Cancer of the Cervix: The Philippine Experience; Has Anything Changed?

Luciano S.J. Sotto, M.D.

The answer is a resounding YES. The basis for this answer will cover our experience of more than 40 years, largely from the Philippine General Hospital. In June 1961, when this author joined the Department of Gynecology of the Philippine General Hospital, Gynecologic Oncology as we know it today, did not exist. Even in the United States of America, it was only in the latter part of the sixties that a formal and structured fellowship training program in Gynecologic Oncology was started. Prior of this, training in the specialty was largely preceptorial in character. Physicians and surgeons interested in the diagnosis and treatment of malignant diseases after their primary residency training, applied in established specialized cancer centers which numbered only a handful at the time. The training was for a limited period of one to two years, but many of them stayed on because of their interest and the research facilities available.

What was the state of affairs in the Philippines then, as far as the treatment of cancer was concerned? There were exactly 2 gynecologists who had the training, exposure and experience in the field of gynecological cancer, both of whom were trained at the Roswell Park Memorial Institute in Buffalo, New York, one of the leading cancer centers in the United States of America then, and they are my friend Dr. Manuel Borja and yours truly. There were 5 trained and practicing radiation oncologists; 3 in PGH, 1 in Jose Reyes Memorial Medical Center and 1 in Manila Doctors Hospital.

Radiation Facilities and Technic of Radiotherapy

The treatment of cervical cancer was undertaken primarily by the radiation oncologists in PGH and the JRMH. Both institutions used ORTHO voltage x-ray machine, which was the only equipment available at the time. External radiation, was given 2-3 times per week and to deliver 4000 rads to the center of the pelvis, or the region of the cervix, it took 4-6 months. Only a few selected patients were treated with brachytherapy. Radium was the only isotope available at the time, and the PGH was the only institution in the country that had sufficient amount of it. The total dose (combined external beam and brachytherapy) was quite low and the total treatment time was long. The standard dose in the American centers at the time was 9-10000 rads given over a period of 6-8 weeks. Very few of our patients came close to this standard, hence very few were cured. The Manila Doctors Hospital was the only private hospital that had a Cobalt machine, which was the most sophisticated machine in the country at the time. This was used to treat private patients of course.

Surgery

The usual surgical intervention done in cancer of the cervix was total hysterectomy, or even subtotal hysterectomy done by the obstetricians/gynecologists

and general surgeons. There were a few consultants in PGH who were doing radical hysterectomy in the fifties.

The Birth of Gynecologic Oncology

Shortly after my appointment as consultant in Gynecology at the PGH, our chairman, the late Dr. Constantino P. Manahan instructed me to organize a Malignancy Service. He assigned 10 beds to the service. Gynecologic Oncology was born. Needless to say, I was overjoyed by this. We lost no time in formulating policies and guidelines for the diagnosis and treatment of all malignant tumors. A malignancy consultation and follow up clinic in the Out Patient Department was one of the first things we organized. All patients with cancer seen in the clinic were admitted for work up and treatment. Patients with clinical stages I & II cervical cancer were prepared for radical hysterectomy and bilateral pelvic lymph node dissection. Those with advanced stages were referred to the Cancer Institute or the Manila Doctors Hospital for radiotherapy.

At this point, I would like to acknowledge the following people who were the residents in Gynecology at the time, who contributed their share in the organization of the Malignancy service. They are Drs. Florante Gonzaga, Genara M. Limson, Augusto Manalo, Rainerio Abad, Virgilio Oblepias and Mildred Pareja. Probably lured by the glamour of radical pelvic surgery which was quite new in our country then, four of them went to the United States of America and took up further training in Gynecologic Oncology. Dr. Genara Limson went to the Downstate Medical Center and Kings County Hospital in New York to work with Dr. Hellman and Dr. Masterson; Dr. Augusto Manalo went to M.D. Anderson Hospital and Tumor Institute to work with Dr. Felix Rutledge; Dr. Rainerio Abad went to Roswell Park in Buffalo New York with Dr. John Graham, and Dr. Virgilio Oblepias to Georgia with Dr. John Thompson and later on to the University of Minnessota with Dr. John Mc. Kelvy. Later on Dr. Oblepias was sidelined in Family Planning, and this was where he made his fame and fortune. Dr. Gonzaga went to Columbis University in New York with Dr. Howard Taylor Jr. and studied Endocrinology and Infertility. After their training they all came back and became consultants in the Department of Obstetrics and Gynecology in PGH. The Gynecologic Oncology Service became the first specialized section, and a powerhouse section of the Department of Obstetrics and Gynecology.

Development of Radiotherapy

In 1965, the Cancer Institute of the PGH acquired two teletherapy units; a Cobalt machine and a Cesium machine. With sufficient radium tubes for brachytherapy, we felt we could now offer adequate radiotherapy to patients with cervical cancer. The initial total dose given was quite low compared with the generally accepted standard in the Western countries. After a few years, the total dose (combined external beam and brachytherapy) was increased and the treatment time shortened to conform with the universal standard at the time.

For almost 3 decades the Cancer Institute of the PGH was the only institution in the country which could offer adequate radiotherapy to patients with cervical cancer. The volume of patients, charity, as well as pay, placed so much strain not only on the resources but on the personnel as well.

To illustrate, let me now cite some figures.

Cervical Cancer Patients Seen in the Charity Clinic

June 1961 - Dec. 1970	597
Jan. 1971 - Dec. 1980	2120
Jan. 1981 - Dec. 1990	3166
Jan. 1991 - Dec. 2000	3933

There has been a marked increase in the number of cases but the sad part about it is the fact that we have not been able to change the stage distribution to a more favorable one. Two thirds of our patients belonged to the more advanced stages of IIb, III and IV. This was true in 1961 and it is still the same today. This means that we have not been diagnosing them early enough. There are several reasons for this, but the most important probably is the failure to use the Papanicolaou smear more widely. This is more of a socio economic problem than a purely medical one.

In 1970, the Makati Medical Center, a private hospital in Makati started operations. It had facilities for radiotherapy in the form of Cobalt machine for teletherapy and cobalt tubes for brachytherapy. In 1972, the Veterans Memorial Medical Center acquired its Cobalt unit. Several years later, other government hospitals likewise got their Cobalt machines and these were Jose Reyes Medical Center, Baguio General Hospital, the Southern Islands

Hospital in Cebu, Davao Medical Center, and lately the Zamboanga Medical Center. In the last 10-15 years several private hospitals organized their Radiation Oncology Centers acquiring the more sophisticated, more powerful, and more expensive state of the art machines both for teletherapy and brachytherapy.

These hospitals include St. Lukes Medical Center, Makati Medical Center, Perpetual Help Medical Center, The Medical City Medical Center, Davao Doctors Hospital, Chinese General Hospital, Cebu Doctors Hospital, Gullas Medical Center, De La Salle University Medical Center, and the Marian Radiation Oncology Center. All of these centers use either the Linear Accelerator or Cobalt Machine and High Dose Rate Brachytherapy. Unfortunately, these radiotherapy centers are located only in Metro Manila, Cebu City and Davao City. Ideally, all the twelve regions of the country should have a radiation oncology center equipped with the latest facilities for radiation, as well as trained staff.

Surgery

Radical hysterectomy with bilateral pelvic node dissection is the standard procedure for early and operable cases of cervical cancer. This operation was first done by Clarke of the United States of America in 1895. Wertheim followed in 1898, and has persisted doing this ever since, inspite of the introduction and great promise of radium therapy in 1903. Because of the absence of radiation facilities when we organized the malignancy service in 1961, we vigorously pursued the use of radical hysterectomy. Even endometrial carcinomas, whose standard treatment in the western countries then was intrauterine radiation followed by total hysterectomy, were treated primarily with surgery. Even after the Cancer Institute acquired the radiotherapy facilities, we continued doing surgery because of the large number of patients which could not all be accommodated by the Radiotherapy Unit. Here are some figures.

Radical Hysterectomy for Cervical Cancer

June 1961 - Dec. 1991	780
Jan. 1992 - Dec. 2001	438
TOTAL	1218

Chemotherapy

In the last 15-20 years, chemotherapy agents active against cervical cancer have been incorporated in the primary treatment. Such agents are given before radiation or surgery, (neoadjuvant) concomitantly with radiation, (chemoradiation), and after surgery or radiation (adjuvant). These active agents are Cisplatin, 5 Fluorouracil, Vincristin, Bleomycin, Mitomycin, Epirubicin, Hydroxyurea, etc. They are given as a single agent or a combination of two or even three drugs.

The one widely used, and the one recommended is Cisplatin, given concurrently with radiation. This is given either weekly at a dose of 40-50 mg per meter square of body surface or 75 mg per meter square every 3 weeks. Upon completion of the radiotherapy, Cisplatin may or may not be continued. It is believed that Cisplatin acts as a radiosensitizer. With chemoradiation, local and regional response rates are greatly improved. Chemoradiation is now considered as the gold standard "treatment of cervical cancer".

As a preoperative medication, it can make the operation technically easier because it reduces the bulk of the tumor, thus increasing the operability rate. It is also possible that with enough courses, distant metastasis or lymph node metastasis will be reduced.

For recurrent cases, these chemotherapeutic agents are given for palliation.

All these drugs are available locally at reasonable and affordable prices. All of the practicing Gynecologic Oncologists can handle these drugs quite well. The following data came from the Gynecologic Oncology Section of the Department of Obstetrics and Gynecology of the UP-PGH Medical Center. From 1999 to year 2001, a total of 103 patients with cervical cancer were treated with chemoradiation. This is a very small fraction of the total number of cervical cancer cases seen. Most of the cases treated had far advanced lesions, stages IIB and III. Two thirds of the patients received the weekly dose. Less than 50 (42%) completed the six courses prescribed.

Fellowship Program in Gynecologic Oncology

In 1975 the State Department of the United States of America discontinued the Exchange Visitors Programs, making it more difficult for foreign doctors to go to America for further training. It was at this time that we thought of organizing a Fellowship Program in Gynecologic Oncology. It took 3 years for the program to be approved and another two years for it to be implemented. There was no funding for the program. It

was a two-year program whose centerpiece was radical pelvic surgery. The other components of the program were pelvic radiotherapy, chemotherapy and surgical pathology. Preference was given to trainees from government hospitals outside Metro Manila and faculty members of medical schools. The first two Fellows graduated in 1982. Five years ago, we increased the training period to 3 years, adding rotation in Colon Surgery, Urology, Medical Oncology, Colposcopy and Ultrasound. By the end of 2001, we have graduated 55 trainees all of whom are now certified Gynecologic Oncologists and Fellows of the Society of Gynecologic Oncologists of the Philippines (SGOP). Thirty one of these Fellows are practicing in Metro Manila, 3 in Cebu City, 3 in Davao, and one each in Ilocos, Baguio City, Dagupan, La Union, Cagayan, Pampanga, Zambales, Cavite, Laguna, Batangas, Quezon, Naga City, Bacolod, Cagayan de Oro, Iloilo, and Zamboanga City. At least 30 are faculty members of several medical schools. Four more trainees will complete their training by the end of this year. The impact of these specialists on the care of women with gynecological cancer is quite obvious.

The Society of Gynecologic Oncologists of the Philippines (SGOP)

In 1984, a handful of Gynecologic Oncologists decided to organize themselves into a society, to promote, develop and upgrade Gynecologic Oncology as a specialty. The objectives and strategies are spelled out in the By Laws. Incorporated in the By Laws are the requirements for training, as well as the certifying Board. Hospitals aspiring to have an accreditation for trianing have to comply with the requirements. Upon completion of the training in an accredited program, the candidate must pass the written examination, the Pathology examination, and finally the oral test. The candidate becomes a Diplomate in Gynecologic Oncology. After one year, the Society of Gynecologic Oncologists of the Philippines (SGOP) may invite him or her to become a Fellow of the Society. The Society now has 55 active certified Fellows and 14 Affiliate Fellows. This was another milestone in the development of Gynecologic Oncology in our country.

The Cost of Treatment of Cervical Cancer

Before I conclude this presentation, please allow me to give you an idea of the cost of treatment of cervical cancer in Metro Manila. These data came from St. Luke's Medical Center and the Philippine General Hospital

St. Luke's Medical Center
Department of Radiation Oncology

Rates for the following procedures; - As of 2001

COBALT TELETHERAPY:		
Charge per session	P470.00x25	P 11,750.00
Treatment Planning		485.00
Verification Film		480.00
Professional Fee	P2,500.00/wkx5	P 12,500.00
TOTAL		P 25,215.00
LINEAR ACCELERATOR		
Charge per session	P1,125.00x25.	P 28,125.00
Treatment Planning		485.00
Verification Film		480.00
Custom Blocks		3,470.00
Professional Fee	P2500/wkx5	12,500.00
TOTAL		P 45,060.00
BRACHYTHERAPY		
First session		P 19,140.00
Succeeding sessions	P6,290.00x3	18,870.00
TOTAL		38,010.00
PROFESSIONAL FEES		
Radiation Oncologists	P5,000.00x4	P 20,000.00
Gynecologic Oncologist	5,000.00x4	20,000.00
Anesthesiologist	3,000.00x4	12,000.00
TOTAL		P 52,000.00
TOTAL COST - HOSPITAL & DOCTORS		P 90,010.00
TOTAL COST OF RADIOTHERAPY		
Teletherapy & Brachytherapy		P135,070.00

COST OF RADIOTHERAPY IN PGH		(Private Patients)
External Beam Cobalt		P 2,500.00
Hospital & Professional Fees		P12,500.00
TOTAL		P15,000.00
Brachytherapy LDR		
Hospital Fees		P10,000.00-P12,000.00
Professional Fees RT Onco		
Gyn Onco		
Anesth		P21,000.00-P23,000.00
TOTAL		P31,000.00-P35,000.00
Total Cost of Radiotherapy LDR PGH		P46,000.00-P49,000.00
Charity Patients		
Cobalt per session		P 64.00- P 75.00
25 sessions		P1,625.00-P1,850.00
Brachytherapy		500.00
TOTAL		P2,125.00-P2,350.00

Charity Patients PGH

Cobalt	P1,625.00-P1,850.00
Brachytherapy	P 500.00-P 500.00
TOTAL	P2,125.00-P2,350.00

Professional Fee ..... Free

COST OF RADICAL HYSTERECTOMY

Private Patient in a ward bed for 10 days

Room	P 4,000.00-P 6,000.00
OR	P 30,000.00-P40,000.00
Medicines	P 10,000.00-P15,000.00
Laboratory	P 10,000.00-P15,000.00
Surgeon	P 20,000.00-P70,000.00
Anesthesiologist	P 7,000.00-P 20,000.00
TOTAL	P81,000.00-P166,000.00

COST OF CHEMOTHERAPY

Price of Cisplatin 50 mg.	P 1,000.00-P 1,500.00
Antiemetic	P 1,500.00-P 1,500.00
Hospital Fee - 1 day	P 1,500.00-P 2,000.00
Professional Fee	P 2,000.00-P 5,000.00
TOTAL	P 5,000.00-P10,000.00
6 C	P 30,000.00-P60.000.00

In conclusion, the answer to the original question, *Cancer of the Cervix, the Philippine Experience: Has Anything Changed?*

I will repeat, the answer is a Resounding Yes. Patients with cervical cancer nowadays have a much better chance of survival and cure. We have the facilities for good radiotherapy, all the specialists involved in its treatment, effective chemotherapeutic agents and the necessary supportive and ancillary treatments.

But, the following problems still have to be addressed.

1. Early Diagnosis - All the programs of the government as well as private programs have to be pursued vigorously.
2. Prevention is the real key. We always preach that cervical cancer is a preventable disease, so that all efforts should be directed towards this goal.
3. Increase the number of radiation facilities especially in the provinces. There should be at least one Radiation Oncology treatment center in each geographic region of the country to be put up by the government.
4. The cost of treatment should be lowered.

Treatment Outcomes of Stage IB2 and Bulky IIA Cervical Cancer at a Tertiary Hospital: A Comparison of Two Different Chemoradiation Followed by Hysterectomy Treatment Regimens

Jean Anne B. Toral, M.D.
Section of Gynecologic Oncology, Department of Obstetrics and Gynecology
Philippine General Hospital, University of the Philippines Manila

Objective: To compare the treatment outcomes in terms of clinical and pathologic responses, toxicities, and overall survival of two neoadjuvant chemoradiation followed by hysterectomy regimens for Stage IB2 and bulky Stage IIA disease of the cervix. **Methods:** Thirty-eight women with Stage IB2 and bulky IIA cervical disease were included in the study. Twenty underwent neoadjuvant external pelvic beam radiation concomitant with single agent cisplatin followed by radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection (Regimen A). Eighteen underwent neoadjuvant external pelvic beam radiation plus intracavitary radiation concomitant with single agent cisplatin followed by extrafascial hysterectomy with bilateral salpingo-oophorectomy (Regimen B). Duration of neoadjuvant treatment, toxicities, clinical responses and pathologic responses were observed. Patients were followed up for treatment outcomes. **Results:** Regimen A was associated with a shorter duration of neoadjuvant treatment time with an average of 40.7 days compared to 75.2 days for regimen B. Regimen B had a higher complete pathologic response rate at 55.6 % compared to only 30 % for regimen A. Hematologic, hepatic, and renal toxicities were the most commonly observed toxicities and were more prevalent in regimen B. However, all of these were reversible. There was one operative morbidity seen in each group. With a median follow-up of 22 months and a mean of 26.3 months, 83.3 % of the patients in regimen A have no evidence of disease. For regimen A, 77.8 % of patients have no evidence of disease with a median follow up of 3 months and a mean of 6.67 months. Fifteen percent of patients in regimen A showed tumor progression compared to 22.3 % for regimen B. Further adjuvant treatment after the definitive hysterectomy was only seen in regimen A. **Conclusion and Recommendation:** Based on this series of patients and with the available length of follow-up, survival data on these two treatment regimens are almost comparable with slightly higher percentages of cure and less toxicity associated with regimen A. Regimen B, on the other hand, results in higher complete histologic responses, thus, reducing the need for adjuvant treatment after surgery. The treatment regimen omitting intracavitary radiation could be an option in areas where such facilities are limited. Longer duration of follow-up is warranted to be able to determine the true value of these treatment options in our setting. A randomized controlled trial to include an arm also on just concomitant chemoradiation as well as neoadjuvant chemotherapy with radical hysterectomy might provide important insights in the management of these patients.

Key words: Stage IB2, bulky cervical disease, neoadjuvant, chemoradiation, radical hysterectomy, extrafascial hysterectomy

Cervical cancer remains a mqjor health problem worldwide. This is so, despite the advances in cervical cancer screening. In 2002, the American College of Obstetricians and Gynecologists (ACOG) recorded 12,900 new cases in the US and 4,400 related deaths.[1] In the Philippines, it remains a formidable disease among women. It is the second most common malignancy among women in the country with about 4,000 new cases reported yearly and half dying of the disease.[2]

The quest for the ideal modality of treatment for cervical carcinoma has not stopped. The five-year survival rates, stage for stage, has not essentially improved, either in developed countries or worldwide. Over the last century, surgery and radiation, and more recently, chemotherapy, have been used in various settings in an effort to improve survival rates of patients with cervical cancer. However, these treatment modalities, if used in their traditional way, may not result in any significant improvement in overall survival. New therapeutic approaches or a better integration of these existing modalities in the primary treatment of cervical carcinoma patients have been considered. This concept of multimodality treatment has long emerged in the management of locally advanced cervical carcinoma.

For the early stage IB1 diseases, retrospective analyses suggest that either radical hysterectomy or pelvic radiation is equally effective. The case of the bulky (> 4 cm) early stage cervical cancer, that is, Stage IB_2 and bulky Stage IIA, remain a therapeutic challenge. The prognostic significance of tumor dimension in early stage cervical cancer has long been established but the optimal management of these patients remains controversial. None of the current treatment strategies satisfactorily leads to a high rate of disease-free survival.

Treatment of these bulky tumors in our institution has also followed the various treatment combinations by our counterparts in Europe and in the USA. Ours, though, works in a less ideal setting with limitations in radiation facilities as well as funds for neoadjuvant chemotherapy. It used to take about 3 to 4 months from external pelvic beam radiation for our patients to undergo intracavitary radiation (brachytherapy). Thus, the treatment plan of omitting brachytherapy and proceeding straight to radical hysterectomy became an acceptable option. Bulky early stage diseases in the late 1990's were treated with concomitant chemoradiation in the form of single agent cisplatin and external pelvic beam radiation followed by radical hysterectomy and bilateral salpingo-oophorectomy with pelvic lymph node dissection. Since June 2001, neoadjuvant chemotherapy with single agent cisplatin together with external pelvic beam radiation and intracavitary radiation followed by extrafascial hysterectomy and bilateral salpingo-oophorectomy have been used following the phase III study of the Gynecologic Oncology Group (GOG) number 123.

