Obstetricians and Gynecologists (ACOG) that the decision should be individualized, the predominant practice is that prophylactic oophorectomy in the low-risk patient should be avoided under the age of 40, should be routinely performed over the age 55, and should be considered and discussed in the interval between.[22]

Fortunately, the risk of hereditary ovarian cancers does not rise dramatically until the late 30's in women with *BRCA*1 mutations and the late 50's for women with *BRCA*2 mutations. This provides women the opportunity to complete their families before undergoing risk-reducing BSO. The past practice of performing risk-reducing surgery based solely on family history should largely be abandoned. Currently, the decision to proceed with risk-reducing surgery is based on the results of *BRCA* mutational analysis. Risk-reducing BSO is widely viewed as the most effective currently available means of decreasing ovarian mortality in *BRCA* mutation carriers.[2]

Prophylactic bilateral salpingo-oophorectomy requires minor modifications of technique in comparison with a standard BSO for other indications. In an ideal setting, this is performed via the laparoscopic approach. Attention should be paid to transecting the ovarian blood vessels at least 2 cm proximal to the ovary. The possibility of occult ovarian cancer in these patients mandates a thorough exploration of the pelvis and abdomen, the use of cytologic analysis at the time of prophylactic BSO, the accessibility of frozen section pathologic analysis, and the availability of a gynecologic oncologist should a formal staging procedure become necessary. In a series of *BRCA* carriers who underwent prophylactic salpingo-oophorectomy in Canada, six of the 94 *BRCA*1 carriers (6.4%) and one of the 65 *BRCA*2 carriers (1.5%) were found to have an occult cancer.[23] Therefore, gross evaluation of extirpated adnexa may not always be sufficient to completely evaluate the presence or absence of malignancy in these organs.

Intraoperatively, if adhesions between the ovary and the pelvic sidewall peritoneum are encountered, they must not simply be lysed. Removal of adjacent and adherent parietal peritoneum with en-bloc removal of the adnexa is mandatory. This is important to prevent ovarian remnant syndrome, a condition where any residual ovarian cells have a high potential to undergo malignant change. There have been reported cases of Primary Peritoneal Carcinoma in women who previously underwent adnexectomies on a theory that incomplete ovarian extirpation provided the "seed" for anaplastic proliferation of cells at the parietal peritoneum.

*BRCA*-associated ovarian cancers are usually invasive serous lesions. There have been rare occurrences of peritoneal serous carcinoma after risk-reducing bilateral salpingo-oophorectomy, which was indistinguishable histologically or

microscopically from ovarian cancer.

Another surgical consideration concerns the fallopian tubes. The available literature suggests that fallopian tube cancers, although very rare, occur in these patients more frequently than would be expected by chance alone. In one study that examined 483 individuals with *BRCA* mutations, the patients were found to have a 120-fold increased risk of fallopian tube cancer (3%) compared with the Surveillance, Epidemiology, and End Results (SEER) Program population-based estimates.[11] Hence, it is important to include the fallopian tubes during the risk-reducing surgery. In the previously mentioned study by Finch, et al. on the presence of occult adnexal metastases in 7 women with the *BRCA*1 or *BRCA*2 gene mutation, three of these occult lesions involved the fallopian tube and not the ovaries.[23]

Risk-reducing BSO is not without its disadvantages. Surgical menopause after the prophylactic surgery is associated with the following sequela: vasomotor symptoms, vaginal atrophy, decreased libido, and early-onset osteoporosis. Though these symptoms may be alleviated and prevented with lifestyle modification and various medications, physicians should adequately counsel individuals in order to strike a balance between quality of life issues from surgical menopause versus the potential risk of developing an ovarian malignancy.

*Risk-Reducing Hysterectomy*

Recommendations for hysterectomy as part of risk-reducing surgery in *BRCA* carriers remain controversial. Women who have already completed their families or who have concomitant benign uterine conditions may elect to have the uterus removed during risk-reducing BSO. Hysterectomy as part of the risk-reducing operation is highly recommended in two clinical situations: in postmenopausal women who are or will be placed on Tamoxifen as adjuvant hormonal treatments and in women with Lynch syndrome. Women who are taking Tamoxifen for receptor-positive breast cancer have a 2-3 fold increased risk of developing endometrial cancer.[2] The study by Chen, et al. on the other hand, showed that hysterectomy and bilateral salpingo-oophorectomy reduce the incidence of endometrial and ovarian cancer in women with Lynch syndrome.[24] Women in either of these situations, therefore, are prime candidates for prophylactic hysterectomy.

*Synchronous Risk-Reducing Operations*

Batista, et al. showed in their study that coordinated prophylactic mastectomy and bilateral salpingo-oophorectomy are feasible procedures for patients at high risk for breast and ovarian cancers.[15] These synchronous risk-reducing operations can be performed with minimal morbidity. Such procedures were found to have three advantages: 1) it allows a single operation and recovery, potentially enhancing the patient's convenience; 2) the oophorectomy may allow for the initiation of aromatase inhibitors for endocrine treatment in premenopausal patients with estrogen receptor disease; and 3) it allows for early ovarian risk reduction, minimizing the theoretical risk of ovarian cancer development in between staged procedures.[15]

Risk-reducing surgeries were performed for our patient and her three sisters. A bilateral salpingo-oophorectomy was done after the cesarean section, even though she did not yet know that she was *BRCA* positive (it was performed only a year after initial diagnosis). Though a hysterectomy would have also benefitted her, this was not essential since she would not receive hormonal treatment (Tamoxifen) because the ER/PR assays were negative. She subsequently had risk-reducing mastectomy of her left breast in July of 2007.

