A Comparison of the Feasibility and Safety of Nerve-sparing Radical Hysterectomy with the Conventional Radical Hysterectomy

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Objective: This retrospective study was conducted to compare the nerve-sparing with the conventional radical hysterectomy in terms of feasibility and safety, including bladder dysfunction, peri- and post-operative complications, and morbidities associated with both procedures. **Methods**: Patients with cervical carcinoma-in-situ, cervical carcinoma stage IA-IB1 or IIA disease, or with central tumor recurrence or persistence after primary radiotherapy, and endometrial carcinoma with cervical involvement treated with radical hysterectomy with or without nerve-sparing technique from January 2002 until July 2007 were included in the study. The peri-operative and postoperative complications and bladder function of these patients were analyzed. **Results**: Ninety-seven patients with cervical cancer and 24 patients with endometrial cancer were subjected to radical hysterectomy with or without nerve-sparing technique in a non-randomized fashion. There was no statistically significant difference between the two procedures in terms of duration of surgery, intraoperative blood loss, duration of hospitalization and morbidity. Patients who underwent the nerve-sparing approach had a statistically significant earlier return of bladder function, with a mean of 9.4 days for the cervical cancer cases (versus 21 days in the non-nerve-sparing group, p=0.01) and a mean of 8.5 days for the endometrial cancer cases (versus 22.6 days in the non-nerve-sparing group, p=0.01). **Conclusion**: The technique of sparing the pelvic autonomic nerves during radical hysterectomy is comparable to the conventional method in terms of peri-operative complications and morbidity, but is superior to it in terms of return of bladder function.

Key words: radical hysterectomy, nerve-sparing radical hysterectomy, bladder dysfunction

Radical hysterectomy has been the treatment of choice for early stage cervical carcinomas for more than a century, with 5-year overall survival rates of more than 80%.[1] Historically, the development of the basic technique was credited to Ernst Wertheim (1898) after he extensively described the different steps of the procedure. Joe Meigs in 1951 extended the radicality of the hysterectomy and included routine pelvic lymphadenectomy in the technique. Although accepted as a standard of care for stage IB-IIA cervical carcinoma, the practice was associated with significant late complications, including bladder dysfunction, sexual dysfunction and colorectal motility disorders that could persist even beyond the first postoperative year.[1] Changes in the way radical surgery is viewed have led to the idea that benefits from oncological surgery must not be evaluated solely in terms of disease control, but also by the functional end results that may affect the patient's quality of life.

Since its introduction in gynecologic oncology, a number of modifications of the original radical hysterectomy have been proposed, with the aim of enhancing the feasibility of the procedure, improving cure rate, and decreasing postoperative complications. Clinical and anatomical studies have identified the pelvic autonomic nerves as the pathway responsible for maintaining neurogenic control of the urinary, anorectal and genital systems. The concept of identification and preservation of the pelvic autonomic nerves was first introduced by the Japanese gynecologists beginning with Kobayashi in the 1960s, more popularly known as the nerve-sparing radical hysterectomy. Subsequently, several other authors developed techniques for nerve sparing which attempt to maintain the full radicality of the operation. All of these procedures have in common the preservation of the autonomic nerves traversing the caudal lateral portion of the uterosacral, cardinal and vesicovaginal ligaments in order to maintain bladder function.

Preliminary feasibility studies on the nerve-sparing radical hysterectomy conducted worldwide demonstrated promising results in terms of preventing early bladder dysfunction[4,5,6,7] without compromising oncological radicality and cure[8], such that the authors proposed that this technique of radical hysterectomy deserves consideration in the quest to improve quality of life among cervical cancer patients.[7] Owing to its recent introduction in gynecologic oncology practice, only one report has been published in literature which compared the nerve-sparing technique with the conventional approaches. In their study, Raspagliesi, et al. (2006) found that the Type III nerve-sparing radical hysterectomy technique has an equal morbidity rate but is superior to the conventional Type III radical hysterectomy in terms of preventing early bladder dysfunction.[9]

Locally, a preliminary feasibility analysis of the first 20 patients who underwent a nerve-sparing radical hysterectomy in a tertiary gynecologic oncology center was conducted.[10] The authors found encouraging results, consistent with those reported in foreign literature, with better quality of life in terms of bladder function, without sacrificing the radicality of the procedure. To date, no study has yet been conducted in the local setting that directly compares the conventional abdominal radical hysterectomy with the nerve-sparing technique.