This investigation is a descriptive study with the aim of comparing treatment outcomes of Stage IB_2 and bulky Stage IIA cervical cancers treated with the two differing concomitant chemoradiation followed by hysterectomy treatment protocols. Specifically, clinical and pathologic response rates, and overall survival will be compared. Toxicities and complications from each of the treatment regimen will also be compared.

Materials and Methods

Subjects

Subjects for this investigation include:

1. All patients with histologically confirmed cervical carcinoma with no previous treatment
2. Of the FIGO Stage IB2 or bulky IIA (bulky defined as cervical tumor with more than 4 cm greatest diameter or expansile barrel-shaped tumors)
3. With Eastern Cooperative Oncology Group (ECOG) performance score of 0-2, good hematologic, hepatic and renal picture and with good cardiopulmonary function to undergo the chemotherapy regimen and the definitive surgery. (ECOG performance score)
4. Above patients who were able to complete either of the treatment regimen at the institution from 1997 up to April 2003.

Treatment regimen

Regimen A: Patients managed from 1997 to June 2001 received the following: Chemotherapy with weekly cisplatin at 40mg/m^2 for 3 to 6 courses or cisplatin 75 mg/m^2 every 3 weeks for 2 courses concomitant with external pelvic beam radiation followed by radical hysterectomy and bilateral salpingo-oophorectomy and pelvic lymph node dissection at least 2 weeks after the radiation treatment. One patient managed after this time also underwent the same regimen.

Regimen B : Patients managed from July 2001 up to April 2003 received the following: Chemotherapy with weekly cisplatin at 40 mg/m^2 for 3 to 6 courses or cisplatin 75 mg/m^2 every 3 weeks for 3 courses concomitant with external pelvic beam radiation and intracavitary radiation (all making use of low-dose rates) followed by extrafascial hysterectomy and bilateral salpingo-oophorectomy. Surgery was done at least 3 weeks after the radiation treatment.

External pelvic beam radiation for both regimens were delivered with the fourfield technique with the treatment field set to encompass the iliacs and the lower common iliac nodes. Fractions of 180 to 200 cGy were given 5 days per week for a total of 5 weeks. Certain delays in administration of radiation are both due to machine breakdown, problem in patient compliance and some patient toxicities, particularly, anemia. External pelvic beam radiation dose ranged from 5000 to 5040 cGy.

Low-dose intracavitary radiation was used in regimen B with a dose ranging from 2369 cGy to 4500 cGy. These were given between 2 weeks and 12 weeks after the external pelvic beam radiation.

For chemotherapy, the choice between the weekly and the every 3 weeks cisplatin was left at the discretion of the attending physician.

Parameters

The following have been noted from the available data and follow-up of patients:

1. Patient characteristics : age. gravidity and parity
2. Initial size of cervical tumor and stage of disease
3. Histologic type
4. Duration of neoadjuvant treatment
5. Interval between end of neoadjuvant treatment and definitive surgery
6. Radiation and chemotherapy doses
7. Toxicities from chemoradiation treatment and surgical morbidities (using the GOG Common Toxicity Criteria Grade of October 1988)
8. Clinical and pathologic response rates.
9. Outcomes and overall survival based on available follow-up data. These were calculated from the date of completion of therapy to the date of the most recent follow-up.

Patient follow-up

Patients while on the neoadjuvant treatment were followed up weekly at the Out Patient Clinic. Internal examinations were performed at the start, middle, and end of the neoadjuvant treatment. Hematologic picture was checked weekly with complete blood counts while liver and renal functions were checked at least every 3 weeks. Appropriate measures for any abnormality including blood transfusions were taken as necessary. Response to treatment was assessed periodically and the feasibility of surgery was determined after completion of the neoadjuvant treatment. Following the surgical management, necessity for additional radiation and chemotherapy was individualized depending on the surgico-prognostic factors found. Patients, upon assessment with no evidence of disease were followed up monthly on the first year, every two months on the second year, and so on. Patient follow-up at this time entailed general physical examination pelvic examination and vaginal vault smears every 3 months for the first year and every 6 months on the second year, and yearly thereafter.

Statistical Analysis

The study is mainly descriptive and analysis of data between the two groups are expressed in percentages only.

Results

Patient demographics, stage, histologic type, and tumor size.

A total of 38 patients from 1997 to April 2003 completed either of the treatment regimen. Twenty patients completed regimen A and 18 have completed regimen B. The clinical characteristics of the patients in each study group are listed in Table 1 . For regimen A, the mean age of patients was 37.4 (range of 25-54) while it was 43.4 (range of 32-56) for regimen B. Gravidity ranged from 1 to 9 for regimen A while there was a nulligravid for regimen B. The highest gravidity in regimen B was a gravida 11.

Data on the stage distribution are seen in Table 2. There were more Stage IB2 than bulky IIA in both treatment groups. Eighty percent of patients in regimen A belong to Stage IB2 while 66.7% of patients in regimen B belong to the same stage.

Data on the histologic type of tumors are seen in Table 3. There is a difference between the two groups in this aspect. Squamous cell carcinoma was the most common histopath in Regimen A accounting for 65 percent. There was one case of small cell carcinoma. In regimen B, the adenocarcinoma histotype accounted for 44.4 percent and was the most common.

Table 1. Clinical characteristics of patient: Age distribution.

Age range	Regimen A (n=20)	Regimen B (n=18)
21-30	3	0
31-40	8	7
41-50	8	7
51-60	1	4
Mean	37.35	43.44
Median	39	44
Range	25-54	32-56

Table 2. Stage distribution.

Stage	Regimen A (n=20)	Regimen B (n=18)
IB2	16 (80%)	12 (66.7%)
IIA	4 (20%)	6 (33.3%)

Table 3. Histologic types of tumor.

Histologic type	Regimen A (n=20)	Regimen B (n=18)
Squamous, large cell non-keratinizing	11 (55%)	7 (38.9%)
Squamous, large cell, keratinizing	2 (10%)	1 (5.5%)
Adenocarcinoma	6 (30%)	8 (44.4%)
Small cell	1 (5%)	1 (5.5%)
Adenoquamous	0	1 (5.5%)

As to tumor size (Table 4), 11 patients (55 %) had a cervical tumor size of 6 cm while 4 (20 %) had 5 cm in regimen A. There was one with a 9 cm tumor size and was the biggest. In regimen B, 7 patients (38.9 %) had a 5 cm tumor size and 5 with 6 cm (27.8 %). There were 2 patients in regimen B which had 8 cm size of lesions.

Treatment Characteristics. (Table 5)

Duration of neoadjuvant treatment for regimen A ranged from 33 to 67 days with an average of 40.7 days. Twelve patients (66.7 %) had their neoadjuvant treatment between 36 to 49 days (5 to 7 weeks). The interval between neoadjuvant treatment and surgery ranged from 12 to 55 days with a mean of 27.5 days. Thirteen patients (65 %) had their surgeries after 3 to 6 weeks from neoadjuvant treatment. The range of external pelvic beam radiation dose received was 5000 to 5040 cGy. Weekly cisplatin doses were given for 2 to 6 courses while the every 3 week regimen was given for 3 courses.

Table 4. Tumor size.

Tumor size	Regimen A (n=20)	Regimen B (n=18)
5 cm	4 (20%)	7 (38.9%)
6 cm	11 (55%)	5 (27.8%)
7 cm	3 (15%)	4 (22.2%)
8 cm	1 (5%)	2 (11.1%)
9 cm	1 (5%)	-

Table 5. Treatment characteristics

5a. Duration of neoadjuvant treatment

Duration	Regimen A (n=20)	Regimen B (n=18)
<=35 d (<=5 wks)	2 (10%)	0
36-49 d (>5 wks to 7 wks)	12 (60%)	1 (5.6%)
50-63 d (>7 wks to 9 wks)	3 (15%)	5 (27.8%)
>63 d (. 9 wks)	0	0
Data not available	3 (15%)	0

5b. Interval between neoadjuvant treatment and surgery

Interval	Regimen A (n=20)	Regimen B (n=18)
< = 18 d (3 wks)	3 (15%)	1 (5.6%)
> 18 d-42 d (>3 wks-6 wks)	13 (65%)	11 (61.1%)
> 42 days (> 6 wks)	1 (5%)	6 (33.3%)
Data not available	3 (15%)	0

Duration of neoadjuvant treatment for Regimen B ranged from 44 to 125 days with a mean of 75.2 days. Twelve patients (66.7 %) had their duration of neoadjuvant treatment for more than 9 weeks. The prolonged duration of neoadjuvant treatment is mainly from the long interval between the end of external pelvic beam radiation and the giving of low-dose intracavitary radiation which ranged from 2 to 12 weeks. The interval between neoadjuvant treatment and surgery ranged from 15 to 177 days with a mean of 49.1 days. Eleven (61.1 %) patients had their surgery between 3 and 6 weeks after the neoadjuvant treatment as prescribed in the GOG 123 protocol while 6 had it after more than 6 weeks. The mean radiation dose was 8,445 cGy with a range of 7,369 to 10, 078 cGy. Weekly cisplatin doses was given for 3 to 6 courses while the every 3 weeks regimen was given for 3 courses.

Clinical and pathologic responses. (Table 6)

Following neoadjuvant treatment using regimen A. there was only one patient with complete clinical response

(5.3 %), 11 with partial clinical response (57.9 %) and 8 with stable disease (42.1 %).

Table 6. Histologic responses

Response	Regimen A (n=20)	Regimen B (n=18)
Complete	6 (30%)	10 (55.6%)
Partial		
Stromal invasion < 50%	9 (45%)	2 (11.1%)
Stromal invasion > 50%	4 (20%)	3 (16.7%)
	• 2 with < 50% invasion had (+) lymph nodes	
	• 1 with > 50% invasion had (+) vaginal cuff	
Abandoned surgeries	1 (5%)	3 (16.7%)

On exploratory laparotomy, one case had the contemplated surgery abandoned due to bladder involvement. This patient was advised brachytherapy but was lost to follow up. Six cases (30 %) had complete histologic responses showing no residual tumor on the specimen. Thirteen patients (65%) had partial histologic response with 9 showing less than 50 percent stromal invasion and 4 with more than 50 percent stromal invasion. Two of those with less than 50 percent stromal invasion, however, had positive pelvic lymph nodes and one with more than 50 percent stromal invasion had positive vaginal cuff margins. One of those with pelvic lymph node involvement was lost to follow-up while the other one was given additional chemotherapy in the form of single agent cisplatin and parametrial boost and, presently, has no evidence of disease after 2 years and 8 months. The patient with positive vaginal cuff was given 3 courses of cisplatin-ifosfamide every 4 weeks subsequently and has no evidence of disease for a month as of last follow-up.

Following neoadjuvant treatment using regimen B, 4 had progressive disease based on the intraoperative findings, 2 had stable disease, 9 had partial clinical response, and 3 had complete responses.

On exploratory laparotomy, 3 cases were abandoned, the first 2 because of bladder involvement and the third one because of grossly enlarged pelvic nodes. Prior to the planned surgery, these cases were evaluated and examinations revealed they may undergo the surgery. There was a case with findings of enlarged pelvic and para-aortic nodes intraoperatively (Patient 3, Table 10) but the hysterectomy was not deferred. On this patient's follow-up, she had persistent disease for which second line chemotherapy with cisplatin-ifosfamide was advised. The patient, however, could not afford the treatment. The 3 abandoned cases followed up 1 to 4 months after the surgery and all have persistent disease with masses in the pelvis. There were no distant metastasis yet as of their last follow-up. All were advised to have second-line chemotherapy with cisplatin-ifosfamide. No one complied.

Among those with available surgical histologic data, 10 patients (55.6 %) had complete pathologic responses while 5 had partial responses with 3 showing more than 50% stromal invasion and 2 with less than 50 percent invasion.

Toxicities and Surgical morbidities. (Table 7)

The most common toxicity encountered during the neoadjuvant treatment for regimen A was hematologic with 10 patients exhibiting grade 2 toxicity, 3 with grade 1 toxicity and 1 grade 3 (total 70%). Forty percent of patients had kidney and bladder toxicity mostly in the form of microscopic hematuria and albuminuria. Fifteen percent had gastrointestinal toxicity in the form of nausea and vomiting and 25 percent had hepatic toxicity, mostly grade 1 from slight elevation of transaminases. All of these were reversible. There was one operative morbidity encountered, a rectal injury requiring transverse loop colostomy. This patient was lost to follow-up. One patient had bladder atony, post-operative, and one developed lymphocyst which was managed conservatively.

Table 7. Toxicities and surgical morbidities

7a. Regimen A

	Gr0	Gr1	Gr2	Gr3	Gr4	Total %
Hematologic		3	10	1		87.5 %
GI			2		1	18.75 %
Liver		4	1			31.25 %
KUB		5	3			50%
Operative						
Bladder atony		1				
Lymphocyst			1			
Bladder Injury						
Bowel injury				1		

7b. Regimen B

	Gr0	Gr1	Gr2	Gr3	Gr4	Total %
Hematologic		5	11	2		100%
GI			2	1	1	23.5%
Liver		8	1			52.9%
KUB		7	5			70.6%
Operative						
Bladder atony						
Lymphocyst						
Bladder Injury		1				

The most common toxicity encountered with regimen B was hematologic with all 18 cases experiencing decreases in hemoglobin levels. More than 70 percent had kidney and bladder toxicity primarily in the form of hematuria and 53 percent had hepatic toxicity manifested by slightly elevated transaminases. All of these toxicities were transient. There was one operative morbidity, a bladder injury involving the trigone which was repaired primarily (Patient 5, Table 10). However, ureteral stricture became its secondary complication requiring a second surgery.

Follow-up and Status. (Table 8)

Mean duration of follow up for treatment regimen A was 26.3 months, median of 22 months, and a range of 1 to 66 months; Fifteen out of the 18 (83.3 %) patients on follow-up have no evidence of disease. Two were known to have recurrent disease and one with persistent progressive disease. Of these three, only one is confirmed to have died of the disease. The other two did not undergo the prescribed treatment for tumor progression and have been lost to follow up.

Table 8. Treatment outcome and status on follow-up

Status	Regimen A (n=20)	Regimen B (n=18)
No evidence of disease	15 (83.3%)	14 (77.8%)
Persistent progressive	1 (5%) * died of disease	4 (22.3%)
Recurrent		0
Local	1 (5%)	
Distant		
Combined	1 (5%)	
No data available	2	

For regimen B which was started only in June 2001, the mean follow-up is 6.67 months with a median of 3 months, and a range of 1 month to 18 months. Fourteen (77.8%) of the patients have no evidence of disease as of their last follow-up. Four have persistent progressive disease. These are the 3 with abandoned surgeries and the one with enlarged nodes on exploratory laparotomy. All of the 18 remain alive.

Discussion

Tumor size remains an important prognostic factor in patients with early stage disease of the cervix. The influence of tumor size on the outcome of patients with Stage IB_2 and bulky IIA cancer of the cervix is such that lymph node metastasis is higher and central recurrences are more frequent.[3,7] Pelvic failure rates after radiation are related to tumor size as shown by Perez et al. Pelvic failure rate for Stage IB disease is 6 percent for less than 3 cm tumor and increases to 30 percent with more than 5 cm tumors.

Previous treatments with just radiation alone have produced only up to 62 percent 5year survival[3-5] and recurrence rates as high as 86 percent.[6] Treatment with primary surgery in the form of radical hysterectomy has only achieved at best 65.9 percent 5-year survival.[7] These poor outcomes from monotherapy prompted several investigators to make use of combination or multimodality treatments in varied sequences.

The combination of the two treatments in the form of neoadjuvant radiation followed by extrafascial hysterectomy has improved survival to as high as 89 percent.[4,8-10] This stemmed primarily from the significant decrease in the incidence of central recurrence with extrafascial hysterectomy. The same was shown by the series of Durrance in M.D. Anderson Hospital.[11] These were, however, retrospective analyses. Subsequent studies on these showed no added benefit for doing the hysterectomy both for pelvic failure rates and overall survival as shown by the study of Eifel, et al. and Mendenhall et al.[12, 25] Thus, the validity of doing the extrafascial hysterectomy after radiation has been questioned.

It was during this time that the GOG embarked on another study to test the validity of doing extrafascial hysterectomy after a radical radiation treatment. It was GOG 71 which addressed the value of extrafascial hysterectomy in this subset of patients which received complete radiation.[13] The results of the said study just came out recently. There was a lower cumulative incidence of local relapse in the RT + HYST group at 5 years (27% vs. 14%). However, there were no statistical differences in outcomes between regimens except for the adjusted comparison of progression-free survival. The authors, thus, concluded that, overall, there was no clinically important benefit with the use of extrafascial hysterectomy.

The other combination with primary surgery followed by tailored postoperative radiation has produced 5-year survival rates up to 88.5 percent in patients with no poor surgico-prognostic factors and 71 percent in patients with

poor surgico-prognostic factors.[23-24] The proponents of this treatment modality felt that optimal selection of patients for aggressive combined modality regimen are best guided after histologic evaluation of the cervix, parametria and lymph nodes. The question, however, on operability and technical feasibility always arises in this kind of sequential treatment The performance of appropriate parametrial dissection and vaginal resection may be difficult even for the seasoned surgeon. There has been only modest interest in approaching these bulky tumors with primary surgery.

Studies involving chemoradiation for cervical cancer started in the 1980's. Chemotherapeutic agents serve as sensitizers of tumor cells to radiation as well as eradicators of microscopic foci. This seems very important especially for these bulky lesions where tissue hypoxia poses a great problem. The greater the volume, the larger is the hypoxic and resting phase cell population with reduced chemosensitivity and with greater probability of developing resistant clones. Cisplatin, in particular, potentiates the sublethal damage induced by radiation and inhibits repair of potentially lethal radiation-induced damage. Other theoretical benefits of neoadjuvant chemotherapy include reduction of bulky tumor mass leading to increase in operability, decrease in the incidence of pelvic lymph node metastasis, and possible improvement in long-term survival.[14]

After the results of the 5 phase III randomized controlled trials on chemoradiation came out, all showing benefit, the National Cancer Institute in the United States has designated chemoradiation as the new standard of care for cervical cancer.

In 1999, Keys et al demonstrated the role of neoadjuvant chemotherapy with cisplatin concomitant with external pelvic beam radiation and intracavitary radiation followed by extrafascial hysterectomy for bulky cervical cancer. There was an 83 percent 3-year survival in the chemoradiation group compared to 74 percent for those without chemotherapy.[15] This is the GOG 123. When this study was started, the results of the GOG 71 study have not yet come out. The authors of GOG 123 still included the extrafascial hysterectomy as part of treatment though they were doubting also at that time regarding its benefit based on the preliminary results of GOG 71. It proved the benefit of concomitant chemotherapy with radiation treatment for this group of tumors.

With the results of GOG 71 and GOG 123 already out, it may be inferred that complete chemoradiation followed by extrafascial hysterectomy will result also in lower cumulative incidence of local relapses. The overall survival, as seen in GOG 123, was still higher for the chemoradiation followed by extrafascial hysterectomy arm. To what then shall we attribute this higher survival rates? Is it the local control provided by the hysterectomy or is it the eradication of the micrometastatic foci from the chemotherapy? This issue on extrafascial hysterectomy following chemoradiation will remain a good topic for discussion among gynecologic oncologists and the other members of the managing team. A randomized controlled trial comparing concomitant chemoradiation alone with concomitant chemoradiation followed by extrafascial hysterectomy following the prescribed interval might provide the answer to this issue.

Another multimodality option of treatment for these bulky tumors is neoadjuvant chemotherapy (NACT) followed by radical hysterectomy. There are theoretical advantages to administering neoadjuvant or "upfront" chemotherapy.[16] Chemotherapy may be more effective if given before tumor blood flow is disturbed by surgery or radiation. Chemotherapy may be less toxic when given before the bone marrow is affected by radiation therapy. Patients with larger tumors are at risk for harboring micrometastatic disease and neoadjuvant chemotherapy may more effectively address this risk for distant failure. After chemotherapy, the removal of residual disease after tumor shrinkage may overcome cell kinetics-based changes which leads to cross-resistance if this were followed by radiation.

At present, there are only 3 Phase III trials published on neoadjuvant chemotherapy (NACT) followed by radical hysterectomy for the bulky early stage diseases. Results seem incongruous. In 1997, Sardi et al have shown that for more than 4 cm lesions there is a survival difference in patients given neoadjuvant chemotherapy (cisplatin-vincristine-bleomycin) followed by radical hysterectomy and pelvic radiation with an overall survival of 65 percent compared to 48 percent for complete radiation only, 41 percent for surgery only, and 54 percent for neoadjuvant chemotherapy plus radiation.[17] Surgical resection was possible in 80 percent of cases of NACT followed by surgery compared to 56 percent for primary surgery. The improved survival here was attributed to the increased operability with free margins and a decrease in pathologic risk factors.