Her other affected sister, also with the *BRCA*1 and *BRCA*2 gene mutations, underwent MRM of the left breast for Invasive Ductal Carcinoma, risk-reducing mastectomy with breast reconstruction of the contralateral breast, and laparoscopically-assisted vaginal hysterectomy and bilateral salpingo-oophorectomy. Her *BRCA* positive but clinically unaffected sisters both underwent risk-reducing bilateral mastectomy with breast reconstruction and laparoscopically-assisted vaginal hysterectomy and

bilateral salpingo-oophorectomy. The breast and pelvic procedures were done separately for each of the patient's sisters. It is noteworthy to mention that one of her unaffected sisters (with *BRCA2* gene mutation) already had Ductal Carcinoma In Situ (DCIS) at the time of the risk-reducing mastectomy. It is thus safe to assume that if this procedure was not performed, she also would have developed breast cancer in the very near future.

## Conclusion

A 38-year old G3P2 (1112) was diagnosed with Invasive Ductal Carcinoma of the right breast on her 23 weeks' AOG. She was given chemotherapy during pregnancy and subsequently had an LTCS with BSO at 36 weeks' AOG. Complete management of her breast cancer continued with a second chemotherapy regimen, MRM, and radiotherapy. Because of *BRCA1* and *BRCA2* positivity from genetic testing, she decided to have risk-reducing simple mastectomy of the contralateral breast. Due to a very strong possibility of a hereditary cancer syndrome in her family, *BRCA* testing was likewise performed on her sisters, who eventually tested positive for the *BRCA* gene mutation in different combinations. Each of them opted to undergo risk-reducing mastectomy and hysterectomy with bilateral salpingo-oophorectomy.

Significant progress in our understanding has been made in the past few decades in defining women who are at increased hereditary and environmental risk for gynecologic cancers, and, in many cases, identifying the specific loci of germ-line mutations through linkage analysis and/or DNA sequencing. However, negative tests pose no guarantee that a hereditary factor is not responsible. Laboratory tests and linkage analysis need to be expanded to encompass all the coding regions of all deleterious mutations. Techniques must be refined and results assured to avoid errors in collection, testing, and reporting. While genetic testing can be highly supportive in making rational management decisions, responsible clinicians should expectedly counsel and wisely follow up those individuals whose extended pedigrees indicate some form of cancer susceptibility traits, even when genetic testing is negative, unavailable, or unacceptable. In addition, when there is paucity of information regarding familial lineage, the occurrence of multiple breast, ovarian, and colorectal cancers in first- and/or second-degree relatives can provide the key to increased hereditary cancer risk, which the astute clinician will be wise to evaluate and follow.

It is thus important that obstetrician-gynecologists be familiar with the options available for screening and surveillance of inherited cancer syndromes and provide the pros and cons of risk-reducing surgeries for patients with a documented genetic predisposition to cancers. As physicians for women, our role is to provide our patients and their families with logical and practical options.

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# Cervical Choriocarcinoma: A Case Report****

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Primary cervical choriocarcinoma is extremely rare. Although rare, it is suggested that choriocarcinoma should be considered a possible cause of hemorrhage in a woman presenting with a cervical mass and a history of previous molar pregnancy. This is a case of a 50 year old woman with irregular vaginal bleeding for 3 weeks. A hemorrhagic cervical mass was detected by visual inspection. She underwent total abdominal hysterectomy and bilateral salpingooophorectomy and postoperative chemotherapy. Biopsy revealed cervical choriocarcinoma.

**Key words:** choriocarcinoma, cervix

Gestational trophoblastic disease is a rare tumor in women. It encompasses a group of interrelated diseases derived from the placental trophoblasts. Histologically, it is classified into hydatidiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumors.[1]

Gestational choriocarcinoma is common among Asian women. Choriocarcinoma is a highly malignant tumor arising from the trophoblasts following any type of pregnancy. It usually occurs in the uterine corpus and invades the myometrium through venous sinuses. The tumor also tends to invade blood vessels and it characteristically forms round hemorrhagic nodules and is prone to metastasize by the bloodstream to the vagina, lungs, liver and brain.

Few cases of choriocarcinoma outside the uterus have been reported. Due to placental implantation, primary cervical choriocarcinoma is extremely rare. Distinguishing it primarily from a uterine choriocarcinoma or other forms of cervical malignancy is often difficult. With this report, the authors share their own experience in its presentation, diagnosis and treatment.

## The Case

R.A., 50-year-old G4P2 (2022), was admitted in our institution last February 19, 2008 for vaginal spotting for three weeks which became profuse three days prior to admission. She had no other medical problems. Her family history was non-

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contributory. Her menstrual history was unremarkable. She had her first coitus at the age of 30 with a single partner. She had an abortion on her first pregnancy for which she underwent completion curettage. She had two full term spontaneous vaginal deliveries. Her fourth pregnancy five years ago was a molar gestation and terminated by suction curettage since she refused hysterectomy. The initial serum human chorionic gonadotropin (hCG) was more than 200,000 mIU/ml. Repeat serum hCG level after the curettage was 7,824 mIU/ml. She claimed that serial hCG levels were taken until it reached zero. However, no follow up with her physician was done thereafter. Last menstrual period was between November to December 2007.