This retrospective study was conducted to evaluate and compare the nerve-sparing radical hysterectomy with the traditional radical abdominal hysterectomy in terms of incidence of bladder dysfunction and peri- and post-operative complications and morbidities.

Materials and Methods

Patients with biopsy-proven cervical carcinoma-in-situ, cervical carcinoma stage IA-IB1 or IIA disease, cervical carcinoma with central tumor recurrence or persistence after primary radiotherapy, and endometrial carcinoma with cervical involvement treated surgically with radical hysterectomy with or without nerve-sparing technique from January 2002 until July 2007 were included in the study.

The patients' sociodemographic profile (i.e. age, parity, civil status, smoking history, age at first coitus, number of sexual partners, history of non-monogamous relationship, history of sexually transmitted diseases [STD], use of oral contraceptive pills [OCP], use of barrier methods of contraception, history of abnormal Pap smear) and the characteristics of the tumor (i.e. stage of disease, histologic type, tumor size) were recorded.

Clinical evaluation was performed jointly by a senior gynecologic oncology fellow-in-training, together with a board-certified gynecologic oncology consultant from a tertiary training institution. Preoperative laboratory work-ups included a baseline hemogram, liver and renal function tests, serum electrolytes, urinalysis and chest radiograph. After adequate preoperative clearance, patients underwent radical abdominal hysterectomy with or without nerve-sparing technique, bilateral pelvic lymph node dissection, paraaortic lymph node evaluation (i.e. palpation, sampling or dissection), with or without bilateral salpingooophorectomy.

The operation was without nerve-sparing procedure if the study period was before 2004. Radical hysterectomy with or without bilateral salpingooophorectomy was either the traditional or

the nerve-sparing technique beginning from the year 2004 onwards, with patients non-randomized to each type of surgery. Pelvic lymphadenectomy was routinely included as part of the surgical procedure, except for patients who already received radiotherapy as primary treatment. Para-aortic lymph node evaluation was likewise performed, and may be in the form of lymph node dissection, sampling, or palpation.

The technique of nerve-sparing radical hysterectomy was based on the anatomical consideration for autonomic nerves innervating the urinary bladder. The surgical technique was modified to spare the nerves at the level of the landmarks referred to below, as described by Raspagliesi, et al. in 2004:[6]

1) During the first step of lymph node dissection, the sympathetic fibers running over the aorta were identified, and the superior and medium hypogastric plexus were detached from the following structures: aorta bifurcation, presacral nodes, and common iliac nodes. (Figure 1) Dissection was carried out cranially to detach the fibers from the para-aortic lymph nodes up to the point at which the inferior mesenteric artery emerges. Then, dissection was done caudally up to the origin of the two hypogastric nerves. The uterosacral ligaments were divided into lateral and medial layers by blunt dissection, and the lateral layer, which contains nerve fibers, is preserved. (Figure 2)

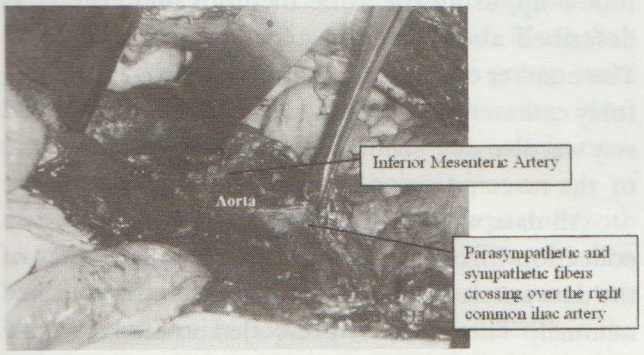


Figure 1. The sympathetic fibers run over the aorta.

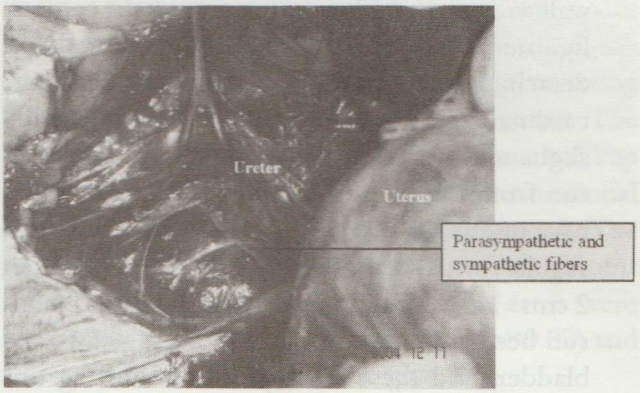


Figure 2.