In 2000, Chang and his colleagues in Taiwan compared the efficacy of neoadjuvant chemotherapy also using the same drugs as Sardi's followed by radical hysterectomy compared to pelvic radiation- The study involved 124 patients with Stage IB_2 and bulky IIA disease. The efficacy of both treatment arm was the same with cumulative survival rates of 81 percent for NACT and 84 percent for RT at 2 years.[18]

In 2001, Benedetti-Panici, et al. published their results from the Italian multicenter study involving stages IB2 to III of cisplatin-based NACT followed by radical surgery compared to exclusive radiotherapy. From their study, survival benefit for NACT seems to favor only patients in the stage IB_2 to IIB group.

From the results of these randomized trials, one may opt to use this NACT followed by radical hysterectomy treatment regimen as well. Toxicities with multiple chemotherapeutic agents must be handled very carefully. The cost of chemotherapy, though, may be prohibitive in our setting. The one factor which may be favorable to this regimen is the fact that radiation, the facilities of which remain wanting in our country, may not be needed until much of the tumor volume has already been eradicated by the first two treatment regimen used.

The combination of NACT followed by radiation has, on the other hand, produced disappointing results with some studies even showing compromised survival.[20] This is, therefore, a treatment regimen which is no longer recommended. Potential explanations of these findings include: the cross-resistance between chemotherapy and radiation when used sequentially, accelerated repopulation of surviving clones to chemotherapy, and the frequently observed prolongation of the whole treatment time, as well as the lower tolerance to radiation after induction chemotherapy. This cross-resistance is overcome by adjuvant surgery making the combination of chemotherapy followed by radical hysterectomy a workable treatment of choice.

In the setting where these 38 patients have been treated, prolonged radiation treatment has always been a problem because of the limited facilities, particularly for intracavitary radiation. The outcomes, therefore, from complete radiation are poor. Scheduling is not within the ideal two week period from the completion of external beam radiation. It should be emphasized that a lot of studies have shown a loss of local control of around 1 percent for every day added to an overall treatment time of 49-52 days.[21] It was at this time, some 6 years back, that the members of the staff decided to try a modification of the treatment for these bulky lesions. Following the dictum of "no two radical forms of treatment for a single patient", the treatment regimen of complete radiation was modified to just external pelvic beam radiation followed by adjuvant surgery with radical hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection.[22] This was aimed at avoiding the delay in intracavitary radiation. Out of the 17 who underwent the surgery, only 4 had complete pathologic responses. Survival data based on their last follow up show 10 of the patients (52.6 %) have no evidence of disease while 4 (21 %) had tumor progression. There were no data for 5 patients.

Subsequently, with the pronouncement of chernoradiation as the new standard of care, radiation treatment here was accompanied by chemotherapy with single agent cisplatin as in regimen A of this study. From this subset of 20 patients, 15 (83.3 %) are known to have no evidence of disease and 3 (15 %) with known tumor progression. This improvement in survival data compared to the previous RT followed hysterectomy treatment may be attributable to the role of chemotherapy of eradicating micrometastatic foci of disease. Post-hysterectomy adjuvant treatment either in the form of added chemotherapy or radiation, on an individualized basis, must have contributed also to the present status of 4 of these patients. This is despite the fact that there was only 30 percent complete pathologic responses in this group. As already proven, residual histologic tumor is a poor prognostic factor for recurrence after radiation treatment.

As to the 3 patients who had known tumor progression in this group, 2 had significant residual in the hysterectomy specimen (one full stromal invasion and one with less than 50 percent stromal invasion) while one had no residual tumor. All 3 did not undergo additional treatment after surgery. No other identifiable factor may have contributed to the tumor progression including their original cervical tumor sizes, disease stages, histopathologic type and duration of overall treatment.

Treatment regimen B which is patterned after GOG 123 seems promising with complete pathologic responses reaching 55.6 percent in this series. However, the disadvantage of this regimen, as far as the institution is concerned, is that radiation treatment is not accomplished in the ideal 5 to 7 weeks duration. Twelve patients (67%) in this group had their radiation in more than 9 weeks.

Cause-specific survival for radiation treatment time less than 7 weeks for Stage IB disease is 86 percent and decreases to 78 percent for 7 to 9 weeks and further to 55% with more than 9 weeks.[21] For Stage IIA, it is 73 percent, 48 percent and 41 percent respectively. Though based on this study which is limited to 18 patients, the duration of neoadjuvant treatment seems not a determining factor since the patients who had abandoned surgeries for tumor progression had more or less similar duration of treatment as those who have no evidence of disease. The only patient with a small cell histopath type had tumor progression. Histologic small cell type is known for its virulence compared to the other subtypes. The interval to surgery of more than 16 weeks must have also contributed to the progression of disease in one patient leading to the abandonment of her surgery. At this interval time, the patient was not receiving any form of treatment. However, the true value of this interval needs to be verified also in a larger series as one patient who had a complete pathologic response and presently has no evidence of disease had her surgery after 25 weeks from chemoradiation.

Overall, 14 patients (77.8%) under regimen B have no evidence of disease while 4 (22.3%) have tumor persistence and progression as of their last follow-up . Complete pathologic responses are higher at 55.6 percent. This brings back the question of whether the adjuvant extrafascial hysterectomy is needed in these cases. Only a randomized controlled trial of concomitant chemoradiation versus concomitant chemoradiation followed by extrafascial hysterectomy might be able to give the answer.

Toxicity wise, a greater number was recorded for regimen B. However, these toxicities from the neoadjuvant treatment are transient and are easily managed.

The two regimens described in this study may provide good treatment options for our Stage IB2 and bulky IIA patients. This is considering the limitations of radiation facilities, as well as the high cost of chemotherapy. Modest outcomes, so far, have been observed for both. Toxicities are transient and manageable. Time element might be one key factor for choosing one regimen over the other. Better histologic responses might mean no more additional cost for treatment after surgery. Limitations in radiation facilities, particularly, intracavitary radiation may sway the health provider to favor one over the other.

A longer time of follow-up may provide insight to the true value of these forms of treatment. Following up patients who just underwent concomitant chemoradiation and observed subsequently may provide answers to the value of the hysterectomy in this treatment regimen.

Conclusion

The two treatment options for Stage IB2 and bulky Stage IIA presented in this paper may provide a good alternative applicable to our setting where radiation facilities are limited and finances for chemotherapy are not easily available. Survival rates based from the available length of follow up are decent. Toxicities in both regimens are acceptable.

References

1. Parham GP. Comparison of cell collection and direct visualization: cervical cancer screening adjuncts. Am J Obstet Gynecol 2003; 158(3):S13-20.
2. Laudico A, Esteban D, Reyes L and Liquido J. Philippine Cancer Society, Inc. 1998 Philippine Cancer Facts and Estimates. 1998, 48 p.
3. Perez CA, Grigsby PW, Nene SM, Camel HK Galakatos A, Kao MS, Lockett MA. Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. Cancer 1992; 69:2796-2806.
4. Rutledge FN, Wharton JT, Fletcher GH. Clinical studies with adjunctive surgery and irradiation therapy in the treatment of carcinoma of the cervix. Cancer 1976; 38:696-602.
5. Lowery GC, Mendenhall WM, Million RR. Stage IB or IIA-B carcinoma of the intact uterine cervix treated with irradiation: a multivariate analysis. Int J Radiat Oncol Biol Phys 1992; 24: 205-210.
6. Van Nagell JR Rayburn W, Donaldson ES, Hanson M, Gay EC, Yoneda J, Marayuma Y, Powell DF Therapeutic implications of patterns of recurrence in cancer of the uterine cervix. Cancer 1979; 44:2354-2362.
7. Piver MS and Chung WS. Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma. Obstet Gynecol 1973; 46:507-512.
8. Perez CA and Kao MS. Radiation therapy alone or combined with surgery in the treatment of barrel-shaped carcinoma of the uterine cervix (Stages IB, 2A, 2B). Int J Radiat Oncol Biol Phys. 1985; 11:1903-1909.
9. Maruyama Y, Van Nagell JR, Yoneda J, et al. Dose-response and failure pattern for bulky or barrel-shaped stage 113 cervical cancer treated by combined photon irradiation and extra-fascial hysterectomy. Cancer 1989; 63:70-76.
10. Gallion HH, Van Nagell JR, Donaldson ES, et al. Combined radiation therapy and extrafascial hysterectomy in the treatment of Stage IB barrel-shaped cervical cancer. Cancer 1985; 56: 262-265.
11. Durrance FY, Fletcher GH, Rutledge FN. Analysis of central recurrent disease in stages I and II squamous cell carcinomas of the cervix on intact uterus. Am J Roentgenol 1969; 106:831-838.
12. Eifel PJ, Morris M, Wharton JT, Oswald MJ. The influence of tumor size and morphology on the outcome of patients with FIGO Stage IB squamous cell carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1994; 29: 9-16.

13. Keys HM, Bundy BN, Stehman FB, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group small star, filled. Gynecol Oncol 2003; 89 (3): 343-353.
14. Vermorken JB. The role of chemotherapy in squamous cell carcinoma of the uterine cervix: a review. Int J Gynecol Cancer 1993; 3:129-142.
15. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky Stage IB cervical carcinoma. N Engl J Med 1999; 340:1154-1161.
16. Moore DH Treatment of stage IB2 (bulky) cervical carcinoma. Cancer Treatment Reviews 2003, XX, 1-6.
17. Sardi JE, Giaroli A, Sananes C, et al. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage IB squamous carcinoma of the cervix: the final results. Gynecol Oncol 1997; 67(1):61-69.
18. Ting-Chanq C, Chyong-Huey L, Ji-Hong H, et al. Randomized trial of neoadiuvant cisplatin, vincristine, bleomycin, and radical hysterectomy versus radiation therapy for bulky stage IB and IIA cervical cancer. J Clin Oncol 18:1740-1747.
19. Benedetti-Panici P, Greggi S, Colombo A, et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: Results from the Italian multicenter randomized study. J Clin Oncol, 2002; 20(1):179-188.
20. Duenas-Gonzalez A, Cetina L, Mariscal I, and de la Garza J. Modern management of locally advanced cervical carcinoma. Cancer Treatment Reviews 2003; XX: 1-11.
21. Erridge SC, Kerr GR, Downing D, Duncan W, Price A. The effect of overall treatment on the survival and toxicity of radical radiotherapy for cervical carcinoma. Radiother Oncol 2002; 63:59-66.
22. Tomacruz RS. Neoadjuvant external pelvic radiation and neoadjuvant chemoradiation followed by radical hysterectomy and pelvic lymphadenectomy for FIGO Stage IB2 and bulky IIA cervical cancer: A preliminary report. 1998 (unpublished).
23. Rettenmaier MA, Casanova DM, Micha JP, et al. Radical hysterectomy and tailored postoperative radiation therapy in the management of bulky stage IB_2 cervical cancer. Cancer 1989; 63: 2220-2223.
24. Bloss JD, Berman ML, Mukhererjee J, et al. Bulky stage IB cervical carcinoma managed by primary radical hysterectomy followed by tailored radiotherapy. Gynecol Oncol 1992; 47:21-27.
25. Mendenhall WM, McCarty PJ, Morgan LS. Stage IB-IIA-B carcinoma of the intact uterine cervix greater than or equal to 6 cm in diameter: Is adjuvant extrafascial hysterectomy beneficial? Int J Radiat Oncol Biol Phys 1991; 21:899-904.

Endometrial Aspiration Using a Feeding Tube (FG 8) Attached to a 30 cc Syringe for the Detection Of Endometrial Pathology

Rhonnel B. Foronda, M.D.
Department of Obstetrics and Gynecology, Batangas Regional Hospital

This is a preliminary prospective study whch aims to determine the accuracy of endometrial aspiration using a feeding tube (FG 8) attached to a 30 cc syringe in detecting endometrial pathology. A total of 107 patients with clinical indications to undergo fractional curettage were included in the study. Histopathologic findings of the endometrial aspirations were compared with the results from curettage and, when available, the hysterectomy specimen. Sensitivity, specificity, accuracy, predictive values, prevalence and likelihood ratios were calculated. There were 102 identical findings and comparisons of both techniques based on abnormal endometrium, uterine malignancy and hyperplasia were made. Results showed that endometrial aspiration is a useful diagnostic procedure for detecting endometrial cancer and its processors. It is highly accurate but must be used with an understanding of its limitations.

Key words: endometrial aspiration, curettage

The endometrial cavity has been invaded by a variety of diagnostic instruments.

The most commonly employed histologic sampling technique is endometrial biopsy. In 1935, Novak[1] introduced his curette with serrated edges. Within that year, the Randall[2] curette also came into the picture with no serrations but has the shape of a small scoop. The advantages of biopsy include its simplicity, economy and universal availability. Disadvantages include the difficulty of introduction of the instrument into menopausic patients with stenotic cervix.

After the Papanicolau's smear method was published in 1943, the most widespread technique for sampling the endometrium was the aspiration smear.[3] In this procedure, a small cannula with an outside diameter of approximately 2.5 millimeters was inserted directly into the endometrial cavity through the cervix without the use of a tenaculum. Suction was then applied and the material retrieved was then smeared on a glass slide and stained. The accuracy of the technique ranged fro 75-92 percent.

A different concept for collection of cytologic material was introduced in 1955 by Ayre.[4] The method employed a thin brush to collect cytologic and histologic material from the endometrial cavity by rotation within the cavity. The processing of retrieved specimen included the use of thin smear (cytologic) and cell blocks prepared from centrifuged sediment from agitation process (histologic). The objections to this technique included its awkwardness,

incidence of increased bleeding in some patients and retention of bristles.

Morton, et al. (1959)[5] attempted to improve the yield of cells from the endometrium by lavaging the cavity with a small amount of saline. This technique achieved an accuracy of 80-95 percent. However, it required special effort to avoid technical problems in the processing of the aspirated fluid.

Dowling and Gravlee in 1964[6] published a new jet wash method of endometrial sampling. The instrument consisted of a double cannula with an outside diameter of 4.6 millimeters. One end of the cannula system was connected to a syringe for generation of negative pressure and the apparatus was connected to a fluid reservoir. The object of the technique was to provide an agitating source within the endometrial cavity so as to dislodge the cells. Advantages of the jet wash method included a high degree of accuracy in identifying endometrial cancer, anesthesia was not required and patients readily accepted it. Disadvantages of this technique included technical difficulty in passing the instrument through a postmenopausal cervix, required a highly specialized laboratory processing and diminished accuracy in detecting precursors of endometrial cancer.[7,8]

In 1970, Chatfield and Watson[9] published sponge biopsy technique by introducing a V-shaped polyvinyl sponge into the endometrial cavity. The sponge was housed inside a Lippes loop introducer and was anchored to a suture material. It was then inserted into the endometrial cavity and withdrawn by traction on the suture. As the sponge passed from the cavity, the V-shaped arms expanded and abraded the walls of the cavity, endocervix and squamocolumnar junction. The sponge was then submitted as a specimen.

Chatfield and Brenner (1972)[10] reported high accuracy rate of the sponge biopsy in detecting endometrial cancer. This method also had a high yield in diagnosing cervical carcinoma. Due to a larger diameter of the introducer of 5 millimeters, technical difficulties were encountered with the cervices of most post-menopausal patients.

In 1968, Jensen and Jensen[11] developed a suction curette that was applicable to the non-pregnant uterus. This instrument had been modified and is currently available as the Vabra aspirator. It is marketed as a disposable instrument and consists of a metal cannula with an overall length of 21 centimeters. The outside diameter is 3 millimeters, wherein it is employed with a vacuum source capable of generating a constant negative pressure of 60 cm Hg within 3-5 seconds of application. The technique has a high accuracy rate of 94-97 percent[2], permits identification of malignant precursors, easy to apply and needs no sophisticated laboratory processing. It is done as an office procedure. Disadvantages include the slight discomfort experienced by some patients and the relatively great expense for mass screening.

Endometrial curettage has long been the gold standard in the diagnosis of endometrial pathology and is the most common gynecologic procedure.[13] This is due to the emphasis on early detection of cancer.

Abnormal uterine bleeding is the indication for curettage in 98 percent of cases. It is a common problem encountered in gynecologic practice and accounts for 20 percent of visits.[14] Most cases occur during the fourth decade and extend up to the sixth decade. Carcinoma of the endometrium and atypical hyperplasia commonly manifest as abnormal uterine bleeding. Its incidence increases with age with most cases occur between 51-60 years of age.[15]

Seventy percent of tissues obtained from curettage reveal benign lesions[16], the need for such a procedure has been questioned considering its cost and possible morbidity. Complications following curettage, though rare, have been reported and occur approximately in 1.5 to 2.1 percent of cases. These include bleeding, pelvic infection, perforation and unanticipated emergency operation. Grimes (1982)[18] reported that curettage has a higher complication rate than the Vabra aspirator.

Exfoliation of abnormal cells from the endometrium is inversely related to the strength of adhesions between these cells. This adhesion is quite strong in normal cells and becomes weaker as cells advance in their abnormality toward invasive cancer.[3] Hence, either a scrapping or aspiration technique can obtain a good yield of normal or pathologic results.

As recommended by the International Federation of Gynecology and Obstetrics (FIGO) in 1988, the diagnostic procedure of choice for women suspected to have endometrial cancer is endometrial biopsy.

The preferred instrument is the Novak curette and the S or Z technique is advocated. It is also not encouraged by the FIGO to do an endocervical curettage. Cervical involvement is best assessed from the definitive specimen after a hysterectomy.

This study attempts to evaluate the use of an aspiration technique as an alternative to the endometrial biopsy as an

office procedure in detecting endometrial pathology. The study will be using a feeding tube (FG8), which is commonly used as an aspirating instrument in newborns and attached to a 30 cc syringe. Both materials are readily available and cheaper compared to the aspirators marketed abroad. There are many different types of endometrial aspirating apparatus currently available in other countries, like the Vabra, Isaacs[12] and Pipelle[20]. These are all disposables and are relatively expensive based on our national standard.

In developing countries like ours, there is a need for a reliable, simple and inexpensive method for screening for endometrial pathology. However, there are many institutions or areas here in our country wherein a Novak curette is not even available.

It is beneficial for patients if a definite tissue diagnosis can be made prior to hospital admission, thus money and time can be saved. In cases wherein a diagnosis is made on the first visit, the chance of losing the patient for follow-up is minimized.

The aspiration technique in this study is simple, easy to apply and causes minimal discomfort. Hence, anesthesia is not required, thereby reducing the risk to a patient who will undergo the procedure. Likewise, hospitalization is not needed thus making the aspiration method less expensive. The delay in diagnosis is lessened because it can be done immediately without the need for scheduling.

It will be of great use to the practicing gynecologist if endometrial aspiration method using a feeding tube (FG 8) attached to a 30 cc syringe is shown to have equal diagnostic accuracy to that of endometrial curettage. Moreover, since this is carried out as an out-patient procedure, it is convenient and saves time for the physician.

Objectives:

General Objective:

To be able to determine the accuracy of endometrial aspiration using a feeding tube (FG8) attached to a 30 cc syringe for the detection of endometrial pathology when compared with the histology results from endometrial curettage and, when available, the hysterectomy specimen.

Specific Objectives:

1. To determine the adequacy of specimens obtained from endometrial aspiration and curettage.
2. To determine the sensitivity, specificity, predictive values, accuracy and likelihood ratios of the histology obtained from endometrial aspiration with those obtained from curettage for abnormal endometrium.
3. To determine the sensitivity, specificity, predictive values, accuracy and likelihood ratios of the histology obtained from endometrial aspiration with those obtained from curettage for endometrial malignancies.
4. To determine the sensitivity, specificity, predictive values, accuracy and likelihood ratios of the histology obtained from endometrial aspiration with those obtained from curettage for endometrial hyperplasia.

Materials and Methods

General Design:

The study was conducted to evaluate the histopathologic findings from endometrial aspiration using the histopathologic results from endometrial curettage as gold standard. In cases wherein a hysterectomy was performed after the procedure, the histology reports of the aspiration/curettage were likewise compared to that of the hysterectomy specimen.

The study was conducted on admitted patients of the Department of Obstetrics and Gynecology, Batangas Regional Hospital who will undergo fractional curettage.

Inclusion Criteria:

1. A clinical indication to undergo fractional curettage.
2. A signed written informed consent to undergo both endometrial aspiration and curettage.
3. A preoperative clearance for curettage if a patient has a medical illness.

Exclusion Criteria:

Patients who had contraindications for fractional curettage, such as pregnancy, pelvic, inflammatory disease and bleeding disorders. A finding of endometrial/endocervical polyp based on ultrasound was also excluded because curettage is the appropriate management in this cases.