*Her present illness started three weeks prior to* admission as brownish vaginal discharge to small amount of light red spotting. On the morning of her admission, she noted profuse vaginal bleeding requiring four to five sanitary pad changes. She consulted her physician who advised admission. The patient on admission was conscious, coherent ambulatory and not in respiratory distress. Vital signs were as follows: blood pressure 110/70mm Hg, pulse rate 82 beats/min, respiratory rate 19 cycles/min. Abdomen was soft and non-tender. Bimanual pelvic examination showed a parous introitus and smooth vagina. Cervix measured 4cm x 5cm. On speculum examination, a 2cm x 2cm hemorrhagic mass at the endocervical area attached at the 8-12 o'clock position was seen. The uterus was small and both parametria were smooth. Transvaginal ultrasound with doppler studies showed a normal sized anteverted uterus measuring 5.6cm x 4cm x 4.2cm, endometrial thickness of 0.78cm with non-specific sonographic appearance. There was a complex mass that appeared to replace the anterior cervical portion and appeared to extend cephalad towards the uterus (Figure 1). The mass appeared bulky and measured 6.9cm x 7.18cm x 5.75cm (Figure 2) with luxuriant Doppler Flow (Figure 3) suggestive of a neoplastic etiology. The ovaries were unremarkable. Initial complete blood count (CBC) showed hemoglobin of 11.5 g/L and hematocrit of 35.2%. The initial plan was to do fractional dilatation and curettage. However, heavy bleeding from the cervical mass was noted. The patient was then referred to a gynecologic oncologist. Vaginal packing was done. The serum hCG level was 591,860 mIU/ml. Two units of type O+ whole blood were transfused. Serum creatinine, chest radiograph and ultrasound of the upper abdomen were within normal. The patient was considered to have Gestational Trophoblastic Neoplasia FIGO Stage I:11 (Tables 2 & 3). Preoperative chemotherapy of methotrexate was given at 0.35mg/kg intramuscularly for 2 doses.

**Table 2.** FIGO classification system of GTN.

| Stage | Anatomic Location |
|---|---|
| I | Confined to corpus uteri |
| II | Metastases outside uterus limited to vagina or pelvic structures |
| III | Metastases to lungs |
| IV | Distant metastases to other sites |
| Substages for each stage as follows | |
| A | Low risk factors |
| B | High risk factors |

Our patient had a stage I disease.

**Table 3.** Prognostic scoring system for GTT.

| Prognostic Factor | 0 | 1 | 2 | 4 |
|---|---|---|---|---|
| Age | <40 | ≥ 40 | | |
| Antecedent pregnancy | H. Mole | Abortion | Term Pregnancy | |
| Months from index pregnancy | <4 | 4-6 | 7-12 | >12 |
| Pretreatment serum bhcg (IU/ml) | $<10^3$ | $10^3$ <$10^4$ | $10^4$ <$10^5$ | $\geq 10^5$ |
| Largest tumor size including the uterus | <3cm | 3-4cm | ≥5cm | |
| Site of metastasis | Lung | Spleen, Kidney | GIT | Liver, Brain |
| Number of metastasis | | 1-4 | 5-8 | >8 |
| Previous failed chemotherapy | | | Single drug | 2 or more drug |

The total score for a patient is obtained by adding the individual scores of each prognostic factor.
Low risk = 0-6 High risk = 7 or higher. Index patient has a high risk score = 11 (embossed)