2) The cardinal ligaments were dissected close to the pelvic side wall. All vascular structures were cut and the loose connective tissue attached to the pelvic side wall was removed radically together with the cardinal ligament.
3) The distal part of the inferior hypogastric plexus runs along the lateral vaginal wall. The ureteral tunnel was developed bluntly after ligation of the uterine artery as it exits the hypogastric artery and the anterior part of the vesicouterine ligament cut. After further dissection of the ureter, the fibers in the lateral vaginal wall were first identified, then the posterior part of the vesicouterine ligament cut. (Figure 3)

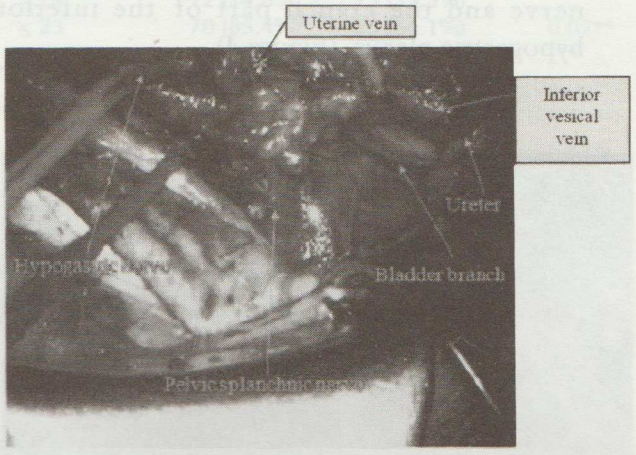


Figure 3.

(4) After dissecting the anterior parametrium, the nerve fibers that run along the lateral vaginal

wall were identified and resection of the cardinal ligaments from the paracolpium was done, detaching it from the vaginal fornix. Then, the cardinal ligament was pulled up, maintaining slight tension on it to uncover the fibers that run from the inferior hypogastric plexus to the base of the bladder. The nerve fibers along the vaginal fornix were gently moved down for about 2 cms. Nerve fibers from the hypogastric plexus run beside the lateral wall of the vagina to the bladder, and these were preserved during this step in surgery, restricting the level of colpectomy to 2 cm below the cervix, instead of resecting the cranial half of the vagina. (Figure 3)

5) The hypogastric nerve and the initial part of the inferior hypogastric plexus are situated in the lateral part of the uterosacral ligament. During dissection of the uterosacral ligament and rectal pillars and after incision of the peritoneum of the Douglas pouch, the prerectal space was developed by blunt dissection. The uterosacral ligament between the prerectal and the pararectal spaces was identified, and the medial uterosacral ligament separated from the lateral nervous fibers. The medial ligaments were resected, while the lateral part was saved. This maneuver preserved the terminal part of the hypogastric nerve and the cranial part of the inferior hypogastric plexus. (Figure 4)

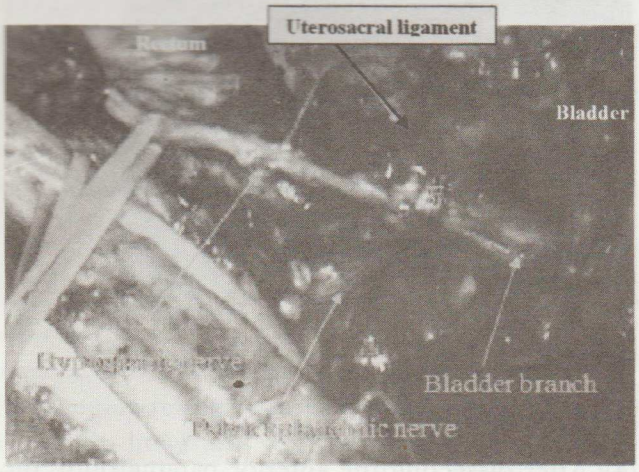


Figure 3.

Pelvic lymphadenectomy consisted of removal of all fatty lymph-node bearing tissue anterior, lateral and posterior to the common, external and internal iliac vessels, as well as the tissues anterior and lateral to the obturator nerve. Para-aortic lymph node dissection was optional, and consisted of removal of all fatty lymph-node bearing tissues anterior to the abdominal aorta and inferior vena cava, up to the emergence of the inferior mesenteric artery and the crossing of the third part of the duodenum over the aorta. All surgeries were performed by a senior gynecologic oncology fellow-in-training or a board-certified gynecologic oncologist.

The duration of the surgery, intraoperative blood loss, need for blood transfusion, number of blood products transfused, and peri- and post-operative complications were recorded.