Sample Size Calculation:

A review of the number of patients who underwent fractional curettage for the last 4 years, starting from 1997

up to 2000 was done to compute for the average cases per year as target size population.

Year	Cases
1997	135
1998	152
1999	164
2000	114

Average number of patients per year was 141.25. Based on the formula [21]

$$N = n / 1 + n \{e\}^2$$

$$N = 141.25/ 1 + 141.25 (0.05)^2 = 104$$

The calculated sample size was based on the prevalence of patients who underwent fractional curettage, since there were no available data for comparison with the same technique of aspiration. Total population of the study was 107.

Description of the Study Procedure:

Screening:

A complete history and physical examination were done on every patient. Essential laboratory tests were routinely requested, including complete blood count, platelet count, pregnancy test (if needed) and Papanicolaou smear.

Transvaginal ultrasound was requested to ascertain any intrauterine lesions when indicated. A preoperative clearance is carried out if patients are known to have medical illness. Patients were informed of the ongoing study and its objectives. They were requested to follow-up for the histopathologic results.

Study Procedure:

A written informed consent was obtained on patients admitted for fractional curettage and endometrial aspiration (see Appendix A). Clinical information was recorded for each patient (see Appendix B), which included age, parity, initial impression, obstetrical history, menstrual history, contraceptive use, previous curettage, and use of hormonal treatment.

Patient was placed in a lithotomy position after the induction of anesthesia. Asepsis and antisepsis observed. The uterus was assessed as to its position by internal examination. Curettage of the endocervix was initially done, followed with the gentle insertion of the hysterometer to measure endometrial depth. The feeding tube (FG 8) attached to a 30 cc syringe was inserted to the endometrial cavity and gradual aspiration of its contents was done. The feeding tube measures 20 centimeters in total length with an outer diameter of 2 millimeters. Curettage of the endometrium immediately followed the aspiration using a sharp curette with complete scrapping of the entire cavity.

The specimens were labelled accordingly and were fixed with 10% formaldehyde. They were processed routinely, embedded in paraffin block and stained with Haematoxylin & Eosin. Specimens were initially read by the pathologist resident on duty and subsequently reviewed by a pathologist consultant. Results were then discussed with the patient.

Adequacy of the sample tissues and its histologic diagnosis of the endometrial aspiration and curettage were noted. For the purpose of the study, samples were said to be insufficient if there is inability to obtain tissues or inability to make a histopathologic diagnosis based on the submitted specimen.

The histopathologic results were divided into 2 main categories: (1) malignant and pre-malignant (all uterine carcinoma and complex hyperplasia with atypia and (2) benign hyperplasia without atypia and normal endometrium - proliferative, secretory, atrophic and other benign conditions not classified in other categories). Results were also classified as abnormal (uterine malignancies, pre-malignant lesions, hyperplasia and disordered proliferative endometrium) and normal endometrium (proliferative, secretory, atrophic) and other benign conditions not classified in other categories.

The classification of different categories was based on the criteria set by the World Health Organization Society of Gynecological Pathologists.[22]

In cases where a hysterectomy was done after the curettage/aspiration, the results were compared to the histopathologic results of both curettage and aspiration.

Data Analysis:

Distribution and frequencies of demographic data were done. Comparisons of the histology results obtained for the aspiration and curettage were also done. The following were computed: sensitivity, specificity, predictive

values, accuracy and likelihood ratios of the findings from endometrial curettage and aspiration in the sample population as demonstrated in the dummy table (Appendix C).

Two by two tables were done for the 2 main criteria: malignant and pre-malignant versus benign lesions, normal versus abnormal endometrium and hyperplasia versus non-hyperplastic endometium.

In cases were hysterectomy was performed, comparisons of the histopathologic results were done for endometrial aspiration/curettage and hysterectomy specimens.

The level of significance was placed at $p < 0.05$. Statistical analysis was done using Two by Two program and Microsoft Excel 97.

Results

There were 125 cases who underwent fractional curettage from January 2001 to December 2001. Eighteen patients were excluded due to findings of endometrial / endocervical polyp (as mentioned in the exclusion criteria).

The average age was 41.50 (SD 7.54 range, 23 - 77). There were 17 (16%) menopausal patients with an average age of 50.30 (SD 7.10, range 48 - 77). Ninety one percent (93%) had a parity of one or higher.

The most common complaint of patients for curettage was abnormal uterine bleeding, 80 percent; mass 14.4 percent and thickened endometrium, 5.6 percent.

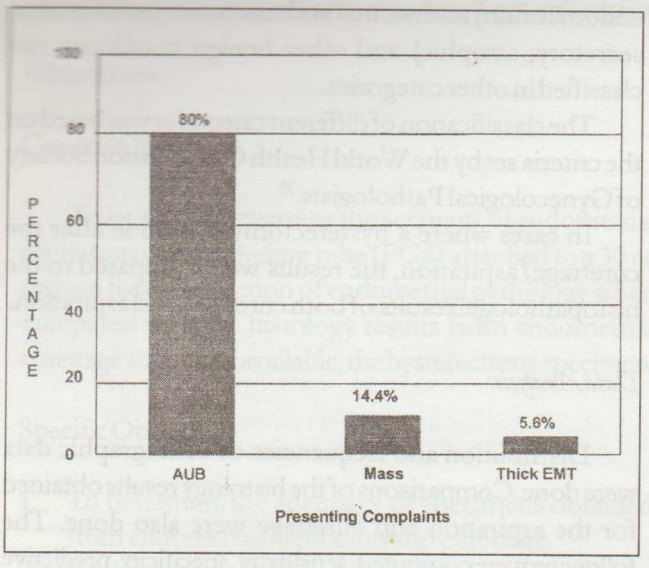

Figure 1. Presenting complaints of patients for curettage.

Adequate specimens were obtained in both aspiration and curettage in 95.3 percent of the 107 cases. The aspiration technique had 3 inadequate specimens out of the 107 (2.8%) compared to the 2 inadequate specimens obtained from curettage (1.9%). There were 107 cases for comparison and 102 cases from both endometrial aspiration and curettage have identifical findings (Table 1). (Figures 2-11)

Table 1. Identical endometrial findings on aspiration and curettage.

Normal Endometrium	49
Abnormal Endometrium	
Malignant	8
Complex hyperlasia	8
Simple hyperplasia	32
Disordered proliferative endometrium	5
Total	102

Figure 2. Curettage specimen showing proliferative endometrium (40X).

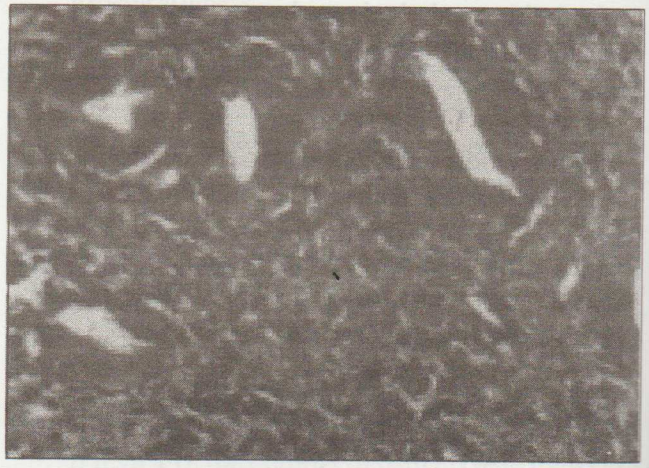

Figure 3. Aspiration specimen showing proliferative endometrium (40X).

Figure 4. Curettage specimen showing disordered proliferative endometrium (10X).

Figure 5. Aspiration specimen showing disordered proliferative endometrium (10X).

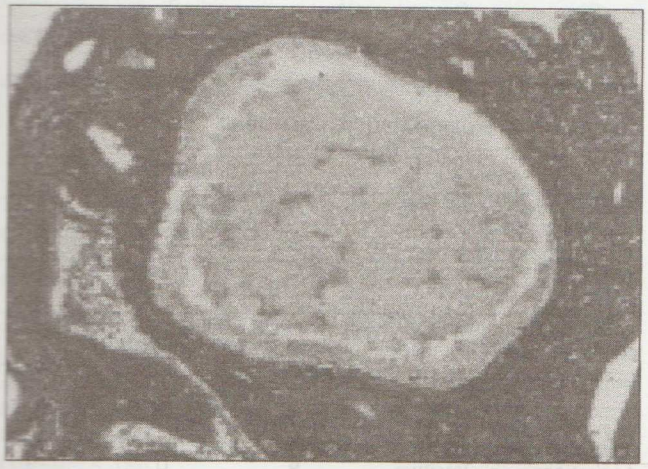

Figure 6. Curettage specimen showing simple endometrial hyperplasia (10X).

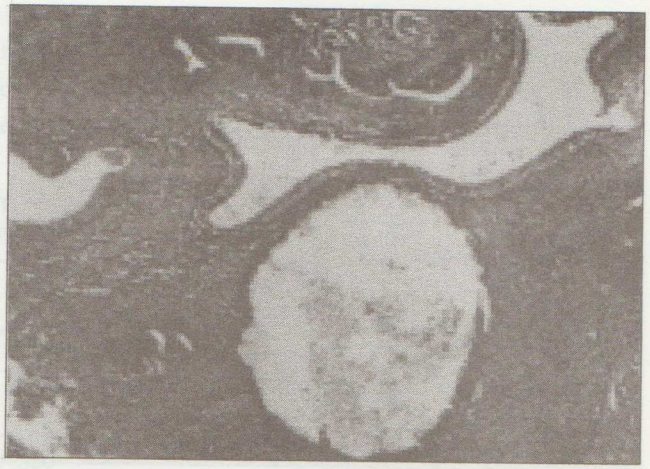

Figure 7. Aspiration specimen showing simple endometrial hyperplasia (10X).

Figureg 8. Curettage specimen showing complex endometrial hyperplasia without atypia (40X).

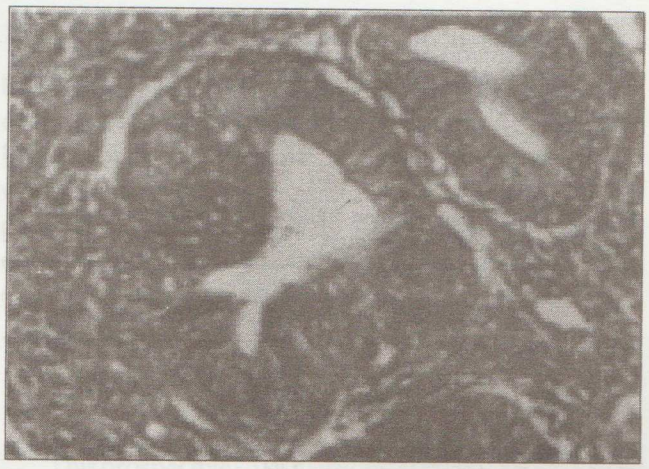

Figure 9. Aspiration specimen showing complex endometrial hyperplasia without atypia (40X).

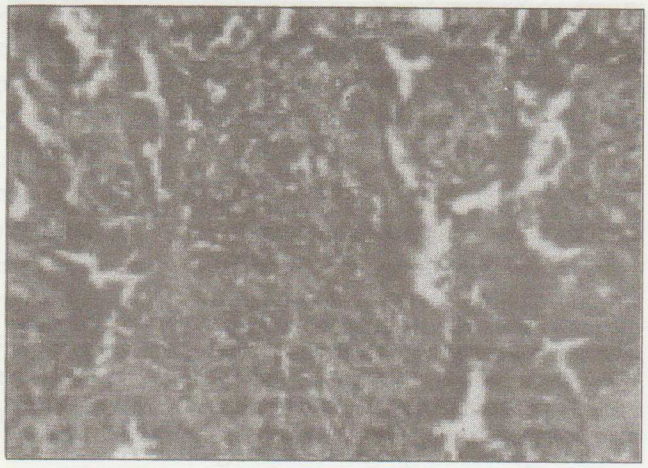

Figure 10. Curettage specimen showing moderately differentiated endometrial carcinoma (40X).

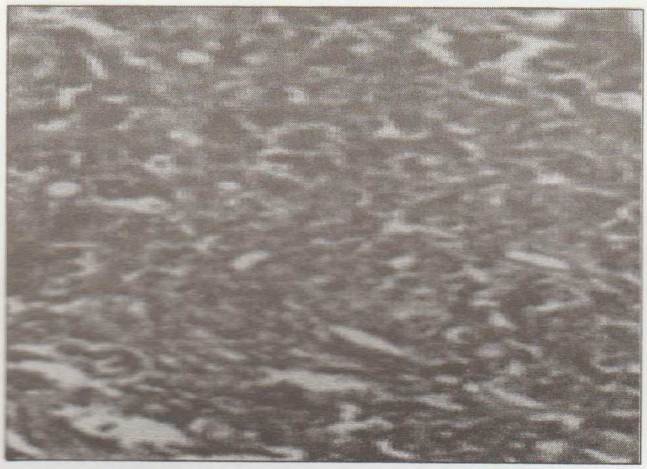

Figure 11. Aspiration specimen showing moderately differentiated endometrioid carcinoma (40X).

Comparison of the histopathologic findings on aspiration curettage based on abnormal endometrium are tabulated and summarized in tables 2-4.

Table 2. Comparison between outcome of aspiration and curettage based on abnormal endometrium.

	Aspiration Freq	%	Curettage Freq	%
Normal	51	96.22	51	96.22
Abnormal	53	98.15	54	100
Chi Square Value =		0.0327	Not significant	
Chi Square Tab (.05) =		3.84		
Probability Value =		> 0.5		

Table 3. Comparison of histopathologic findings of aspiration and curettage based on abnormal endometrium.

		Curettage Positive	Curettage Negative	
Aspiration	Positive	53	2	55
	Negative	3	49	52
		56	51	107

Table 4. Summary of outcomes of aspiration and curettage based on abnormal endometrium

Outcome	Value (95% CI)
Sensitivity rate	94.6%
Specificity rate	89.09%
Accuracy rate	95.33%
Positive predictive value	96.36%
Negative predictive value	94.23%
Prevalence rate	52.34%
Likelihood ratio (positive test)	8.67
Likelihood ratio (negative ratio)	0.06

A positive result indicates an abnormal endometrium and a negative result indicates normal endometrium.

Comparison of findings between aspiration and curettage based on uterine malignancy are tabulated and summarized in tables 5 to 7. A positive result indicates all cases of uterine malignancy and pre-malignancy. There was one case of complex endometrial hyperplasia with atypia both diagnosed by aspiration and curettage. There was one diagnosed case of endometrial carcinoma at an early age of 32. The remaining patients with malignant findings were 49 years old and above. A negative result indicates benign endometrial conditions.

Table 5. Comparison of aspiration and curettage based on uterine malignancy/pre-malignancy.

	Aspiration Freq	%	Curettage Freq	%
Benign	95	96.94	96	97.96
Malignant/pre-malignant	9	100	9	100
Chi Square Value =		0.000388 Not significant		
Chi Square Tab (.05) =		3.84		
Probability Value =		> .05		

Table 6. Comparison of histopathologic findings of aspiration and curettage based on uterine malignancy/pre-malignancy.

		Curettage Positive	Curettage Negative	
Aspiration	Positive	9	0	9
	Negative	0	98	98
		9	98	107

Table 7. Summary of outcomes of aspiration and curettage based on uterine malignancy/pre-malignancy.

Outcomes	Value (95% CI)
Sensitivity rate	100%
Specificity rate	100%
Accuracy rate	100%
Positive predictive value	100%
Negative predictive value	100%
Prevalence rate	8.4%
Likelihood ratio (positive test)	-
Likelihood ratio (negative test)	-

Comparison of findings between aspiration and curettage based on endometrial hyperplasia are tabulated and summarized in tables 8 to 10. A positive result indicates both simple and complex hyperplasia.

Table 8. Comparison of aspiration with curettage based on hyperplasia.

Outcome	Aspiration Freq	%	Curettage Freq	%	Total
Hyperplasia	40	97.56	41	100.00	81
Non-hyperplasia	64	96.97	64	96.97	128
Chi Square Value =		0.008	Not significant		
Chi Square Tabular		3.840			
Probability Value =		> .05			

Table 9. Comparison of findings of aspiration with curettage based on hyperplasia.

		Curettage Positive	Negative	
Aspiration	Positive	40	0	40
	Negative	1	66	67
		41	66	107

Table 10. Summary of outcomes of aspiration and curettage based on endometrial hyperplasia.

Outcomes	Value (95% CI)
Sensitivity rate	97.56%
Specificity rate	100%
Accuracy rate	99.07%
Positive predictive value	100%
Negative predictive value	98.51%
Prevalence rate	38.32%
Likelihood ratio (positive test)	-
Likelihood ratio (negative ratio)	0.02

There were 3 cases of inadequate tissues obtained from endometrial aspiration. Table 11 presented the comparison of inadequate tissues obtained from endometrial aspiration with findings on curettage.

Table 11. Inadequate tissues obtained from endometrial aspiration with findings on curettage.

	Curettage					
Aspiration	Proliferative Endometrium	Secretory Endometrium	Simple hyperplasia	Complex hyperplasia w/o atypia	Complex hyperplasia w/ atypia	Cancer
Tissue Insufficient	2	0	0	1	0	0
Total	2	0	0	1	0	0

There were 2 cases of inadequate tissues obtained by curettage which were diagnosed by the aspiration technique as presented in Table 12.

Table 12. Comparison of inadequate curettage with findings on endometrial aspiration.

Curettage	Endometrial Aspiration				
	Proliferative	Secretory Endometrium	Atrophic Endometrium	Hyperplasia	Cancer
Insufficient tissues	1	1	0	0	0
Total	1	1	0	0	0

There were 8 malignant and 1 pre-malignant cases both diagnosed by aspiration and curettage. However, only 7 patients underwent hysterectomy and the histopatologic findings of the hysterectomy specimen were similar to both aspiration and curettage. Two patients were lost to follow up. Due to the small number of cases that were followed by hysterectomy, generalizations can not be made.

Discussion

This prospective study demonstrates that endometrial aspiration is a safe and effective procedure in diagnosing

pathology of the endometrium. Tissue diagnosis for aspiration provided 97.20 percent of the cases with no significant difference ($p>0.05$) with curettage which was 98.13 percent.

The diagnostic accuracy was 95.33 percent based on abnormal endometrium, 100 percent based on uterine malignancy/pre-malignancy and 99.07 percent based on hyperplasia when compared with curettage.

The aspiration technique showed a higher sensitivity rate for the detection of endometrial pathology based on malignancy/pre-malignancy and hyperplasia findings compared with abnormal findings. A low sensitivity suggests that we cannot reassure patients that there is no abnormality present based on negative results.

Results showed a higher specificity rate based on findings of malignancy/pre-malignancy and hyperplasia compared with abnormal results. This signifies that a high specificity suggests to us that there is a high probability of disease with a positive result. This can be a very useful guide for physicians in treating their patients. It can also save time and money.

False negative results have significant implication for follow up management of the patients. Feldman, et al. (1994)[3] conducted a two year follow up study on 263 patients with benign or negative biopsy results. There were 86 patients (33%) who became symptomatic and underwent repeat biopsy or curettage or hysterectomy. There were 4 cases (2%) who had uterine malignancies, 5 (2%) complex hyperplasia and the remaining 96 percent did not have symptoms. This emphasizes the importance of patient counseling for follow up.

It is common knowledge that complex endometrial hyperplasia with atypia can readily progress to carcinoma. On the other hand, hyperplasia without atypia, whether it is simple or complex is usually self-limited. In a long term study by Kurman, et al. (1998)[22] with untreated hyperplasia of 170 patients, 80 percent of the cases diagnosed with simple and complex hyperplasia without atypia regressed. Only one percent of the cases with simple hyperplasia and 3 percent of complex hyperplasia progressed to carcinoma. Findings of the study implicates the presence of atypia as the most useful criterion in predicting progression to cancer. Thus hyperplasia without atypia can be managed conservatively.

Likelihood ratio expresses the odds that a positive result of a diagnostic test would be expected in a patient with the disorder. The likelihood ratio for a positive test result (with abnormal endometrium on biopsy) is 8.67. This means that a positive result is almost 9 times as likely to come from a patient with abnormal endometrium as from a patient with normal endometrium.

The likelihood of a negative result (normal endometrium on biopsy) is 0.06 and that means that the biopsy result is less than one-tenths as likely to come from a patient with abnormal endometrium as from patients without abnormal pathology.

Likelihood ratios are peferable to predictive values since they do not change with the change in prevalence of the target disorder.