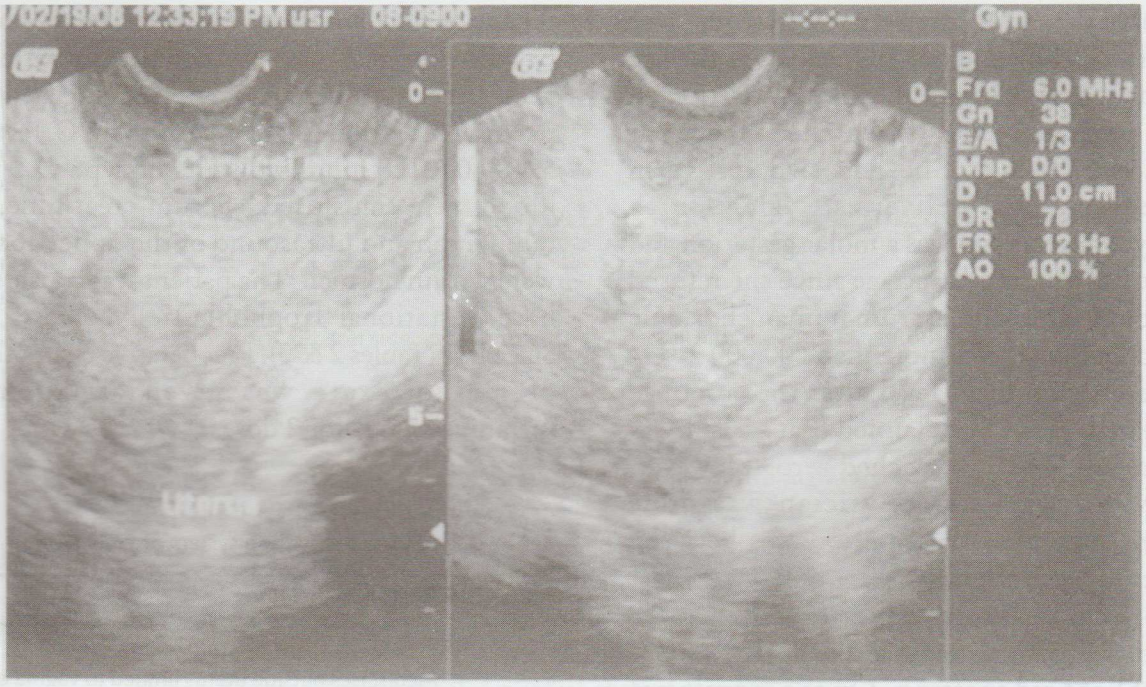


**Figure 1.** Transvaginal ultrasound of the uterus and cervical mass.

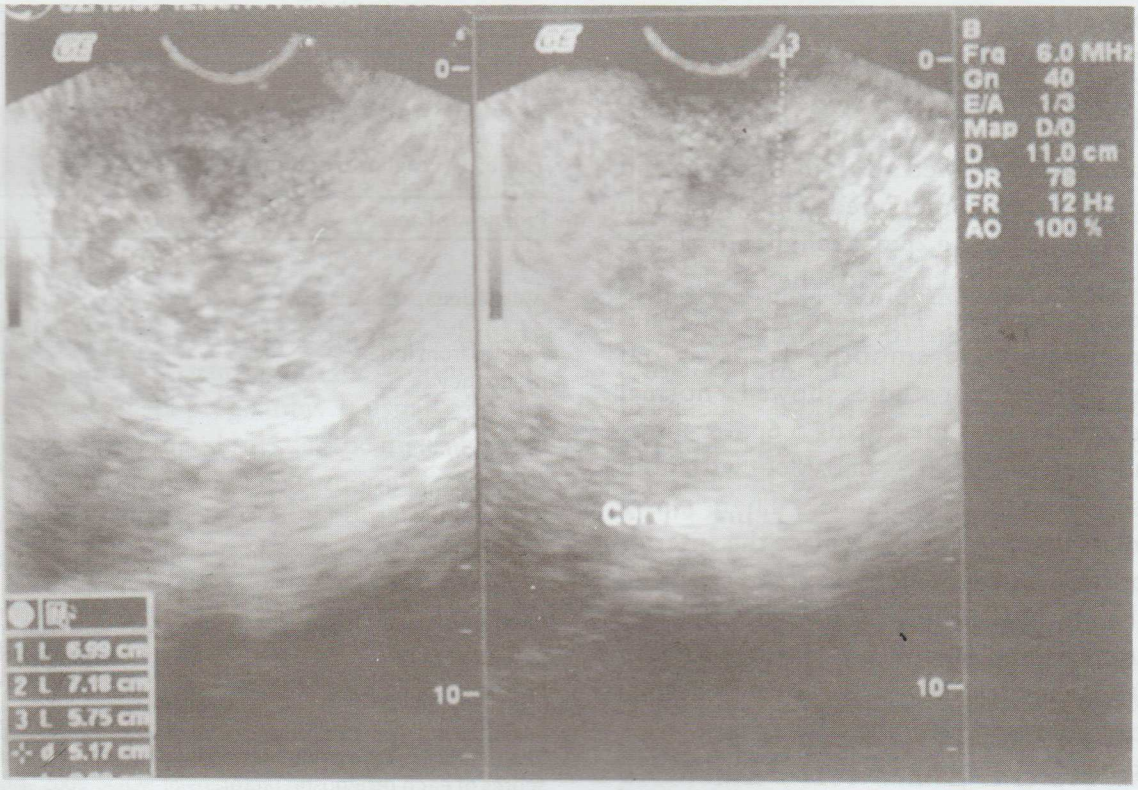


**Figure 2.** Transvaginal ultrasound of the cervical mass.

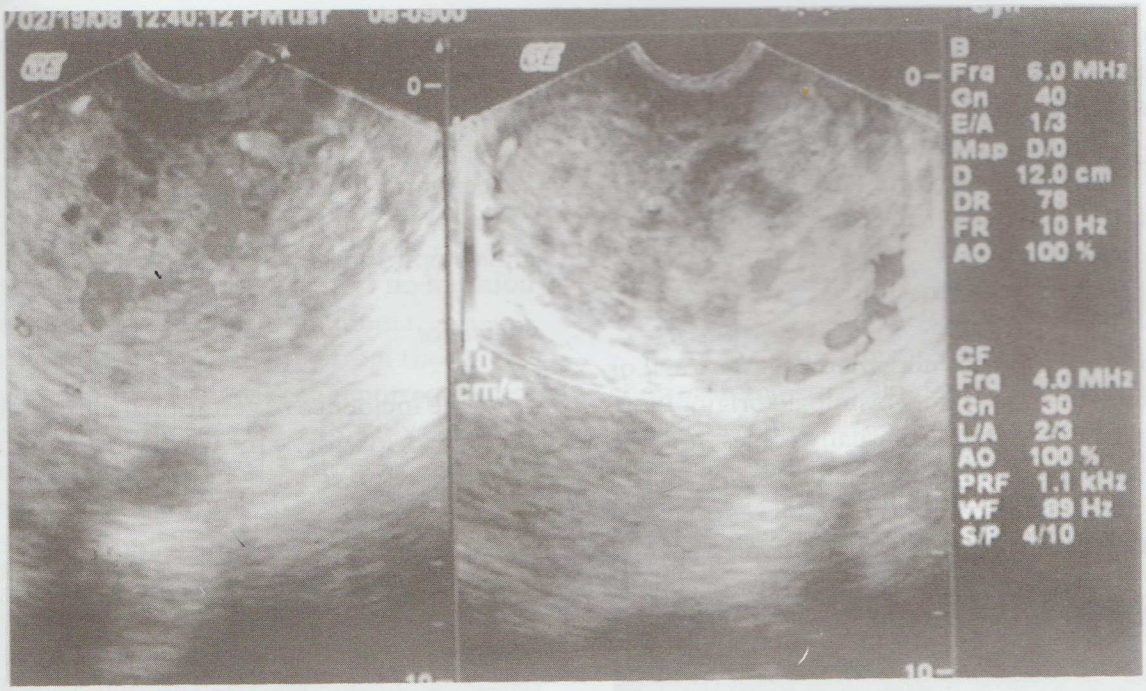


**Figure 3.** Transvaginal ultrasound with color flow of the cervical mass.

On the second hospital day, repeat hematocrit was 33.6%. Vaginal pack was removed. Profuse vaginal bleeding was noted with an estimated blood loss of about 800cc to 1 liter. Repeat CBC revealed hemoglobin of 9.1g/L and hematocrit of 27.5%. Additional two units of type O+ whole blood were transfused. An emergency total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. On laparotomy, the uterus was small and the ovaries were atrophic. No ascites was noted. The uterus measured 11cm x 6cm x 3.2cm. The ectocervix was irregular in shape. There was a 6.5cm x 6cm x 4cm dark reddish boggy necrotic mass at the cervical os which involved the ectocervix, endocervix and endocervical-endometrial junction. The endometrial cavity was small in size but it was regular in configuration (Figure 4). The other organs were grossly normal. The microscopic findings revealed a cervix with a polypoid lesion with proliferation of epithelial tumor cells. The parenchyma is composed of poorly differentiated trophoblastic epithelial cells demonstrating pleomorphism, enlarged nuclei, clumped chromatin and abnormal mitoses. Final histopathology report revealed choriocarcinoma of endocervix with superficial involvement of the endocervical-endometrial junction (Figures 5 & 6). Four cycles of methotrexate at 0.35mg/kg intramuscularly for 5 days every 10-14 days were administered postoperatively and serum hCG was noted to regress (Figure 7). Laboratory work up revealed a hemoglobin of 11.5 g/L, hematocrit of 33.0%, creatinine 0.78 mg/dl and SGPT of 36 U/L. On the fifth cycle of her chemotherapy, SGPT was 36 U/L, Creatinine of 0.78 mg/dl, hemoglobin 11.5 g/L, hematocrit of 33.9%, WBC count 3.98 and platelet of 963,000. On the sixth cycle of her chemotherapy, serum BhCG level was noted to elevate and became persistently elevated in her subsequent chemotherapy (Figure 7). On the seventh cycle of the patient's chemotherapy, ultrasound of the upper abdomen including the liver, gallbladder and common bile duct were negative. On the eighth cycle of chemotherapy, SGPT was 64 U/L, creatinine 0.75mg/dl, hemoglobin 11.8 g/L, hematocrit of 34.6, WBC