In our study, out of the 8 patients with histopathologic findings of malignancy, there is one case diagnosed at a young age of 32. She is nulligravid, single, obese, with a history of menorrhagia and diagnosed to have endometriod carcinoma well differentiated by aspiration and curettage and this was confirmed by the hysterectomy specimen. Crissman, et al. (1980)[6] cited that malignancy was noted only in 2.9 percent of all endometrial curettings from patients less than 40 years old.

Endometrial aspiration offers several advantages over curettage. Anesthesia is not needed, hence it may be done as an office procedure. It is convenient for both the patient and the physician. It is cost effective in evaluating patients complaining of abnormal uterine bleeding.

The aspiration technique described in this study will be of great benefit to developing countries like ours, since there are remote or economically depressed areas in some regions of our country where a Novak curette is not even available. This technique can be readily done in our health centers, municipal and district hospitals or even in private clinics.

The use of a feeding tube (FG8) attached to a 30 cc syringe to aspirate endometrial tissues offers several advantages in our local setting. These include cost effectiveness, high patient acceptability due to less discomfort, less complications like uterine perforation, and health worker user-friendliness.

Limitations of the study and areas for future research

In this study, two procedures were performed inside the endometrial cavity, first is aspiration and second, curettage. There is a possibility that the aspiration can remove a lesion and thus would be missed by curettage. This could lead to a false positive result. A false negative

result could also occur if both aspiration and curettage would not detect a lesion when compared to a hysterectomy specimen. It is recommended to utilize a higher sample size to further evaluate results of this study.

The aspiration technique was done under anesthesia, hence we cannot make conclusions regarding patient acceptability of the procedure. It is then recommended that a follow-up study be conducted to assess patient acceptance of the aspiration biopsy when not done under anesthesia.

The 30 cc syringe used was arbitrarily chosen for aspirating endometrial contents. It is suggested that other syringe sizes be evaluated as well.

The feeding tube (FG 8) seems to be an ideal aspirating tool since it has a small diameter and it is flexible. Additional holes in the distal end can be made so as to increase its aspirating capacity.

Conclusions and Recommendations

Endometrial aspiration using a feeding tube (FG 8) attached to a 30 cc syringe is a useful and rapid office diagnostic procedure for detecting endometrial cancer and its precursors. It could obviate the need of hospitalization and anesthesia. It has a high accuracy rate but must be used with an understanding of its limitations. Correlation with patient symptomatology and other diagnostic tests like transvaginal ultrasound must be done by the clinicians.

In cases where there is insufficient tissue obtained for diagnosis, or benign histopathologic findings but suspicion of malignancy is high, curettage under anesthesia may be performed. Curettage under anesthesia is advised if technical difficulties are encountered in patients with closed or stenotic cervices.

Considerations presented will minimize delay in making a correct diagnosis hence will benefit both the physician and the patient.

References

1. Hofmeister FJ, Vondrak B, Barbo D. The value of the endometrial biopsy. Am J Obstet Gynecol 1996; 95:91-97.
2. Hofmeister FJ. Endometrial biopsy : Another look. Am J Obstet Gynecol 1974; 118: 773-784.
3. Cohen CJ, Gusberg SB. Screening for endometrial cancer. Clin Obstet Gynecol 1975; 18: 27-39.
4. Ayre JE. Rotating endometrial brush: New technique for the diagnosis of fundal carcinoma. Obstet Gynecol 1955; 5: 137-148.
5. Morton DG, Moore JG, Chang N. Lavage of the endometrial cavity as an aid in the diagnosis of carcinoma of the uterine corpus. Am Obstet Gynecol 1959; 31:520-531.
6. Dowling EA, Gravlee LC. Endometrial cancer diagnosis: A new technique using a jet washer. Am J Obstet Gynecol 1969; 34:168-182.
7. Twiggs LB, DiSaia PJ, Morrow CP, Townsend DE, Schwinn CE, Gravlee. Jet irrigator : Efficacy in diagnosis of endometrial neoplasia. J Am Med Assoc 1976; 235: 2748-2750.
8. Abate SD, Edwards CL, Vellios F. A comparative study of the endometrial jet-washing technique and endometrial biopsy. Am J Clin Pathol 1972; 58: 118 - 122.
9. Chatfield WR, Watson AA: Diagnosis of intrauterine disease by sponge biopsy technique. Lancet 1970; 1:21-32
10. Chatfield WR., Brenner AD. Intrauterine sponge biopsy. A new technique to screen for early intrauterine malignancy. Obstet Gynecol 1972; 39:323-331.
11. Jensen JA, Jensen JG. Outpatient curettage without anesthesia. A report of 350 cases. Danish Medical Bulletin 1970; 17: 199-208.
12. Haack-Sorensen PE, Starklint H, Aronsen A, Kern Hansen M, Kristoffersen K. Diagnostic vabra (Aspiration) curettage danish Medical Bulletin 1979; 26:1-6.
13. Feldman S, Shapter A, Welch W, Berrkowitz R. Two-year follow-up of 263 patients with post / perimenopausal vaginal bleeding and negative initial biopsy. Gynecol Oncol 1994; 55:56-59.
14. Chambers J, Chambers S. Endometrial sampling: When? Where? Why? With what? Clin Obstet Gynecol 1992; 35:28-39.
15. Morse AR, Ellice RM, Anderson MC, Beard RW. Reliability of endometrial aspiration cytology in the assessment of endometrial status. Obstet Gynecol 1982; 59:513-518.
16. Crissman J, Azoury R, Barnes A, Schellas H. Endometrial carcinoma in women 40 years of age or younger. Obstet Gynecol 1980; 57:699-704.
17. Word S, Gravlee C, Wideman G. The fallacy of simple uterine curettage. Obstet Gynecol 1958; 12:642-648.
18. Grimes D. Diagnostic dilatation and curettage: A reappraisal. Am J Obstet Gynecol 1982; 142:1-6.
19. Feldman S, Berkowitz R, Tosteson A. Cost effectiveness of strategies to evaluate postmenopausal bleeding. Obstet Gynecol 1993; 81:968-975.
20. Fothergill D, Brown V, Hill A. Histologic sampling of the endometrium - a comparison between formal curettage and the Pipelle sampler. Br J Obstet Gynecol 1993; 99: 77-80.
21. Best JW. Research in Education. Fourth Edition. New York: Alemar's Prentice Hall Inc. 1985.
22. Kurman R, Mazur M. Benign diseases of the endometrium. In: Kurman R. (ed.): Blaustein's Pathology of the Female Genital Tract. New York: Springer-Verlag Inc., 1998.

Accuracy of Pap Smear Using the Cervex Brush and Correlations of Cytology, Colposcopy, and Histology: Preliminary Results from the Experience of a Tertiary Hospital

Jean Anne B. Toral, M.D.
Section of Gynecologic Oncology, Department of Obstetrics and Gynecology
Philippine General Hospital, University of the Philippines Manila

Objectives: To determine the accuracy of Pap smear using the Cervex brush in detecting epithelial cell abnormalities and to determine correlations between cytology, colposcopy,and histology on the set of patients referred to the Colposcopy Clinic of a tertiary hospital in Manila. **Methods:** A review of the records of patients seen at the Colposcopy Clinic from March 2000 to February 2001 was done. Pap smear results were correlated with colposcopy or histopath from colpo-guided biopsies for the determination of accuracy. Kappa statistics were used for the correlation between cytology and histopath, cytology and colposcopy, and colposcopy and histopath. **Results:** A total of 197 patients were included. The test characteristics of Pap smear using the Cervex brush are: Sensitivity = 47.37 %; Specificity = 92.13 %; Positive Predictive Value = 39.13%; Negative Predictive Value = 94.25 %; and Likelihood Ratio = 6.0226. Correlations between the three are poor with kappa values of 0.36 for cytology and histology; 0.20 for colposcopy and histology; and 0.11 for cytology and colposcopy. **Conclusion:** The results suggest disappointing outcomes in terms of accuracy for the use of the Pap smear with Cervex brush. The correlations between cytology, colposcopy and histopath are also disappointing and warrant some form of reassessment and review among those who do the procedures.

Key words: cervex brush, Pap smear, colposcopy

Carcinoma of the uterine cervix is the sixth most common solid malignant neoplasm in the United States. The American Cancer Society estimates that there were 13,700 new cases of invasive cervical carcinoma in the US in 1999.[1] It is expected in the United States during 2001 that another 12,900 cases of invasive cancer would have been diagnosed and "4,400 will have died of their disease.[2] Philippine statistics show that the cervix is the fourth leading site for both sexes and the second among women. In 1998, an estimated 4,536 new cases and 2,204 deaths were seen.[3]

These figures remain high, though comparing it with figures some 30 years back, its incidence and the associated morbidity have decreased by as much as 40 percent. This decrease has been attributed to the success of mass screening using the Pap test to diagnose premalignant or early stage cases. However, Pap tests have shortcomings: high specificity in Pap smear testing cannot be achieved without reducing sensitivity. False negative Pap smears are mainly due to sampling errors and detection errors.

In the past decade, the sampling material for Pap smear has been studied extensively as to which would give

the highest yield of results. A lot of the studies have shown that the use of the cotton swab is already out-of-date and new sampling materials have come forth to become better tools. At the Department of Obstetrics and Gynecology of this tertiary institution, the Cervex brush was started to be used in March of 2000 to conform to the recommendations of many international studies. No review has been made yet as to the test characteristics of the Pap smear using the Cervex brush in detecting epithelial cell abnormalities in this institution.

Colposcopy, on the other hand, has emerged to be a very good diagnostic tool to verify suspicious gross cervical findings and abnormal Pap smears. Its clinical impact is that it provides significant information that validates or disputes the results of cervical cytology.[4] Since its inception in the Department, the Colposcopy Clinic headed by the Oncology Section of the department has been receiving referrals from the General Ob-Gyn Service for suspicious looking cervices and for abnormal Pap smears.

Colposcopy and colposcopically-guided biopsies serving as gold standard may clarify inconclusive cytological and gross findings. Correlation between cytology, colposcopy, and histology is necessary to make the accurate and rational decisions about management and treatment.

The objectives of this study were: first, to determine the accuracy the of the Pap smear using the Cervex brush in detecting epithelial cell abnormalties in this hospital; second, to determine correlations between cytology, colposcopy and histology as seen from the cases referred to the Colposcopy Clinic.

Materials and Methods

Records of patients seen at the Colposcopy Clinic for a one-year period from March 2000 to February 2001 were reviewed. These patients were referred to the Colposcopy Clinic from the General Ob-Gyn Out-Patient Service either for a suspicious looking cervix, abnormal Pap smear, or in a minority of cases, for screening. The time period covered was the first year of use of the cervex brush in the General Out-Patient Service.

Excluded in the study were patients referred without Pap smear results, those with Pap smears done in other institutions, and those who had undergone previous hysterectomies and/or radiation treatment.

The following data were noted on the chart:

a. reason for referral to the Colposcopy Clinic
b. gross findings of the referring physicians if indicated
c. age
d. gravidity and parity
e. Pap smear result (Bethesda System of 1991 was used)
f. Colposcopy findings (Reid's scoring was used)
g. Results of colposcopically-guided biopsies if done

Notations used include the following:

a. for the Pap smear:
    1) positive Pap smears were those with squamous epithelial cell abnormalities: Atypical cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma (SCCA); and glandular cell abnormalities as well (Atypical glandular cells of undetermined significance - AGUS, and adenocarcinoma)
    2) negative Pap smears were those within normal limits and those with benign cellular changes (BCC) either due to infection or reactive and reparative changes
b. for colposcopy
    1) positive colposcopy: The Reid's colposcopic index was used (Appendix B). Reid's scores of 0-2 equivalent to CIN I or colpo grade 1, score 3-5 equivalent to CIN II or colpo grade 2, and score 6-8 equivalent to CIN III or colpo grade 3 were all designated positive. Findings of carcinoma on colposcopy was also considered positive. (CIN= cervical intraepithelial neoplasia)
    2) Negative: normal colposcopic findings, everted cervices, polyps
c. for histology from colposcopically-guided biopsies
    1) positive are those with CIN I-III, carcinoma-in-situ and carcinoma
    2) negative are those with chronic cervicitis, polyps, tuberculosis; and those were no biopsies were done for a normal colposcopy

Pap smears in these cases were performed by the General Ob-Gyn residents or by rotating interns. These were processed at the Cytology Section of the Department of Obstetrics and Gynecology. Cytoscreeners read the slides. Abnormal Pap smears were also sent to cytopathologists for verification and final reading.

Colposcopies were performed by the members of the Oncology Section during their rotation in the said clinic. Biopsies, if done, were read by the Pathology residents and re-read and signed out by assigned consultants in Pathology.

Statistical analysis used to determine accuracy of the Pap smear using the cervex brush include: sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio. Colposcopy and colposcopically-guided biopsies were used as gold standard.

For the correlation between Pap smear and colposcopy, between Pap smear and histology, and between colposcopy and histology, kappa statistic was used as a measure of binary agreement, that is, how well the two tests agree on a diagnosis. Other data on correlations within subgroups were expressed in percentages.

Results

A total of 197 cases were included in the study after observing the exclusion criteria. Average age of patients was 42 years with a range of 19 to 68. The age distribution is seen on Table 1. The average gravidity and parity is 4.

As to the indications for the referrals, 23 or 11.7 percent were referred for abnormal Pap smears with

Table 1. Age distribution of patients included in the study.

Age range (years)	Number of patients
< 20	1
20-29	25
30-39	49
40-49	81
50-59	28
60-69	13

ASCUS as the most common abnormality. Nine patients were seen for screening. One hundred sixty five or 83.8 percent were referred for suspicious-looking cervices as adjudged by the resident physician who saw them. A breakdown of these specific indications are seen in Table 2. There were patients who had at least two gross findings to be labelled as a suspicious looking cervix. A good number of patients (51 of them) were referred as suspicious cervix with no gross finding indicated on the referral for the suspicion

Table 2. Indications for referral to the Colposcopy Clinic.

Indications	Number of patients
Screening	9
Abnormal Pap smear	23
ASCUS	11
LSIL	6
HSIL	5
AGUS	1
Suspicious Cervix	
Nodular	20
Cysts	7
Abnormal vessels	26
Infection/inflammation	2
Polyps	11
Everted	11
Erosion/abrasion	11
Plaques	4
Erythematous	11
Bulky	6
None indicated	51

Cytology and Histology

Table 3 shows the Pap smear results as correlated with histologic findings. Observing the definitions for positivity of Pap smear and histology, only 9 cases qualified as true positive. Among these 9 cases, 6 were at the same or within one grade of correlation with their histopath finding. Only 1 out of the 11 cases of ASCUS was in the appropriate grade of histopath finding for a 9 percent correlation. One turned out to be a higher grade with CIN III. Out of the six LSIL cases, only 1 was within the grade of histopath finding for a 16.7 percent correlation. One had a higher grade with CIN III. In the 5 HSIL cases, 4 turned out to be CIN III for an 80 percent correlation. Nine cases of ASCUS, 4 cases of LSIL and 1 case of AGUS turned out to be normal on colposcopy or chronic cervicitis on biopsy. Ten cases which were actually just referred for suspicious looking cervices and had normal Pap smear in 2, bloody smear in 1 , and benign cellular changes in 7 had epithelial cell abnormalities. Most serious were 5 cases: 2 with CIN II, 2 with CIN III, and 1 with carcinoma. All 5 had benign cellular changes on Pap smear. There was one case of cervical tuberculosis which had benign cellular changes on Pap smear. One hundred sixty-three patients with negative Pap smears were also negative on histopath.

Table 3. Correlations of Pap smear results and histopathologic findings.

Histo / Pap	no biopsy	Chronic cervicitis	Polyp	TB	CIN I	CIN II	CIN III	SCCA
Normal	26	17	4	-	1	1	-	-
Bloody	-	2	-	-	-	1	-	-
BCC	51	55	8	1	2	2	2	1
ASCUS	3	6	-	-	1	-	1	-
LSIL	2	2	-	-	1	-	1	-
HSIL	-	-	-	-	1	-	4	-
SCCA	-	-	-	-	-	-	-	-
AGUS	-	1	-	-	-	-	-	-

The test characteristics for Pap smear using the cervex brush in this study population is as follows: Sensitivity= 47.37 %; Specificity = 92.13 %; Positive predictive value = 39.13 %; Negative predictive value = 94.25 %. The likelihood ratio is 6.0226. The prevalence of epithelial cell abnormalities in this series is 9.69 percent. The binary agreement value kappa is 0.3611 (P pos=0.4286, P neg=0.9318).

Cytology and Colposcopy

Table 4 shows the colposcopy results using the Reid's scoring index as correlated with the Pap smear results. Eighty seven cases with Pap smear results of "within normal limits" and "benign cellular changes" referred for colposcopy for suspicious cervix turned out to be normal. Thirty-two these cases were everted cervices. Six had endocervical polyp as colposcopic finding. Three had unsatisfactory colposcopic findings, endocervical curettage of which all revealed chronic endocervicitis. Thirty-nine with suspicious looking cervices had Colpo grade 1 (Reid's score 0-2), 24 with Colpo grade 2 (Reid's score 3-5), and 12 with Colpo grade 3 (Reid's score 6-8). Three were adjudged to be carcinoma by colposcopy.

Table 4. Correlations of Colposcopy results and Pap smears

Colpo / Pap	Normal (including everted)	Polyps	Unsatis-factory	Grade 1	Grade 2	Grade 3	SCCA
Normal	27	2	2	13	3	2	-
Bloody	-	-	-	1	2	-	-
BCC	60	4	1	25	19	10	3
ASCUS	3	-	-	2	4	2	-
LSIL	3	-	-	1	1	1	-
HSIL	-	-	-	1	-	3	1
SCCA	-	-	-	-	-	-	-
AGUS	1	-	-	-	-	-	-

Among the 23 with with epithelial cell abnormalities on Pap smear, 7 had normal colposcopy findings: 3 of ASCUS, 3 of LSIL, and the lone AGUS. The 8 other ASCUS cases had 2 getting colpo grade 1 (score 0-2), 4 getting colpo grade 2 (score 3-5), and 2 getting calpo grade 3 (score 6-8). Only 2 cases were within the acceptable colpo grade for epithelial abnormality for an 18 percent correlation. For LSIL, the 3 other cases were each graded (CIN I, II, III, therefore, only one case was the appropriate colposcopic grade for a 16.7 percent correlation. For HSIL, only one case was downgraded by colposcopy to CIN.[1] The 3 others were graded CIN III and one was carcinoma for an 80 percent correlation. Overall, the kappa value for cytology and colposcopy is 0.1057 (P pos=0.2735, Pneg= 0.6931).

Colposcopy and Histology

Table 5 shows the colposcopy results compared with the histopathologic findings. In 78 cases (39.6 %), there was overgrading of colposcopy. All of them turned out to be chronic cervicitis. The most number came from those with colpo grade 1 in 43 cases. The lone case of TB was actually adjudged carcinoma on colposcopy. Only 3 cases out of 46 with colpo grade 1 had true epithelial cell abnormality for a 6.5 percent correlation. Of these 3 cases, only 2 was within the appropriate grade and one had a higher grade which will lower further the correlation to 4.3 percent. For Colpo grade 2, only 4 out of the 30 cases had epithelial cell abnormalities with 3 turning out to be high grade lesions with CIN III for a 10.3 percent correlation. For the 18 cases with colpo grade 3, 10 had epithelial cell abnormality with 8 having high grade lesions or carcinoma for a 44.4 percent correlation. Overall, the kappa value for colposcopy and histology is 0.2019 (Ppos=0.3304, Pneg=0.7240)

Table 5. Correlations of colposcopy results with histopath findings.

Histo / Colpo	No biopsy	Chronic cervicitis	Polyp	TB	CIN I	CIN II	CIN III	SCCA
Normal	55	1	-	-	-	-	-	-
Everted	32	3	-	-	-	-	-	-
Polyp	-	-	7	-	-	-	-	-
Unsat	-	3	-	-	-	-	-	-
Grade 1	-	43	-	-	2	-	1	-
Grade 2	-	25	-	-	1	3	-	-
Grade 3	-	7	-	-	2	1	6	1
CA	-	2	-	1	-	-	1	-

Discussion

Cervical cancer remains to be a great health problem for women especially in developing countries. This remains so despite the presence of the near ideal cervical cancer screening method, the Pap smear. Much is still to be done in widening the base of women to be included in cervical cancer screening projects. Many have also said that the large variation in disease detection in cervical smears may be partly due to differences in the sampling devices. From the conventional cotton swab has emerged already the Ayre's spatula, the cytobrush, and the Cervex brush. Liquid-based cytology has already been developed with the aim of minimizing both sampling and detection errors while computerized screening attempts to decrease detection error.[5]

Based on the latest Cochrane review on collection devices for obtaining cervical cytology samples from 34 trials and six observational comparative studies, the most effective combination appears to be the combination of the cytobrush with an extended tip spatula.[6] The same is the finding from the European experience as reported by Fokke et al. which recommended the Ayre's spatula and the endocervical brush.[7] Buntinx and Brouwers, however, in their meta-analysis of randomized and quasi-randomized studies involving 85,000 patients in 29 studies found out that there were no substantial differences in the yield of cytological abnormalities between the Ayre spatula, the cytobrush, and the cotton swab then used alone.[8] They further added that there were also no substantial differences in the yield of cytological abnormalities between the extended tip spatula, the Ayre spatula combined with the Cytobrush or cotton swab, or the Cervex brush. The Ayre spatula, Cytobrush, or cotton swab used alone generally performed significantly worse that the combinations, the extended tip spatula, or the Cervex brush.

Based on these findings, the Department of Obstetrics and Gynecology adapted in late 1999 the use of the Cervex brush to conform to international standards. This was, however, only implemented in March of 2000. Previous to this, only cotton swabs were used for Pap smear in this institution.

A study conducted in 1993 to 1994 by Retizos[9] in the same institution involving 380 subjects revealed a sensitivity of 56 percent, specificity of 98 percent, positive predictive value of 45 percent and negative predictive value of 95 percent for the Pap smear using cotton swabs. Comparing these with the results from the calculated test characteristics from the Pap smear using the Cervex brush from this study, these are all higher for the cotton swab. The DOH Cervical Cancer Screening Health Operations Research also had the lowest sensitivity for the Pap smear using the Cervex brush at 17.3 % but had a high specificity at 99 %.[10]

Our results do not conform with the findings of bigger studies done abroad. What are the possible explanations for this? This author theorizes that sampling error could be one reason. The physicians and rotating interns had to be oriented through lectures as to the proper use of the device which they will be using for the first time, however, no actual checking or return demonstration were undertaken, Rovers, the manufacturer of the Cervex brush, recommmends 4-5 turns on the cervix with light pressure for maximum sampling. This device actually offers the advantage of sampling both the endocervix and ectocervix with a simple one step procedure, thereby reducing the potential for air drying.[11] Other possible causes include detection errors both in the cytoscreeners' and cytopathologists' end and the pathologists reading the definitive biopsy specimens.

As a screening tool, what we want is still a test which has a high predictive value, that is, when we get a positive result will give us the highest chance that the patient has the disease. Equally important is for this test to be highly specific which is congruent with a test with a higher positive predictive value as well as a test with a high likelihood ratio. Second, we need a test that can be easily applied to a large group of women, inexpensive, and be able to diagnose the disease ideally in the premalignant phase. With results of only 39.13 percent positive predictive value for the Cervex brush, much is still to be done by the primemovers of cytology in the present hospital; setting to improve on the pick-up rates of Pap smears.

Correlations of cytology, colposcopy, and histology remain important in management decisions. Cells seen on cytologic examination, particularly for high-prade lesions, not adequately explained by biopsy specimens from colposcopy is an indication for conization.[12] Reliable patients with ASCUS or LSIL can have follow-ups and repeat Pap smears.

From correlation analysis of the Pap smear results and histology, it can be gleaned that correlation is very low for low-grade lesions (ASCUS = 9%; LSIL = 16.7 %) but is high for high-grade lesions (HSIL=80 %) What is bothersome are the 6 cases of high grade lesions (CIN II

carcinoma) on biopsy which were read as bloody smear in 1 and benign cellular changes in 5. It is rather fortunate that they were referred for suspicious looking cervices. Overall, the binary agreement value kappa for cytology and histology is 0.3611, the highest among the three correlated diagnostic procedures but in itself, is still very low.

With the changes in the Pap smear nomenclature in Bethesda 2001[13] wherein the category benign cellular changes has been removed, it is hoped that pathologists can commit to the negativity for epithelial cell abnormality with only a dichotomy for the general categorization existing.

Tritz, et al.[14] pointed out etiologies for non-correlating cervical cytologies and biopsies. The most common cause was colposcopic biopsy sampling with errors in biopsy interpretation. In the present study, no slide review by a single pathologist was done. The final reading by the assigned pathologist was taken as is. There is virtue in subjecting the biopsy specimens as well as the Pap smear slides to be read by another pathologist to concur or disagree with the diagnosis of the previous. Other possible sources of non-correlation are technical, those which have to do with the processing of specimen, both in cytology and histopath.

With regards to correlations of colposcopy and histology, this remains necessary for proper management decisions. A quality-control study established an 86 percent correlation of colposcopic impression with histology in an analysis of 3,252 consecutive patients examined by 35 colposcopists.[15] The degree of correlation becomes a measure of colposcopic expertise and validates the colposcopic impression. In the study of Retizos[9], there was only an 18 percent correlation between colposcopy and histology. In the present study, the kappa value for colposcopy and histology was 0.20, way below the acceptable 80 percent correlation. It seems that the colposcopists have not made any breakthrough towards improving their competencies after almost a decade. This can be explained, though, by the fact that colposcopists here come and go as new physicians come in to train. The learning curve seems to be at the same state every time new trainees come in.

The correlation between colposcopy and histology is lower compared to the correlation between Pap smear and histology in this same study. All correlations for individual colpo qrades were low, the lowest being 6.5 percent for Colpo grade 1 and highest for colpo grade 3 at 44.4 percent. These results seem not to agree with the results of 3 quality assurance studies showing that there is a higher colposcopic accuracy in diagnosing low-grade lesions at 87.5 % compared with high-grade lesions at 30.2 %.[16-18]

This low kappa value seems to put in question the colposcopic impression made by the colposcopists in the institution. There seems to be a tendency for overgrading colposcopic findings particularly for low-grade or insignificant lesions as seen in the results wherein 43 cases of CIN I turned out to be chronic cervicitis. These were also seen in 25 colpo grade 2 cases, 7 colpo grade 3 cases, and 2 cases diagnosed as carcinoma on colposcopy This must have resulted in several undue biopsies. The 80 percent quality control index may be a critical measure of proficiency for training purposes. Thus, with a low score from this study, the physicians manning the Colposcopy Clinic should, from time to time, update themselves with their training on colposcopy.

This low correlation also points to the limitations of colposcopy as an investigative technique. This technique is subjective and depends highly on two things: the experience of the colposcopist and the physiologic state of the cervix at the time of examination.

As to the correlation between cytology and colposcopy, the kappa value is lowest for this at 0.1057. Correlations with those with abnormal Pap smears were highest for HSIL at 80 percent. Findings on ASCUS and LSIL were low at 9 and 20 percent respectively. What is crucial to point out in these correlations is the reason for the referral of the general Ob Gyn residents to the Colposcopy Clinic for suspicious cervices but with normal cytologic findings or at most benign cellular changes. Eighty-seven cases or 44.2 percent referred as suspicious turned out to be normal on colposcopy with 32 cases being only cases of everted cervix. The terminology Suspicious looking cervix actually needs to be defined. It is one term that is not found in standard Gynecology textbooks but has just become a convenient term for referral to Colposcopy. What it really means must be cleared with the referring physicians and a better documentation in referral letters should be a must. Even on the study of Retizos,[9] the correlation of gross findings and histopath was low at 21 percent.

Wilkinson[19] points out the other causes of non-correlation between cytology and coposcopy: first, the

cervical lesion may be in the endocervical canal or not in the cervix; second, the colposcopic findings are not apparent to the examiner though it is present (e.g in atrophic cervices); third, the biopsy performed did not include the visualized lesion; fourth, wrong interpretation by the cytopathologist with metaplastic cells or atrophic squamous cells being interpreted as high-grade lesions or wrong interpretation on the histopath specimen. Again, competence both of the colposcopist and the pathologist are important considerations.

Conclusions and Recommendations

The use of the Cervex brush in place of the cotton swab, indeed, is a great leap for the Department of Obstetrics and Gynecology of this institution to conform with the recommended standards. The results on accuracy, however, from this subset of patients on its first year of use seem disappointing with lower computed sensitivities, specificities, and predictive values. Perhaps, more adequate demonstration and hands-on lectures should be given to rotating interns, Ob-Gyn residents, and other physicians as to the proper use of the device. The department must be suffering "birth pains" with its first time use. The adequacy of Pap smears with the use of the Cervex brush was not dealt in this paper. This could be another aspect which can be looked into with the shift from the cotton swab to the Cervex brush.

The correlations between cytology, colposcopy, and histology are, likewise, disappointing, based on this subset of patients. A bigger picture can be discerned if this study were extended in its time scope or if this be converted to a prospective study under controlled conditions. Nonetheless, the colposcopists must update themselves, time and again, to improve on their skills. This is very crucial to the quality of health care to be delivered to our women patients in the fight to reduce the morbidities and mortalities from cervical cancer.

References

1. Stehman F, Perez C, Kurmar R and Thigpen J. Uterine cervix. In W Hoskins, C Perez and R. Young (Editors): Principles and Practice of Gynecologic Oncology. 2000: pp 841-918.
2. Greenlee RT, Hill-Harmon MB, Murray T, et al. Cancer Statistics 2001. CA Cancer J Clin. 2001; 51:15-36.
3. Laudico A, Esteban D, Reyes L and Liquido J. 1998 Philippine Cancer Facts and Estimates. Philippine Cancer Society, Inc. 1998. 48 pp.
4. Limson G and Llave C. Colposcopy for Beginners. 2nd ed., 1996. 22 pp.
5. Cohn D and Herzog T. New innovations in cervical cancer screening. Clin Obstet Gynecol 2001; 44 (3):538-549.
6. Martin-Hirsch P, Jarvis G, Kitchener H and Lilford R. Collection devices for obtaining cervical cytology samples (Cochrane Review). In: The Cochrane Library,3, 2001. Oxford: Update Software.
7. Foke CM, Salvatore MEI, Schipper and Bleker OP. A randomized trial of three methods of obtaining Papanicolau smears. Eur J Ob Gyn Repro Biol 1993; 103-106.
8. Buntinx F and Brouwers M. Relation between sampling device and detection of abnormality in cervical smears: a meta-analysis of randomized and quasi randomized studies. Br Med J 1996 ; 313 (7068): 1285-1290.
9. Retizos AP. An evaluation of gross findings. Papanicolau smear and colposcopy as tools in detecting pre-cancerous and cancerous lesions of the cervix. 1995. (unpublished).
10. Ngelangel CA, Limson GM, Cordero CP, et al. University of the Philippines Manila, Department of Health and Department of Interior and Local Government - Cervical Cancer Screening Health Operations Research. Delineation of an Appropriiate and Replicable Cervical Cancer Screening Program for Filipino Women:ValidityReliability-Acceptability Study, 1998-2001. Pp. 22-27.
11. Sparrow MJ, Fauck R, and Gupta RK. A trial of two methods of taking cervical smear: the Aylesbury spatula plus cytology brush compared to the Cervex broom. N Z Med J 1997; 110 (1052): 356-358.
12. Herbst AL. Intraepithelial neoplasia of the cervir. In: Stenchever MA, Droegemuller W, Herbst A and Mishell DR (Editors): Comprehensive Gynecology, 4th ed. 2001 Pp. 857-888.
13. Solomon D, Diane D, Kurman R, et al. The 2001 Bethesda system terminology for reporting results of cervical cytology JAMA 2002; 287(16): 2114-2119.
14. Tritz DM, Weeks JA, Spires SE, et al. Etiologies for non-correlating cervical cytologies and biopsies. Am J Clin Pathol 1995; 103 (5): 594-597.
15. Benedet JL, Anderson GH, Matistic JP and Miller DM. A quality control program for colposcopic practice. Obstet Gynecol 1991; 78: 872-875.
16. Cristoforoni PM, Gerbaldo D, Perino A, et al Computed colposcopy. Results of a pilot study and analysis of its clinical relevance. Obstet Gynecol 1995; 85: 1011-1016.
17. Ferris DG and Miller MD. Colposcopy practice and training in family practice residency programs. J Am Board Fam Pract 1992; 5: 153-156.
18. Bars R, Corpuz F, lonesco M and De Brus J. Human papilloma viruses and cervical intraepithelial neoplasia: The role of colposcopy. Gynecol Oncol 1987; 27: 197-207.
19 Wilkinson EJ. Clinical management/ Natural history of cervical dysplasia and related findings (Lecture at the University of Florida College of Medicine.)

Gestational Trophoblastic Neoplasia with Choroidal Metastasis: A Case Report

Alma Joy P. Bitera-Morin, M.D.
Department of Obstetrics and Gynecology, Philippine General Hospital,
University of the Philippines Manila

Background: Gestational choriocarcinoma is a malignant trophoblastic tumor that obtains nourishment by invasion of maternal blood vessels and subsequently spreads primarily through the hematogenous route to the highly vascular organs. The most commonly involved organs are the lungs and the vagina. Choroidal metastasis of choriocarcinoma is rare. This is the first reported case in the Philippines. **Case:** A 29 year-old G3P2 who previously underwent curettage for H-mole presented with ophthalgia, headache, vomiting and amenorrhea with gradual loss of visual acuity of the left eye. Diluted serum b-HCG titer was 327,600 mlU/ml. Transvaginal ultrasound revealed gestational trophoblastic neoplasia with full-thickness invasion of the myometrium. Chest x-ray and cranial CT scan showed multiple pulmonary and brain metastases. Ophthalmic evaluation was consistent with choroidal metastasis to the left eye. Systemic chemotherapy with the EMACO regimen and 3600 cGy of whole brain irradiation was given. Complete remission was achieved after 9 courses of chemotherapy. There was gradual restoration of vision of the left eye after treatment. **Conclusion:** Only a few cases of choroidal metastasis from choriocarcinoma have been reported worldwide. Furthermore, it is rare for gestational choriocarcinoma with metastasis to present primarily with decreased visual acuity. The achievement of complete remission after systemic chemotherapy and brain irradiation suggests that like gestational trophoblastic tumors metastasizing to other organs, choroidal metastasis is also chemo-sensitive.

Key words: Gestational trophoblastic neoplasia, choriocarcinoma, choroidal metastasis

Gestational trophoblastic neoplasia is one of the most highly malignant pelvic neoplasms in women. Originating from fetal tissues forming the chorionic villi (trophoblast), it may be preceded by a hydatidiform mole, abortion, ectopic, or a normal pregnancy.[1] It is known to appear without warning and to follow a devastating clinical course. It commonly presents as irregular uterine bleeding during the puerperium but may also present years from the last known antecedent pregnancy[2]. It may present with a non-gynecological symptom like hemoptysis or stroke, depending on the site of the metastasis. Often, a high index of suspicion is needed to make the diagnosis.[3]

Choriocarcinoma is locally invasive, and metastasizes in more than 50 percent of cases.[1] It invades the maternal blood vessels and spreads primarily through the hematogenous route. The most common site of metastasis

is the lungs (>75%) followed by the vagina (50%). Other less common sites of metastasis are the liver, brain, ovaries, intestines and kidneys.[2] Rare sites of metastases include the skin, bone, urinary bladder, thyroid and right ventricle of the heart.[4]

Metastasis to the eye is extremely rare. Since 1926, there have only been a total 22 reported cases worldwide. This case is the 23rd in the world and the first ever reported in the Philippines.

The Case

A 29 year-old G3P2 (2-0-1-1) from Bacolod City, Negros Occidental presented with a two-month history of ophthalgia and periorbital swelling at the left associated with headache, vomiting and amenorrhea for 6 weeks.

Six weeks prior to admission, she was initially admitted at a government hospital for hydration after two weeks of persistent vomiting. The pregnancy test was positive. The working impression was an early intrauterine pregnancy. She was referred to an ophthalmologist for an evaluation of her left eye. The diagnosis was sclerosis of the left ophthalmic vein. She was prescribed an unrecalled ophthalmic drop with no relief.

Two weeks after discharge, persistent vomiting and blurring of vision of the left eye prompted consult with an obstetrician who requested for a transvaginal ultrasound and b-HCG titer. Result of the ultrasound revealed retained products of conception versus gestational trophoblastic disease. Urine b-HCG titer was positive up to 1:2048 dilution or 5,089,280 IU/24 hour urine sample. Choriocarcinoma with brain metastasis was entertained.

Two weeks prior to admission, she was admitted for further work-up. Chest x-ray revealed pulmonary metastasis. Cranial CT scan revealed non-enhancing hypodense foci in the right medial occipital lobe as well as left frontal and right posterior parietal gray-white junction. Irregular, inhomogeneously enhancing nodules in the right parietal subcortical area and periventricular white matter measuring 2.3 x 1.4 cm and 1.2 x 1 cm, respectively were also noted. These lesions were interpreted as brain metastases. The orbits in the scan were unremarkable. The patient was subsequently referred to PGH for chemotherapy and brain irradiation.

On admission, the patient complained of occasional vomiting, headache and blurring of vision at the left. She had stable vital signs. There was hyperemia of the left eye with slight periorbital swelling. There were clear breath sounds. Internal examination revealed normal external genitalia, a parous and smooth vagina, the cervix was closed and smooth, the corpus was enlarged to 10 weeks age of gestation. No adnexal masses were palpated. No tenderness was elicited. Neurologic examination revealed intact cranial nerves except for the left eye which was not able to perceive hand movement and only had inferotemporal light perception. On funduscopy, the red-orange reflex was absent. Findings on the right eye were essentially normal with a 6/6 visual acuity using the pocket Snellen chart. The pupils were equal and reactive to light, 3-4 mm in size. Range of motion of the extraocular muscles were full and tonometry was 17.3 mm H_20 for both eyes. Follow-up evaluation of the left eye by an ophthalmologist using direct and indirect ophthalmoscopy showed bullous retinal detachment. There were solid, flat, plaque-like, mottled yellow-brown lesions in the fundus. The cup disc was not visualized.

The past medical, family and personal-social history of the patient was unremarkable.

She had three previous pregnancies, the first of which was delivered full-term via spontaneous vaginal delivery 7 years prior to admission. Labor was prolonged. The baby died on his first day of life. The second pregnancy was a hydatidiform mole for which she underwent suction curettage 3 years prior to admission. Monitoring of serum b-HCG titers was not done. The third pregnancy was carried to term and was delivered via primary low segment cesarean section for breech presentation 11 months prior to admission. Her menses came at regular monthly intervals, lasting for 5-7 days. On admission, she had been amenorrheic for 13 weeks.

Confirmatory transvaginal ultrasound showed a heterogeneous mass measuring 3.9 x 4.1 x 3.5 cm with full-thickness invasion in the posterior wall of the uterus. Diluted serum β-HCG titer was 327, 600 mIU/ml. A repeat chest x-ray showed multiple nodular densities of different sizes on the left lower lung field consistent with pulmonary metastasis. Holo-abdominal ultrasound was negative for metastasis. On review of the cranial CT scan by a radiologist retro orbital metastasis at the left was noted. An ocular ultrasound confirmed the presence of an intraocular mass at the left with retinal detachment. Choroidal metastasis to the left eye was primarily considered.

On the basis of amenorrhea, elevated b-HCG titer and evidence of an invasive uterine mass on ultrasound with metastatic lesions to the lungs, brain and left eye, the patient was admitted in the Department of Obstetrics and Gynecology with a diagnosis of Gestational Trophoblastic Neoplasia Stage IV 14, Previous Suction Curettage for Hydatidiform Mole (Bacolod Hospital, 1999). Staging was based on the International Federation of Gynecology and Obstetrics (FIGO) Staging System for Gestational Trophoblastic Disease. Prognostic scoring was based on the Modified World Health Organization (WHO) Prognostic Scoring System for Gestational Trophoblastic Disease adopted by FIGO. Confirmatory biopsy of the lesions (in the uterus; lungs, brain and eye) was not done considering the risk of bleeding and invasiveness of procedure. The patient was co-managed by the Departments of Ophthalmology, Neurology and Radiology.

Systemic chemotherapy using the Etoposide-Methotrexate-Actinomycin-Cyclophosphamide-Oncovin (EMACO) Regimen for high-risk gestational trophoblastic disease was given. Whole brain external beam irradiation with a total tumor dose of 3600 cGy for 18 fractions was done. The radiation field included the left retro-orbital mass, sparing the ipsilateral and contralateral lenses to preserve vision. Immediate intracranial decompression was not necessary because the lesions were relatively small and clinically silent. Dexamethasone and Phenytoin were started prior to the radiotherapy to prevent possible peri-lesional edema due to inflammation and convulsions brought about by radiotherapy.

Hysterectomy was not a treatment option since the patient expressed desire for future pregnancy.

After completing 6 courses of the EMACO regimen, normal serum b-HCG titers were achieved (<5 mIU/ml). Three clean-up courses were subsequently given. The treatment course was slightly protracted due to neutropenia experienced after the 2nd, 4th, and 5th cycles of chemotherapy. Financial constraints prevented the use of Granulocyte-Stimulating Factor (GSF). Instead, chemotherapy was temporarily discontinued until the neutrophil count was normal. Aside from neutropenia, the patient also experienced alopecia due to the chemotherapy.