count 6.6, platelet 306,000. Chest x-ray PA view was suspicious for nodes in the right upper lobe. CT scan of the chest showed two tiny (2-4mm) nodules in the lateral portion of the apical segment of the right upper lobe suggestive of an inflammatory process versus neoplastic in etiology.

## Discussion

Choriocarcinoma is classified as gestational or non-gestational based on its histologic origin. Non-gestational choriocarcinoma usually comes from the ovary, testis, lung, mediastinum and base of the skull before period of maturity. Gestational choriocarcinoma arises from the trophoblasts of any gestational event. It includes heterochronic (interrupted, post molar, post partum, post menopausal, or post hysterectomy) and heterotopic (ectopic) pregnancy and may develop anytime after conception.[2,3,4] It follows an antecedent mole in 50% of cases, abortion in 25%, term deliveries in 20% and ectopic in 5%.[5]

*Incidence*

The incidence of gestational choriocarcinoma varies worldwide. In Western countries, it is

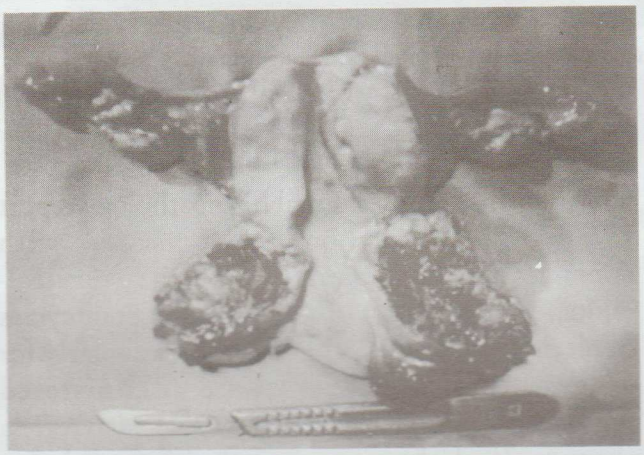

Figure 4. Surgical specimen.

Figure 5. Microscopic view of the cervical choriocarcinoma (LPO).

Figure 6. Microscopic view of the cervical choriocarcinoma (HPO).

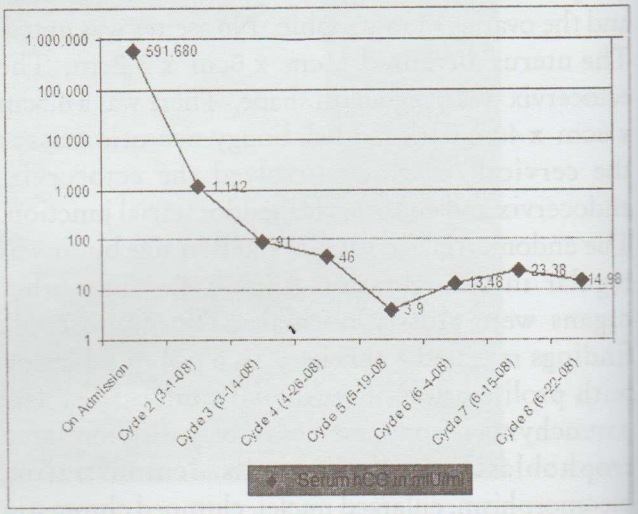


Figure 7. Patient's serum hCG regression curve.

reported between .014 and 0.2 per 1000 pregnancies. In the US, it is about 1 per 20,000 pregnancies. In Southeast Asia, 1 per 500-3000 pregnancies is recorded.[6] In the Philippines, Gestational Trophoblastic Disease including choriocarcinoma occurs in 2.2 per 1,000 pregnancies from the period of 1995 to 1997.[7] However, there was no mention of incidence of cervical choriocarcinoma.

Choriocarcinoma originating from the genital areas outside the uterus have been reported such as in the tubes, ovaries, vagina and vulva besides extragenital regions like the lungs, omentum, gastrointestinal tract and brain.[8] Gestational choriocarcinoma usually involves the uterine corpus and rarely occurs in the cervix. Primary cervical choriocarcinoma is an extremely rare disease.