The 18 fractions of brain irradiation was completed on the 2nd cyle of EMACO and the treatment was tolerated well by the patient. The only radiotoxicity experienced by the patient was dermatitis which spontaneously resolved. No seizure episodes were experienced. Repeat cranial CT scan after radiotherapy revealed absence of focal brain parenchymal lesions. However, a hyperdensity at the posterolateral aspect of the left globe was still present.

The multiple nodular densities at the left lower lung field were noted to gradually decrease in size and number during the monthly chest x-rays until no chest lesions were noted on the chest x-ray done during the 3rd clean-up course.

After the 4th cycle of EMACO, the posterofundal mass seen in the uterus on transvaginal ultrasound decreased in size to 1.3 x 1.4 cms. After the 6th cycle of EMACO, a repeat transvaginal ultrasound showed no evidence of disease.

Ophthalgia and left peri-orbital swelling gradually resolved. Repeat ophthalmic evaluation after the chemotherapy revealed hand movement and light perception of the left eye. The red-orange reflex was noted. There were still areas of focal retinal detachment.

The patient was discharged on her 213th hospital day. Upon the patient's request, she had out-patient follow-up with a trophoblastic disease specialist and ophthalmologist in Bacolod City.

Discussion

Choriocarcinoma is a highly malignant trophoblastic tumor grossly presenting as a well-demarcated, hemorrhagic and necrotic lesion, varying in size within or replacing the myometrium and may protrude into the uterine cavity.[2] It is a histologic diagnosis, belonging to a spectrum of malignant trophoblastic diseases. More commonly, however, a histopathologic examination is not possible: biopsy entails the risk of profuse bleeding and in most cases difficult especially with its propensity to metastasize to the lungs or brain. As in this case, for example, diagnosis was made on the bases of a high index of suspicion in the background of elevated b-HCG titers. The term Gestational Trophoblastic Neoplasia or Gestational Trophoblastic Tumor has been coined especially for these cases.[3]

Although a relatively rare disease entity in the Western countries, the incidence of gestational trophoblastic neoplasia is 5-15 times more common in the Philippines and other Southeast Asian countries[6]. Invading maternal

blood vessels and spreading through the hematogenous route, its common sites of metastasis are the highly vascular organs such as the lungs, brain and liver.[5]

The frequency of choroidal metastasis in patients with cancer is estimated to be approximately 2 to 7 percent. It is the most common malignant neoplasm of the adult eye and it commonly occurs via hematogenous spread. The frequency of ocular metastasis, however, varies significantly among primary sites. The most common primary tumor sites are the breasts (40-49%) and the lungs (14-30%)[7] followed by the kidneys, testis and prostrate.[5]

Metastasis of gestational choriocarcinoma to the choroid is extremely rare. Furthermore, it is rare that ophthalmic signs and symptoms are the first and primary findings that lead to its discovery.

The earliest of the reported cases of choriocarcinoma metastasizing to the choroids was in 1926. The patient had metastases to the choroids, lung, kidney and intestine. There had been 16 other reported cases worldwide from 1926-1976. Seven of the cases have been male subjects, usually from the testis.[5] An extensive literature search revealed only 6 reported cases worldwide since 1980. Making a total of 22 cases reported around the world.

Our case is the 23rd reported case in the world and is the first case in the Philippines. Four of the cases had histopathologic evidence from tissue materials from lung biopsy, hysterectomy, and an enucleated eye (in 3 of the cases). Although there was no histopathologic evidence that the choroidal mass was metastatic from the uterine tumor in our case, the resolution of the lesions and symptoms with the systemic chemotherapy and brain irradiation strongly suggests that it is metastatic gestational choriocarcinoma.

It is not clear which of the pregnancies caused the malignant trophoblastic growth. As previously mentioned, gestational trophoblastic neoplasia can be derived from normal term pregnancies, spontaneous abortions and ectopic pregnancies and molar pregnancies. With absence of symptoms prior to the 3rd pregnancy and with resumption of regular menstruation after the 3rd pregnancy, it is most likely that is was derived from the 3rd pregnancy which was a term pregnancy.

From the uterus, the malignant cells most likely were transported through the venous sinuses, to the inferior vena cava, to the lungs through the heart where they proliferated at the left lower lobe then out to the internal carotid artery and to the middle cerebral artery through the left side of the heart to proliferate in the brain and to the highly vascular choroid of the left eye, the most common site of metastasis to the eye.

It is noteworthy that as in our case, all the 6 cases reported since 1980 (including this case) had visual complaints as the initial symptom of disease. Clinical signs of choroidal metastasis of choriocarcinoma consists of a usually unilateral choroidal mass, which often demonstrates rapid growth and results in secondary retinal detachment and hemorrhages.[5] The majority of symptomatic patients note a decreased visual acuity at the time of presentation. Other presenting signs or symptoms include diplopia, photophobia, ptosis, blepharitis, metamorphopsia, pain, flashes and floaters, uveitis, exophthalmos, and secondary glaucoma. There are many other conditions which can be mistaken for metastatic disease, therefore, a careful evaluation is necessary for a correct diagnosis. The presence of metastatic disease to the eye is obviously high in the differential diagnosis of ocular lesions when a primary cancer is present elsewhere.

The diagnosis of ocular metastases is based primarily on clinical findings supplemented by imaging studies. The fundus photograph in this case is the classic picture of choroidal metastasis: the presence of solid, flat, plaque-like, mottled, yellow-brown lesions. All these provided the bases from which the diagnosis of choroidal metastasis (although rare) was made primarily. Aside from the ultrasound, another ancillary procedure which could have aided in the diagnosis, and perhaps would have confirmed it is the performance of fine-needle aspiration biopsy. The invasiveness of the procedure, however, prevented its use in this patient.[7]

Most of the 7 cases died shortly after the onset of eye symptoms. The prognosis of patients with choroidal metastasis was very poor and median survival is 6 to 7 months from diagnosis. This was largely due to the absence of an effective combination chemotherapy for metastatic choriocarcinoma. With the discovery of very effective chemotherapeutic regimens against choriocarcinoma, however, the prognosis of this condition appears to be improving. Barondes, et al. in 1989 achieved complete remission of choroidal and lung metastasis from gestational choriocarcinoma after hysterectomy and intravenous and intrathecal chemotherapy. They also reported a similar case wherein complete remission was achieved after chemotherapy and radiotherapy.[8] Ino, et al. in 1999 achieved complete remission of choriocarcinoma

metastatic to the lungs and choroid with systemic chemotherapy alone.[5] Like in our case, the diagnosis was made clinically. In our case, however, external beam radiotherapy may have contributed greatly to the fast achievement of complete remission since numerous publications have documented the ability of external-beam radiotherapy to successfully treat ocular metastasis effectively. Response rates in these series ranged from 33 to 89 percent, with majority in the 80 percent range. In most of these studies, vision either improved or stabilized in a high percentage of patients.[7] In both cases, however, despite remission, full recovery of vision was not obtained due to the secondary retinal detachment.

As of the present the most commonly applied treatment for choroidal metastasis is external-beam radiotherapy.[7] However, a number of cases suggest that metastasis of choriocarcinoma in the choroid, as well as in other organs, is chemo-sensitive. The specific therapy chosen for a patient should therefore be individualized and the clinical condition of the patient should be considered.

References

1. Keates R, Stuart B. Metastatic uveal choriocarcinoma. Arch Ophthalmol 1970; 84:381-384
2. Baja-Panlilio H. Textbook of Obstetrics and Gynecology 1995 1st Ed.
3. Ilancheran A. Optimal Treatment in Gestational Trophoblastic Disease 1998;27 (1):698-704.
4. Gangadharab VP, Prakash NP, Chitrathara K, Sasidharan K, Ramachandran K. Ocular metastasis of choriocarcinoma. Br J Radiol 1999;7211:1216-1217.
5. Ino K, Mitsui T, Nomura S, Kikkawa F and Mizutani S. Complete remission of gestational choriocarcinoma with choroidal metastasis treated with systemic chemotherapy alone: Case report and review of literature. Gynecol Oncol 2001; 83(3):601-604
6. Page RD. Gestational Trophoblastic Tumors. MD Anderson Cancer Center.
7. Small W. Management of Ocular Mestastasis. H Lee Moffit Cancer Center and Research Institute.
8. Barondes MJ, Hamilton AM, HungerFord J, Rustin GJS. Treatment of choroidal metastasis from choriocarcinoma. Arch Ophthalmol 1989; 107:796-798.
9. Kohorn EIM. The New FIGO Staging and Risk Factor Scoring System for Gestational Trophoblastic Neoplasia.

Primary Peritoneal Carcinoma

Carol Marjorie H. Pacioles, M.D.
Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines Manila

Primary peritoneal carcinoma is an uncommon disease characterized by peritoneal carcinomatosis without other identifiable primary tumor. A case of primary peritoneal carcinoma is reported. This 57 year old presented with abdominal enlargement which on ultrasound revealed marked ascites and was diagnosed to have ovarian new growth, malignant. Laparotomy revealed grossly, normal uterus, ovaries, and fallopian tubes. However, there was note of caked omentum and nodular implants at the peritoneal surface of the upper abdominal wall with fibrin deposits at the pelvic cavity. Total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy, and tumor debulking were- done. Microscopic examination showed adenocarcinoma, moderately differentiated, involving the omentum and serosal surfaces of the ovaries, uterus, fallopian tubes, appendix, and peritoneal implants. Post-operatively, she was treated with chemotherapy in the form of Paclitaxel and Carboplatin. The clinical features, origin, problems of diagnosis and prognosis of this uncommon disease are discussed.

Key words: primary peritoneal carcinoma, carcinomatosis, papillary serous peritoneal carcinoma

Primary peritoneal carcinoma is a relatively newly defined entity. First described by Swerdlow in 1959[1], this entity was first reported as "mesothelioma resembling papillary ovarian adenocarcinoma", [2] and since then, through several clinicopathologic studies, has become an established entity. Many names have been applied to tumors arising primarily from the peritoneum, including serous surface papillary carcinoma of the ovary, primary peritoneal carcinoma, multiple focal extraovarian serous carcinoma, primary peritoneal papillary serous adenocarcinoma, serous surface carcinoma of the peritoneum, extraovarian peritoneal serous papillary carcinoma, extraovarian mullerian adenocarcinoma, normal-sized ovary carcinoma syndrome, papillary serous carcinoma of the peritoneum, and peritoneal papillary carcinoma[3]. Lack of strictly defined diagnostic criteria and absence of unity in nomenclature have resulted in persisting confusion concerning this disease. Since most reported cases of primary peritoneal carcinoma have been of a papillary serous subtype[1], which is also the most common type in epithelial ovarian cancer, additional confusion has resulted because of the many similarities both clinically and histopathologically between the two. This disease diffusely involves peritoneal surfaces, while sparing or superficially

involving the ovaries. It may develop years after salpingo-oophorectomy for a benign disease or after prophylactic salpingo-oophorectomy for a family history of ovarian cancer.

In this paper, a case of primary peritoneal carcinoma is presented - the first ever reported in our institution and in the Philippines.

Case Protocol

This is the case of LM, 57 year old, G4P1 (1-0-3-1), from Sampaloc, Manila who was admitted for the first time on November 21,2001 with the chief complaint of abdominal enlargement.

The patient has a history of hypertension for one year. Her highest blood pressure is 160/100, with her usual blood pressure at 110-120/70-80. She is not on any maintenance medication. The patient also has a history of excision of a benign right breast mass during the 1970s also at our institution. The patient has no history of diabetes, asthma, pulmonary tuberculosis, heart disease, kidney disease, or cancer.

The patient has a family history of diabetes in the mother and brother, a history of hypertension in the brother, but no history of asthma, pulmonary tuberculosis, nor heart/kidney disease. A maternal uncle has a history of throat cancer and a sister has a history of a uterine mass (biopsy unknown).

The patient is married and a government employee. She has no vices. Her first coitus was at 31 years old with a single, non-promiscuous sexual partner. She allegedly has a history of recurrent vaginal infections. The patient has no history of oral contraceptive pill/ intrauterine device/ hormone replacement therapy use.

The patient had her menarche at 15 years old with subsequent menstrual periods coming at regular monthly intervals, 5 days duration, using 2 pads/day. She had her menopause at 42 years old. The patient is a G4P1 (1-0-3-1). Her only full term vaginal delivery was in 1975 and her 3 subsequent pregnancies were spontaneous abortions with no dilatation and curettage done.

The history of present illness started 5 months prior to admission when the patient experienced intermittent moderate grade fever relieved by intake of paracetamol associated with occasional non-productive cough, bilateral paravertebral pain, and easy fatigability. No consult was done.

Four months prior to admission, there was persistence of the above-mentioned signs and symptoms with progression of the easy fatigability and associated gradual weight loss and anorexia. The patient consulted with the company physician and was given co-trimoxazole BID with temporary relief of fever. She also self-medicated with guaifenesin with note of relief of cough.

Three months prior to admission the patient consulted at a local hospital because of the persistence of fever. She was assessed to have allergy and advised immunization. The patient was then lost to follow-up. During this time, there was note of abdominal heaviness, gradual abdominal enlargement, but no abdominal pain.

Two months prior to admission, the patient consulted another private physician. A rectal examination was done and there was note of a pelvic mass. The patient was subsequently referred to a gynecologist. However, upon consult with the gynecologist, no mass was appreciated during internal examination. A Pap smear and transvaginal ultrasound was then requested. Pap smear result was normal and the ultrasound (UTS) revealed marked ascites, atrophic uterus and non-visualized ovaries. Abdominal computed tomography (CT) scan was also requested which showed the following: moderate peritoneal fluid, minimal right-sided pleural effusion, caking at the upper anterior omentum, and tubular and irregular soft tissue densities in the right lower posterior pelvic cavity just on top of the uterus which cannot be separated from the sigmoid colon. Initial impression was abdominopelvic Koch's and patient was started on quadruple anti-Koch's. Patient was again lost to follow up.

Three weeks prior to admission, the patient was admitted at another institution for dyspnea and weakness. Thoracentesis was initially done and pleural fluid was submitted for gram stain, acid-fast bacilli, cell block and aerobic culture. The pleural fluid showed no organism and was negative for acid fast bacilli. However, it was positive for malignant cells. A series of tests were performed: repeat abdominal CT scan, chest CT scan, carcinoembryonic antigen (CEA) which were all unremarkable. However, ascitic fluid cytology also showed an elevated value of 24,500 U/ml. The impression then was to consider ovarian carcinoma. The patient was advised surgery and subsequently was admitted at our institution.

Review of systems showed the following: (+) 30% weight loss in 2 months and anorexia, (-) fever, headache,

loss of consciousness, chest pains, nausea, vomiting, jaundice, pruritus, abdominal pain, urinary nor bowel disturbances, signs of GI bleeding. However, the patient experienced 2-pillow orthopnea and slight difficulty of breathing.

On admission the patient was fairly developed, cachectic, and pale. She had the following vital signs: a blood pressure of 110/70, a heart rate of 104, a respiratory rate of 22, and was afebrile. She had pale palpebral conjunctivae, anicteric sclerae, no cervical lymphadenopathy, and no tonsillo-pharyngeal congestion. There was note of a chest lag on the right. Patient had clear breath sounds with no rales or wheezes. She had essentially normal cardiac findings. The abdomen was globular with a leathery texture, with normoactive bowel sounds, with fluid wave and note of slight tenderness at the lower abdomen. No mass was palpated. She had full and equal pulses, pink nailbeds, and no edema.

Internal examination showed the following: normal external genitalia, smooth, parous vagina, atrophic cervix, fornices formed, corpus small, there was a huge, slightly tender, tensely cystic mass, with the left greater than the right and was adherent to the pelvic sidewall, with note of nodularities on the right parametrium.

Assessment was ovarian new growth, bilateral, malignant, Stage IV, rule out primary peritoneal carcinoma. The patient underwent total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy, tumor debulking, and chest tube thoracostomy on the right.

Intraoperative findings were as follows: (+) 2 liters of straw colored ascitic fluid; the uterus, ovaries, and fallopian tubes were grossly normal; there was note of caked omentum; there were nodular implants at the peritoneal surface of the upper abdominal wall, however, the liver, spleen, stomach, kidneys, intestinal surfaces were grossly normal; there were peritoneal implants with fibrin deposits at the pelvic cavity which were fusing the pelvic structures together; there were no palpable pelvic and para-aortic nodes.

Post-operatively, the patient was stable with febrile episodes. On the 5th post-operative day, pleurodesis with tetracycline was done. On the 11th post-operative day, the chest tube was removed and there were no more episodes of fever. She was then started on her first session of chemotherapy with paclitaxel and carboplatin on the 14th post-operative day and was discharged the following day.

The final diagnosis was: primary peritoneal carcinoma, stage IV; status post exploratory laparotomy, total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, infracolic omentectomy, tumor debulking, and chest tube thoracostomy, right; status post carboplatin-paclitaxel I. The plan was to continue chemotherapy.

The patient has already completed 4 cycles of carboplatin-paclitaxel. Her CA-125 values showed a decrease from an initial of 24,500 U/ml to 256 U/ml after the third course. Latest chest x-ray and CT scan was essentially normal after the third course, approximately 3 months post-op.

Histopathologic examination of the definitive specimen revealed the following: Sections from the omentum show islands of tumor cells embedded within the adipose tissue of the omentum (Figure 1) and papillary structures within dilated glandular spaces (Figure 2). Occasional glandular formations composed of large cells with abundant eosinophilic cytoplasm, pleomorphic nuclei and prominent nucleoli are also noted (Figure 3). In other areas, the tumor appeared as solid nests set within a cellular stroma with abundant extracellular mucin (Figure 1) and the said solid areas showed a patternless sheet of tumor cells with occasional psammoma bodies (Figure 4). Sections from the ovary showed tumor involvement limited to the surface epithelium (Figure 5) with no cortical invasion (Figure 6). Sections from the uterine serosa showed superficial tumor involvement over the serosal surface with the tumor forming glandular patterns as described earlier. Tumor was also seen involving the serosal surfaces of the tube and appendix (Figure 7).

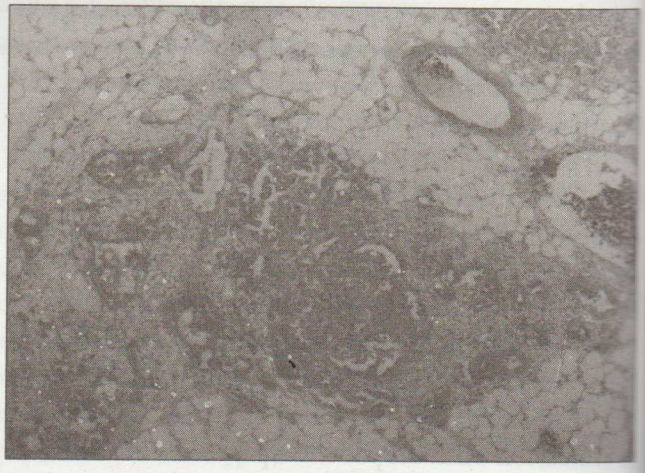

Figure 1. Omentum. Picture shows islands of tumor cells embedded within the adipose tissue of the omentum. The tumor appears as solid nests set within a cellular stroma with abundant extracellular mucin (H & E staining)

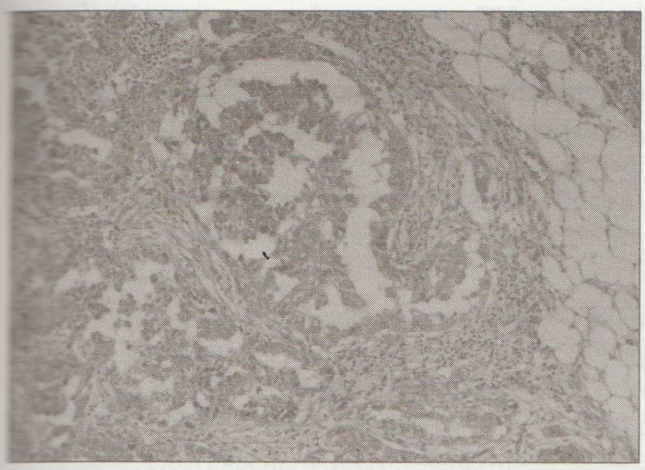

Figure 2. Omentum. Picture shows papillary structures within dilated glandular spaces (H & E x 100).