When choriocarcinoma arises outside of the uterine corpus, it is called ectopic choriocarcinoma. In 1965, Saito, et al. did an extensive survey of the Japanese literature on ectopic choriocarcinoma.[2,4,5] They defined the criteria of ectopic choriocarcinoma as follows: 1) there is no focus of choriocarcinoma in the uterine corpus, 2) the histopathological diagnosis should be confirmed as choriocarcinoma, 3) extrauterine choriocarcinoma coexisting with hydatidiform mole or intrauterine pregnancy should be excluded, and 4) intramural choriocarcinoma in the uterine corpus should not be considered as ectopic choriocarcinoma. Yakata's review of cases in the Japanese literature identified 18 cases of primary cervical choriocarcinoma. Eleven cases were preceded by hydatidiform mole, five cases by term delivery and two cases by spontaneous abortion.[3,4] Latent period from the preceding pregnancy was less than 12 months in eight cases and more than 24 months in seven cases. Age ranged from 23-52 years. A review of cases of primary cervical choriocarcinoma by Y. Fu, et al. in the Chinese literature identified one case preceded by hydatidiform mole, five cases by term pregnancy and seven cases by abortion.[2] The time from antecedent pregnancy to diagnosis was less than 12 months in two patients and more than 24 months in 16 patients. There are already 86 reported cases of primary cervical choriocarcinoma (Table 1). Majority are in the fourth decade of life (50%). The latency period is 12-64 months.[2,4] The patient has a latency period of 60 months. Although the majority of choriocarcinoma develop shortly after the preceding gestation, long latency (> 10 years) between the gestation and diagnosis can occur.[9]

*Pathologic Features*

The predominant symptom of cervical choriocarcinoma is abnormal vaginal bleeding.[10] Thus, the clinical diagnosis of primary cervical choriocarcinoma is often difficult to make. In the second and third decades, these patients are often misdiagnosed to have cervical pregnancy, polyp, threatened or incomplete abortion. In the fourth or fifth decades, cervical malignancy is often suspected. Discriminating choriocarcinoma from other carcinomas either within the uterus or at other sites usually is overlooked. Thus, primary cervical choriocarcinoma should be included in the differential diagnosis of cervical lesions in the presence of a cervical mass associated with profuse bleeding. Grossly, they form dark reddish, soft, boggy, polypoid or round, nodular, placenta-like, necrotic tumor masses in the cervix. Characteristically, all trophoblastic tumors are perfused by fragile vessels; hence, highly vascular and frequently hemorrhagic. They often tend to bleed profusely after cervical biopsy. A biopsy of choriocarcinoma may show the classic dimorphic or biphasic pattern with alternating arrangement of syncytiotrophoblasts and either cytotrophoblasts or intermediate trophoblasts. The trophoblasts are usually pleomorphic with varying degrees of cytologic atypia and mitotic activity. Chorionic villi are not present.[6]

*Pathogenesis*

Theoretically, there are three mechanisms for developing cervical choriocarcinoma. One, the patient initially had a cervical pregnancy followed by malignant transformation. Second, it may result from metastasis from the primary tumor of the corpus which had disappeared. Third, it may be due to the transport of trophoblasts from the

Table 1. Eighty-six cases of primary cervical choriocarcinoma recorded in literature.

| Author | Cases(s) | Derivation | Language/Country |
|---|---|---|---|
| Rashbaum | 13 (12 from lit) | Am J Obstet Gynecol 1952; 64: 451-5 | English/America |
| Saito | 18 (from lit) | World J Obstet Gynecol 1965; 17: 459-84 | Japanese/Japan |
| Minegishi | 6 | Sanfujinka Jissai 1965; 14: 763-7 | Japanese/Japan |
| Ooguchi | 7 | J Jpn Obstet Gynecol Soc 1966;18:1083-92 | Japanese/Japan |
| Koga | 1 | J Jpn Obstet Gynecol Soc 1966;13:245-9 | Japanese/Japan |
| Danek | 1 | Minerva Ginecol 1969;21:1707-11 | Italian/Italy |
| Momose | 1 | Obstet Gynecol Ther 1970; 21: 468-71 | Japanese/Japan |
| Pavlica | 1 | Zentralbl Gynakol 1971;93:72-4 | German/Germany |
| Tsukamoto | 1 | Gynecol Oncol 1980;9:99-107 | English/Japan |
| Tripathi | 1 | Br J Obstet Gynaecol 1982;89:267-9 | English/India |
| Meriah | 1 | J Gynecol Obstet Biol Reprod (Paris) 1983;12:519-24 | French/France |
| Martin | 1 | Am J Obstet Gynecol 1983;147:343-4 | English/America |
| Bogdanowicz | 1 | Ginekol Pol 1984;55:527-30 | Polish/Poland |
| Bhalla | 1 | Indian J Pathol Microbiol 1987;30:51-3 | English/India |
| Tsai | 4 | Aisa Oceania J Obstet Gynaecol 1988;14:285-92 | English/Taiwan |
| Ben-Chetrit | 1 | Am J Obstet Gynecol 1990;163:1161-3 | English/Israel |
| Lee | 1 | Acta Obstet Gynecol Scand 1992;71:479-81 | English/Taiwan |
| Heyn | 1 | Geburtshilfe Frauenheilkd 1993;53:498-500 | German/Germany |
| Herts | 1 | J Ultrasound Med 1993;12:59-62 | English/America |
| Abboud | 1 | J Gynecol Obstet Biol Reprod (Paris) 1994;23:149-51 | French/France |
| al Hassani | 1 | Trop Geogr Med 1995;47:308-9 | English/Qatar |
| Yahata | 1 | Gynecol Oncol 1997;64:274-8 | English/Japan |
| Lema | 1 | East Afr Med J 1997;74:600-2 | English/Malawi |
| Baykal | 1 | Gynecol Oncol 2003;90:667-9 | English/Turkey |
| Fu | 11 (from lit) | Shi Yong Zhong Liu Za Zhib 2003;18:412-3 | Chinese/China |
| Huang | 2[c] | Zhong Nan Da Xue Xue Bao Yi Xue Ban 2004;29:108-9 | Chinese/China |
| Roopnarinesingh | 1 | Ir Med J 2004;97:147-8 | English/Israel |
| Peko | 1 | Med Trop (Mars) 2005;65:498 | French/France |
| Fu | 4 | Int J Gynecol Cancer 2007;17:715-719 | English/China |

[a]Lit, Literature; [b]This journal cannot be searched by PubMed; [c]Clinical diagnosis only for one case, no pathologic diagnosis.

preceding pregnancy as emboli which stay dormant and later gave rise to malignant transformation.[10] The authors favor the third explanation for the development of their patient's primary cervical choriocarcinoma. The patient underwent suction curettage for molar pregnancy five years ago. They believe the trophoblastic tissues from her molar gestation were carried to the cervix during the curettage, but did not regress. Instead, these trophoblastic tissues remained dormant until they transformed into cervical choriocarcinoma.

Al Hassani, et al. in 1995 reported a similar case of a 40 year old Indian woman who developed primary cervical choriocarcinoma three years after her curettage for cervical pregnancy. They also believed that the curettage performed could be the source of trophoblastic implantation in the cervix followed by malignant transformation.[11]

The course after curettage alone depends on the malignant potential of the removed uterine contents. From many studies, it is clear that 80 to 90% of moles remain benign and give no further difficulty. Ten percent develop into invasive moles and 2.5% into choriocarcinoma.[12]

Choriocarcinoma has a tendency toward early vascular invasion with widespread dissemination. Metastasis occurs in about 4% of patients after evacuation of a complete hydatidiform mole.[13] Choriocarcinoma is prone to metastasize via the bloodstream. The lungs are the most common site of distant metastases (>90% of patients with metastatic disease) but the brain and the liver may also be involved. Vaginal involvement was reported in up to 30% of patients.[14]

*Diagnosis*

The diagnosis of choriocarcinoma is usually based on a high index of suspicion from history alone. Since this tumor also produces chorionic gonadotropin (hCG), levels of this hormone in the serum may serve as a marker of the presence of viable tumor in the body. Imaging studies such as radiographs, MRI and CT scan are useful for detection of metastasis and staging of the disease. Color and Pulsed Doppler ultrasonography are useful for diagnosis by detecting the abundant blood flow and central necrosis of the tumor. It has been shown that most gestational trophoblastic tumors have increased uterine and adnexal vascularities similar to those pregnancy-related diseases.[3] Hepatic, thyroid and renal function tests are also included. On occasion, IVP, brain scan, EEG or selective angiography can also be utilized. Occasionally, diagnosis of cervical carcinoma is also difficult for pathologists. The cells of cervical squamous carcinoma may have abundant eosinophilic cytoplasm as seen in cytotrophoblasts and may have more than one nucleus, thus resembling syncytiotrophoblasts.[2] The diagnosis of cervical choriocarcinoma can be confirmed by immunohistochemical staining for hCG and human placental lactogen.

*Management*

The management for primary choriocarcinoma of the cervix follows that for gestational trophoblastic neoplasia. The tumor is staged and scored according to the 2000 FIGO staging (Table 2) and risk factor scoring system (Table 3). A patient's stage and score is expressed by allotting a Roman numeral to the stage and an Arabic numeral to the risk score separated by a colon.[15] The prognostic risk score was developed by Bagshawe to predict the likelihood of drug resistance and to assist in proper selection of appropriate chemotherapy. A score of 7 or more is considered high risk and requires intensive combination chemotherapy.

*Chemotherapy*

Treatment for choriocarcinoma is dependent on the extent of the disease using the FIGO staging. Stage I regardless of prognostic score and Stage II-III low risk category are treated with a single agent chemotherapy (Table 4) Methotrexate or Actinomycin D every 7-10 days as a 5 day regimen. Induced complete remission is 91.2% of cases in Stage I and 80.0% of cases in Stage II-III low risk category.[13] This is followed by two clean up courses after the first normal titer. For resistant cases,

remission is achieved with primary intensive combination chemotherapy.

**Table 4.** Single agent regimen for gestational trophoblastic tumor.

| Drug Option | Dosage |
|---|---|
| Methotrexate | 0.4mg/kg body weight (maximum 25mg) intravenously or intramuscularly daily for 5 days every 2 weeks |
| Actinomycin D | 10-12 ug/kg intravenously daily for 5 days every 2 weeks |
| Methotrexate followed by leucovorin | 1-1.5kg/kg intramuscularly or intravenously on days 1, 3, 5 and 7 followed by citrovorum factor rescue (leucovorin) 0.1-0.15 ug/kg intramuscularly on days 2, 4, 6 and 8. |

Stages II-III high-risk patients, are given primary intensive combination chemotherapy every 14 days until the hCG titer becomes normal. The preferred regimen is EMACO, MEA (Table 5) followed by three clean up courses. Stage IV disease is given an initial combination chemotherapy (EMACO Regimen) every 14 days followed by three clean up courses after the first normal titer. For patients with brain metastasis, intrathecal methotrexate is given on first day of systemic chemotherapy.