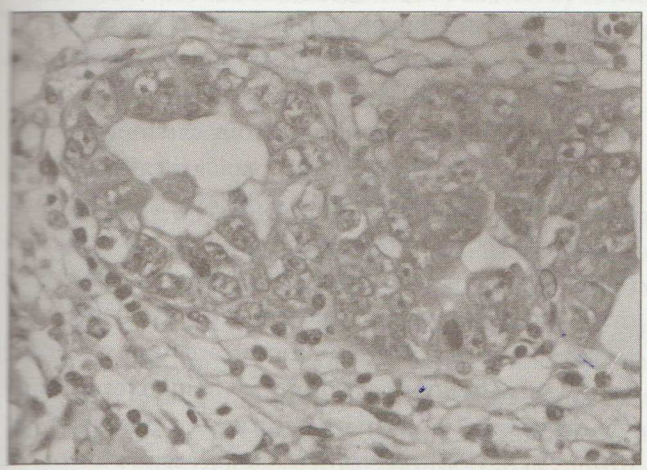

Figure 3. Omentum. Occasional glandular formations composed of large cells with abundant eosinophilic cytoplasm, pleomorphic nuclei, and prominent nucleoli. (H & E x 400)

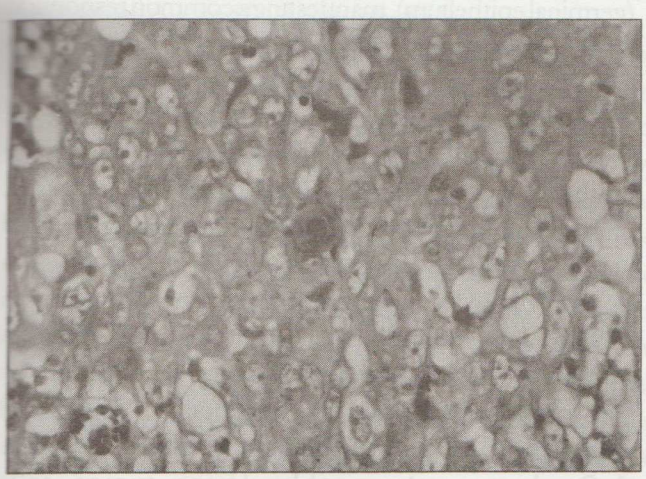

Figure 4. A high power magnification of the solid areas shows a patternless sheet of tumor cells with occasional psammoma bodies (H & E x 400)

Figure 5. Ovary. Section from the ovary showing the tumor involvement limited to the surface epithelium (H & E staining).

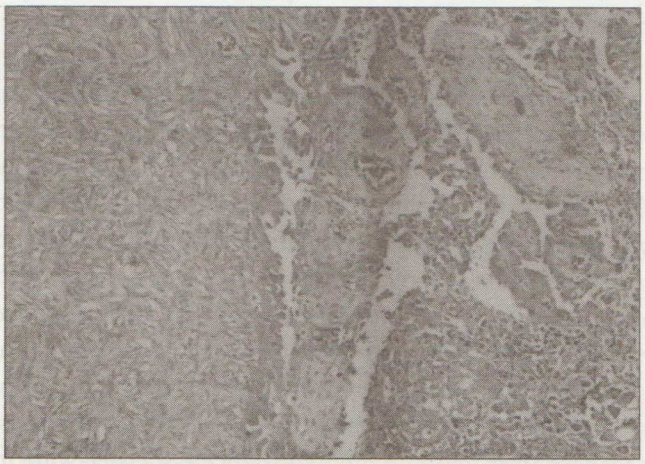

Figure 6. Ovary. A low power view showing involvement confined to the surface epithelium with no crucial invasion (H & E x 100)

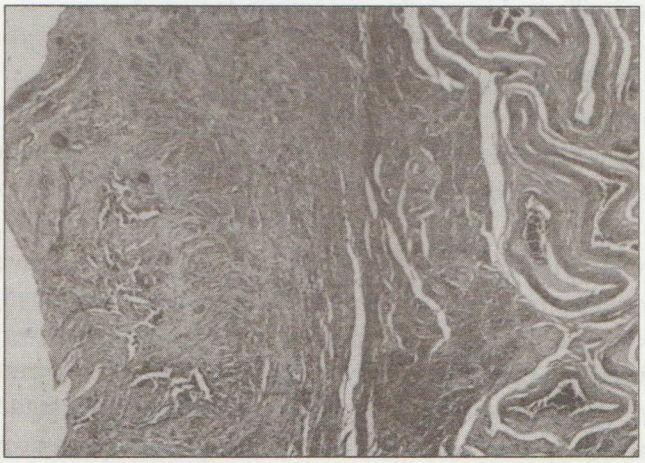

Figure 7. Uterine serosa. Picture showing superficial tumor involvement over the serosal surface forming glandular patterns (H & E staining).

The final histopathologic diagnosis was: Adenocarcinoma, moderately differentiated, involving the omentum and serosal surfaces of the ovaries, fallopian tubes, uterus, appendix, and specimen labeled peritoneal implants. Small leiomyoma, intramural; adenomyosis; endometrial polyp; senile cystic endometrium; chronic cervicitis.

Discussion

Definition

The main features of primary peritoneal carcinoma are widely disseminated malignancy along the peritoneal surfaces, the omentum, and abdominal viscera, with minimal or no ovarian involvement. To better define primary peritoneal carcinoma, the Gynecologic Oncology Group has established inclusionary criteria for diagnosis which are the following: (1) both ovaries must be either physiologically normal in size or enlarged by a benign process; (2) the involvement in the extraovarian sites must be greater than the involvement on the surface of either ovary; (3) microscopically, the ovarian component must be nonexistent, or confined to ovarian surface epithelium with no evidence of cortical invasion, or involving ovarian surface epithelium and underlying cortical stroma but with any given tumor size less than 5 x 5 mm, or the tumor less than 5 x 5 mm within ovarian substance associated with or without surface disease; (4) the histological and cytological characteristics of the tumor must be predominantly of the serous type that is similar or identical to ovarian serous papillary adenocarcinoma, any grade [3].

Incidence

The true incidence of primary peritoneal carcinoma remains unknown, although estimates place its frequency relative to ovarian cancer as 1:10 - 1:15.[1,4] To date, relatively few cases of primary peritoneal carcinoma have been reported in literature and as previously mentioned, most cases are of the papillary serous subtype; however, mucinous, endometrioid, clear cell Brenner, and malignant mixed Mullerian types have also been described.[4] Retrospective reviews have estimated that 7-14 percent of cases originally diagnosed as ovarian papillary serous carcinoma are likely to represent primary peritoneal carcinoma[3]. The mean age of presentation is 50-65 years[5] and occurs almost exclusively in women. It has also been reported that although primary peritoneal carcinoma has been mainly seen in Caucasians, it also occurs among Asian people. Our index patient is a 57 year-old female and an Asian (Filipino). To my knowledge, this is the first reported case of primary peritoneal carcinoma in the Philippines.

Etiology

The exact etiology or pathogenesis of primary peritoneal carcinoma is unknown. However, two theories have been proposed to explain the development of this disease entity and to explain the similarities shared with its ovarian analogue.

The first theory suggests that primary peritoneal carcinoma arises from malignant degeneration of nests of ovarian tissue remnants that are left within the peritoneum during the process of embryonic gonadal migration. The similarities between papillary serous carcinoma of the peritoneum and serous ovarian papillary carcinoma are based on the common origin of the ovarian epithelium and peritoneum from mesoderm that has mullerian potential. This may explain why this disease behaves in many ways like ovarian cancer. It may also explain the reported cases of primary peritoneal carcinoma occurring many years after oophorectomy for benign reasons and the occurrence of primary peritoneal carcinoma after prophylactic oophorectomy in families with a history of ovarian cancer. The second theory suggests that field carcinogenesis occurs with the coelomic epithelium lining the abdominal cavity (the peritoneum) and the ovaries (germinal epithelium), manifesting a common response to an oncogenic stimulus.[3,4,6]

There is also some controversy as to whether or not primary peritoneal carcinoma is a multifocal disease. Previously it has been demonstrated that in advanced stage epithelial ovarian cancer, the pattern of allelic loss, X chromosome inactivation, and p53 mutation are identical at primary and metastatic sites which is consistent with a unifocal origin for these tumors. However, Muto, et al. in 1995, demonstrated in their study that p53 mutation occurring at some but not all tumor sites in primary peritoneal carcinoma as evidence of multifocal involvement[7]. In another report, the multifocal nature was defined more thoroughly. Using tumor cells microdissected from paraffin-embedded samples, loss

of heterozygosity, a molecular genetic approach used to identify tumor suppressor genes, was found commonly in sporadic peritoneal carcinoma. At least 2 foci were affected, both on chromosome 17: the p53 gene on the short arm and the BRCA1 gene on the long arm.[5]

Signs and Symptoms

Presenting signs and symptoms included abdominal distention caused by ascites with positive cytology, abdominal pain, constipation, nausea, vomiting, decreased appetite, malaise, weight loss, dyspnea and fatigue. Generally, most patients would present with no palpable pelvic mass. Laboratory data would also show significant elevation of serum CA 125 values.[1,8,9] Our index patient presented with abdominal distention caused by ascites with positive cytology, weight loss, dyspnea, and fatigue. Serum determination of CA 125 was also elevated.

Pathology

Grossly, on laparotomy, the most common sites of involvement were the omentum and abdominal and pelvic peritoneum, sometimes with minimal involvement of the surface of the ovaries. The omental tumor was usually bulky and occasionally, smaller tumors may appear as discrete nodules arising from multiple peritoneal surfaces. Ovaries were normal or atrophic in size in most cases and no gross lesion was found in the substance of the ovaries. Intraoperative findings in our patient showed a caked omentum, with nodular implants on the peritoneal surface of the upper abdominal wall and grossly normal uterus, ovaries, and fallopian tubes.

Microscopically, the tumor primary in the peritoneum is morphologically identical to the serous adenocarcinoma arising in the ovary. Typical appearance include foci showing a papillary or tubopapillary pattern lined by tumor cells that were non-ciliated, cuboidal to columnar with modest amounts of eosinophilic cytoplasm, had poorly defined cell borders, and round to oval nuclei and usually showing glandular formation. Psammoma bodies may be few to numerous. The tumor may range from that which is similar to grade 1 tumors of the ovary, to sheets of undifferentiated cells similar to grade 3 neoplasm of the ovary.[5] Microscopic findings in our patient showed papillary structures within dilated glandular spaces and occasional glandular formations composed of large cells with abundant eosinophilic cytoplasm, pleomorphic nuclei and prominent nucleoli were also noted. The tumor also appeared as solid nests set within a cellular stroma with abundant extracellular mucin which on high power magnification showed a patternless sheet of tumor cells with occasional psammoma bodies. The histopathology result of our patient was a moderately differentiated adenocarcinoma involving the omentum and serosal surfaces of the ovaries, fallopian tubes, uterus, appendix, and specimen labeled peritoneal implants.

Differential Diagnosis

In cases showing diffuse involvement of the peritoneum by a papillary tumor without an obvious primary, aside from primary peritoneal carcinoma, metastatic papillary carcinoma from an occult primary and diffuse malignant mesothelioma should be included as differential diagnosis.

Clinically, mesothelioma is closely related to asbestos exposure and is more frequent in men, while primary peritoneal carcinoma has been reported almost exclusively in women and is unrelated to asbestos. Histologically, certain tumor patterns of malignant mesothelioma may present similarly as primary peritoneal carcinoma and metastatic adenocarcinoma such as the tubulopapillary pattern. However, such pattern may be distinctive particularly when the lesional cells are characteristic of mesothelial cells, that is, polygonal cells with moderate amount of eosinophilic cytoplasm. The presence of columnar cells favors a diagnosis of adenocarcinoma. In contrast to most malignant mesotheliomas, serous carcinomas frequently contain cells with bizarre nuclear features and many psammoma bodies.[10] Most of the primary peritoneal adenocarcinomas are of the papillary serous type and are indistinguishable from primary ovarian serous carcinomas. However, using the inclusion criteria established by the Gynecologic Oncology Group, these two entities may be differentiated.

Histochemical and immunohistochemical stains may also be helpful in the differential diagnosis of malignant mesothelioma and adenocarcinoma. Malignant mesothelioma is characterized by an absence of neutral mucins (in contrast to adenocarcinoma) and the presence of acid mucin (predominantly hyaluronic acid) within vacuoles appreciable as alcian blue-positive, digested periodic acid-Schiff-negative, hyaluronidase-sensitive

material.[10] An array of immunohistochemical markers may help in separating primary peritoneal carcinoma and metastatic ovarian serous carcinoma from malignant mesothelioma. However, to separate the first two disease entities, good markers have not been identified. The immunohistochemical overlap among these three tumors may be explained by the notion that they have a common origin in the mesothelium, whereas differences may be related to the presence or absence of mullerian influence on the original mesothelium. From the practical point of view, calretinin, thrombomodulin, and keratin 5/6 are the best positive markers for distinguishing between epithelial malignant mesotheliomas and papillary serous carcinomas diffusely involving the peritoneum. Among the antibodies that are considered to be negative markers for mesothelioma, MOC-31, B72.3, Ber-EP4, CA19-9, and Leu-M1 proved to be the best diagnostic discriminators. Immunostaining for CEA, epithelial membrane antigen, placental alkaline phosphatase, vimentin, HBME-1, CA-125, or S-100 protein has little or no practical diagnostic utility in differentiating between epithelial mesotheliomas and serous carcinomas. A periodic acid-Schiff test was done on our patient showing focal positive staining cells pointing to an adenocarcinoma. However, no immunohistochemical tests were done.

Another diagnostic test that may help distinguish primary papillary serous carcinoma of the peritoneum from malignant mesothelioma and metastatic disease is the use of the CT scan. In a study by Stafford-Johnson et al (1998), they identified three CT features that may help distinguish these disease entities. The first feature was the absence of an ovarian mass in primary papillary serous carcinoma of the peritoneum. A large ovarian mass (often >10 cm at presentation) is a characteristic CT feature of serous papillary ovarian carcinoma. A second CT finding of primary papillary serous carcinoma of the peritoneum was the presence of extensive areas of peritoneal calcification. Calcification is not a characteristic feature of peritoneal mesothelioma, although diffuse peritoneal calcification has rarely been reported in well-differentiated mesotheliomas. The third CT finding in primary papillary serous carcinoma of the peritoneum is omental masses, with marked omental calcification, which is not a recognized association of either mesothelioma or metastatic disease. The abdominal CT scan of our patient showed caking at the upper anterior omentum with the absence of an ovarian mass.[6]

Diagnosis

As previously mentioned, the principal requirement for the diagnosis of primary peritoneal carcinoma would be meeting the inclusionary criteria established by the Gynecologic Oncology Group. Currently, there is no accepted staging system for peritoneal carcinoma. However, because of its similarity with serous papillary ovarian carcinoma, most authors followed the FIGO staging for ovarian cancer.

Aside from the baseline laboratories such as complete blood count, renal and liver function tests, recto-vaginal exam, chest x-ray and pelvic ultrasound, other diagnostic exams would include a barium enema, upper gastro-intestinal series, proctosigmoidoscopy, KUB-IVP, abdominal CT scan, MRI, and appropriate tumor marker, which in this case would be CA-125.

Treatment

Treatment for primary peritoneal carcinoma is similar to advanced stages of malignant epithelial ovarian carcinoma because its histologic pattern and behavior approximate each other. This is in the form of cytoreductive surgery followed by systemic chemotherapy.[12] Surgery is in the form of total hysterectomy with bilateral salpingo-oophorectomy, partial omentectomy, peritoneal fluid cytology and tumor debulking. Chemotherapy is platinum based. Monitoring for response would include a thorough physical exam and rectovaginal exam, CA-125 values and/or pelvic UTS or abdominal CT scan. In some studies, reassessment laparotomy was performed in patients after completion of chemotherapy to document response.[13] Our index patient underwent exploratory laparotomy, total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, infracolic omentectomy, and tumor debulking. She has also completed 4 cycles of carboplatin-paclitaxel. Her CA-125 values showed a decrease from an initial of 24,500 U/ml to 256 U/ml after the third course. Latest chest x-ray and CT scan were essentially normal after the third course.

Prognosis

In the study done by Halperin, et al. comparing primary peritoneal serous papillary carcinoma (PPSPC) with ovarian serous papillary cancer (OSPC), they found

a significantly worse median survival rate for PPSPC patients (17 months) than for OSPC patients (40 months) for the first 3 years. Previous studies were contradictory in reporting survival of PPSPC patients as compared to OSPC patients. Several reports presented significantly worse survival, while others reported a similar survival rate for patients suffering from either malignancy. Possibly, the main difference in survival occurs in the first three years, and the survival curve of OSPC later approaches that of PPSPC. This assumption warrants further testing.[1]

Primary peritoneal carcinoma is a definite clinicopathologic entity. Its clinical and biological behavior mimics that of ovarian serous papillary carcinoma and should be considered in any female who has carcinoma of unknown origin.

References

1. Halperin R, Zehavi S, Langer R, Hadas E, Bukovsky I, Schneider D. Primary peritoneal serous papillary carcinoma: A new epidemiologic trend? A matched-case comparison with ovarian serous papillary cancer. Int J Gynecol Cancer 2001; 11:403-408.
2. Dalrymple JC, Bannatyne P, Russell P, et al. Extraovarian peritoneal serous papillary carcinoma: A clinicopathologic study of 31 cases. Cancer 1989; 64:110-115.
3. Olsen T, Nycum L, Graham R, Alagoz T. Primary peritoneal carcinoma presenting on routine Papanicolaou smear. Gynecol Oncol 2000; 78:71-73.
4. Eltabbakh G, Piver S, Natarajan N, Mettlin C. Epidemiologic differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer. Obstet Gynecol 1998; 91:254-259.
5. Robboy S, Anderson M, Russel P. Pathology of the Female Reproductive Tract. Churchill-Livingstone 2002; 808-809.
6. Stafford-Johnson D, Bree R, Francis I, Korobkin M. CT appearance of primary papillary serous carcinoma of the peritoneum. Am J Roentgenology 1998; 171:687-689.
7. Muto M, Welch W, Mok S, Bandera C, Fishbaugh P. Evidence for a multifocal origin of papillary serous carcinoma of the peritoneum. Cancer Res 1995; 55:490-492.
8. Ransom D, Patel S, Keeney G, Malkasian G, Edmonson J. Papillary serous carcinoma of the peritoneum. A review of 33 cases treated with platin-based chemotherapy. Cancer 1990; 66:1091-1094.
9. Zhou J, Iwasa Y, Konishi I, et al. Papillary serous carcinoma of the peritoneum in women. A clinicopathologic and immunohistochemical study. Cancer 1995; 76:429-436.
10. Kurman R. Blaustein's Pathology of the Female Reproductive Tract, 4th ed., Springer-Verlag New York, Inc. 1994; 119-121.
11. Ordonez N. Role of immunohistochemistry in distinguishing epithelial peritoneal mesotheliomas from peritoneal and ovarian serous carcinoma. Am J Surg Pathol 1998; 22(10):1203-1214.
12. ESMO Minimum Clinical Recommendations for Diagnosis, Treatment, and Follow-up of Cancers of Unknown Primary Site. Ann Oncol 2001; 12:1057-1058.
13. Menzin A, Aikins J, Wheeler J, Rubin S. Surgically documented responses to paclitaxel and cisplatin in patients with primary peritoneal carcinoma. Gynecol Oncol 1996; 62:55-58.
14. Garrett A, Ng S, Muto M, et al. ras gene activation and infrequent mutation in papillary serous carcinoma of the peritoneum. Gynecol Oncol 2000; 77:105-111.
15. Nishimura M, Masato W, Hashimoto T, et al. Papillary serous carcinoma of the peritoneum: Analysis of clonality of peritoneal tumors. Gastroenterol 2000; 35:540-547.
16. Piver M, Jishi M, Tsukada Y, Navas G. Primary peritoneal carcinoma after prophylactic oophorectomy in women with a family history of ovarian cancer. A rreport of the Gilda Radner familial ovarian cancer registry. Cancer 1993; 71:2751-2755.
17. Wall J, Mandrell B, Jenkins III J, Smiley L, Pratt C. Effectiveness of paclitaxel in treating papillary serous carcinoma of the peritoneum in an adolescent. Am J Obstet Gynecol 1995; 172: 1049-1052.
18. Weir M, Bell D, Young R. Grade 1 peritoneal serous carcinomas: A report of 14 cases and comparison with 7 peritoneal serous psammocarcinomas and 19 peritoneal serous borderline tumors. Am J Surg Pathol 1998; 22(7):849-862.
19. Eltabbakh G, Werness B, Piver S, Blumenson L. Prognostic factors in extraovarian primary peritoneal carcinoma. Gynecol Oncol 1998; 71:230-239.
20. Fishman D, Chilukuri K, Stack S. Biochemical characterization of primary peritoneal carcinoma cell adhesion, migration, and proteinase activity. Gynecol Oncol 1997; 67:193-199.