**Table 5.** EMACO regimen.

| Day | Drug/Dosage | |
|---|---|---|
| 1 | Etoposide: 100mg/m² IV over 30 mins | E |
| | Methotrexate: 100mgm² IV push | M |
| | Methotrexate: 200mg/m² IV infusion in 1L D5W over 12hrs | |
| | Actinomycin D: 0.5mg IV push | A |
| 2 | Etoposide: 100mg/m² IV infusion in 250ml NS over 30min | |
| | Actinomycin D: 0.5mg IV push | |
| | Folinic Acid:15mg IM q12hrs x 4 (24hrs after Methotrexate) | |
| 3 | Cyclophosphamide: 600mg/m² IV | C |
| | Vincristine: 1.0mg/m2 IV push | O |

Repeat cycle on days 15, 16 and 22 (every 2 weeks)
* Comprehensive Gynecology Chap 35 p 1058 table 35-5

Hammond, et al. reported that when single agent chemotherapy was administered at a fixed time interval and induced remission in patients with non-metastatic gestational trophoblastic tumor, relapse recurred in 2 percent of patients.[16] In 1984, Bagshawe described a new combination regimen that include Etoposide, Methotrexate, Cyclophosphamide and Vincristine (EMACO). He reported 83% remission in patients with metastases and a high risk score and 93% for non metastatic and low risk category.[17] Clean up courses are usually given to prevent relapse.

*HCG Regression Curve*

Serum B HCG should be measured weekly after each course of chemotherapy. The hCG regression curve serves as the primary basis for determining the need for additional treatment. An adequate response is defined as a fall in the hCG level by one log 18 days after a course of chemotherapy.[13]

*Surgery*

Surgery may be instituted for appropriately selected patients to decrease the tumor load and the number of chemotherapeutic courses to be given. Surgery in the course of chemotherapy is done in select cases. Chemotherapy can be safely administered at the time of hysterectomy without increasing the risk of bleeding and sepsis. In this particular case, two doses of adjuvant methotrexate were given preoperatively. Theoretically, adjuvant chemotherapy maintains a cytotoxic level in the blood and tissues in case viable tumor cells are disseminated at surgery or occult metastasis may already be present at the time of surgery.[13] Hysterectomy is indicated in the control of profuse uterine bleeding, 35 years old and above with completed family size, inability to repair a tumor perforation, and drug resistance.

*Conservative Management*

Nearly all the reported cases of cervical choriocarcinoma were treated by hysterectomy and

chemotherapy. In recent years, with the dramatic effect of chemotherapy on gestational trophoblastic tumors, hysterectomy is less indicated in patients who wish to preserve reproductive function. In 1990, Ben-Chetrit, et al. reported a successful conservative treatment of primary cervical choriocarcinoma with a 0.5cm x 1cm lesion with no active bleeding and an initial hCG level 32u/L. In 2004, Huang, et al. reported two cases of primary cervical choriocarcinoma successfully cured with chemotherapy alone.[2] However, the effect of chemotherapy alone for primary cervical choriocarcinoma remains to be seen.

*Follow up*

When the pelvic examination and chest radiographic findings are negative, metastatic involvement of other sites is uncommon. However, non-metastatic gestational trophoblastic tumor or disease confined to the uterus without evidence of distant metastasis should be seen with greater frequency if the index of suspicion is high. Follow up for Stage I-III includes a serum hCG weekly until three negative hCG levels are obtained. Monthly levels are taken until normal for 12 consecutive months. For Stage IV, monthly levels should be taken until normal for 24 consecutive months. Prolonged follow up is recommended because of high risk of late recurrences. Transvaginal ultrasound every six months is required for those who did not undergo hysterectomy. If at the time of completing treatment, there is still radiographic evidence of residual tumor, further radiographs are required yearly.

Patients on multiple courses of combination chemotherapy may have elevated luteinizing hormone (LH) level and may present problems with cross- reactivity. Therefore, they should be placed on oral contraceptive pills to suppress the rising LH resulting from damaged ovarian steroidal function.

Pregnancy should be avoided for a span of two years from the first normal hCG titer to have accurate hCG monitoring.

*Persistent Low Levels of hCG*

Our case presented with persistent low levels of hCG. The dilemma of whether this is tumor progression or a phantom hCG makes us suggest further analysis in discriminating the type of hCG, specifically, the hyperglycosylated hCG. Hyperglycosylated hCG is an absolute marker of invasive choriocarcinoma.[18] It is important to determine if the hCG measured is real and management would differ. A referral to the USA hCG Reference Center is advisable.

*Pulmonary Nodules*

Admitting chest x-ray of our patient was negative. The follow up CT scan however, showed two pulmonary nodules. It would have been better if there was an admitting CT scan for the patient if not for financially constraint, chest x-ray was done instead. This would have ruled out fibrosis, infection or lung metastases.

In the guidelines for management of incidental small pulmonary nodules detected on CT scan approved by the Fleischner Society, it has been the accepted standard of practice for pulmonary nodule of less than or equal to 4 mm to follow up CT scan at 12 months in high risk patients. If the scan is unchanged, then no further follow up is needed.[19]

However, since our patient had cervical choriocarcinoma, it is imperative to follow the protocol for the management of choriocarcinoma. A close follow up interval scan is highly recommended.

*Prognosis*

In a review of reported cases, the prognosis of cervical choriocarcinoma is good. It showed a low incidence of metastasis (27%) and the prognosis is better than for other types of ectopic choriocarcinoma.[4]

## Summary

Choriocarcinoma of the uterine cervix is an extremely rare entity. It should be included as a

differential diagnosis of any cervical lesion despite its rarity. Diagnosis can be missed if early evaluation is not initiated. Early diagnosis is made with a high index of suspicion based on a history of molar gestation, abnormal vaginal bleeding and presence of a cervical mass. It is confirmed by an elevated serum beta hCG level, Doppler studies and biopsy.

## Conclusion

The present case is one of an ectopic choriocarcinoma. They believe that its development is due to the transport of trophoblasts from previous molar gestation and later gave rise to a malignant transformation. Curettage and biopsy for cervical choriocarcinoma carry a high risk of massive hemorrhage. Life threatening hemorrhage frequently requires an emergency hysterectomy. Chemotherapy is the cornerstone for the management of primary cervical choriocarcinoma. Choriocarcinoma has a very good prognosis since it is a chemosensitive tumor.

## References


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