Postoperatively, patients who underwent a nerve-sparing radical hysterectomy were tested for return of bladder function 72 hours after surgery. At this time, the foley catheter was removed, and the first two spontaneously voided urine as well as the post-void residual urine volumes were taken and recorded in milliliters. Bladder function was considered normal if the post-void residual urine volume was $\leq$ 30 percent of the spontaneous voided urine output. Residual urine amounting to more than 30 percent of the total urine volume after the patient's second spontaneous voiding was an indication for re-insertion of the indwelling catheter. In such cases, the residual urine volume was assessed weekly until the post-void residual urine volume was within 30 percent of the voided urine output. Patients who underwent the conventional radical hysterectomy were tested for residual urine on their first outpatient follow-up, using the same methods and criteria as described above for the nerve-sparing approach. The number of days required to retain the indwelling foley catheter was recorded. The length of hospital stay was also documented. Pathologic characteristics of the resected tissues were also noted.

All data were collected using a pilot tested data collection form. The completeness and accuracy of the data entered in the form were randomly checked manually. The data were pre-coded entered to digital format using MS Excel software. The digital data was checked for range and randomly correlated with

the data collection form to check for keystroke error. Descriptive statistics like mean, standard deviation, frequency observation and percentages were used for the general description of the sociodemographic profile of patients and the tumor characteristics of the patients included in the analysis. An independent t-test, chi-square analysis and test of proportion were employed to determine differences in the distribution of sociodemographic profiles and tumor characteristics of patients who underwent either of the two techniques of radical hysterectomy.

The perioperative complications, including the duration of surgery, blood loss, and the length of indwelling catheter and hospital stay were analyzed using either a test of proportion, or an independent t-test to determine difference between the means.

Results

A total of 247 patients underwent radical hysterectomy at the gynecologic oncology unit of a tertiary institution from January 2002 until July 2007. Nerve-sparing technique was employed in 45 of these cases, while the rest (202 patients) underwent the traditional radical abdominal hysterectomy. Unfortunately, almost half of the patients' inpatient and outpatient records were irretrievable and unavailable for review, so that only 82 patients from the conventional radical hysterectomy group and 39 from the nerve-sparing radical hysterectomy group were evaluable and included in the analysis.

The patients' sociodemographic and clinical profiles are summarized in Table 1. The mean age of patients in the conventional group was 47.8 (SD 10.6) with a range of 25-73 years old. The mean age of patients in the nerve-sparing group was 47.7 (SD 9.8) with a range of 29-62 years old. More than half of women belonging to either group were married, and had 1 to 5 obstetrical deliveries. Most patients were non-smokers. Approximately two-thirds had their first coitus beginning at an age of 23 or earlier. Majority had only a single partner with a history of promiscuity in only 33-37% of cases. The prevalence of sexually transmitted diseases was likewise low in this population (1.2 and 5.1% in the conventional and nerve-sparing groups, respectively). Oral contraceptive use beyond 5 years was not popular, comprising less than 10 percent in either group of population. On the other hand, the use of barrier methods is frequent, approximating 80 percent of patients in both treatment arms. The incidence of an associated history of abnormal Pap smear was small as well (6.1% in the conventional group and 25.6% in the nerve-sparing group). The sociodemographic factors which showed significant differences between the two treatment arms were civil status (p=0.02), age at first coitus (p=0.02) and a history abnormal Pap smear (p=0.01).

Table 1. Sociodemographic and clinical profile of patients included in the study.

	Radical Hysterectomy (n=82)	Nerve-sparing Radical Hysterectomy (n=39)	p value
Mean age	47.8 (SD 10.6)	47.7 (SD 9.8)	0.93*
Parity			
0	3 (3.6%)	5 (12.8%)	
1-5	62 (75.6%)	30 (76.9%)	
≥ 6	15 (18.3%)	4 (10.3%)	0.11**
Civil status			
Married	51 (62.2%)	25 (64.1%)	
Widow/separated	26 (31.7%)	6 (15.4%)	
Single	5 (6.1%)	8 (20.5%)	0.02**
Smoking	17 (20.7%)	5 (12.8%)	0.29***
Age at first coitus			
≥ 24	12 (14.6%)	13 (33.3%)	
≤ 23	70 (85.4%)	25 (64.1%)	0.02**
Number of sexual partners			
Single	51 (62.2%)	26 (66.7%)	
Multiple	31 (37.8%)	12 (30.8%)	0.64**
Non-monogamous sexual relationship	31 (37.8%)	13 (33.3%)	0.63***
History of STD	1 (1.2%)	2 (5.1%)	0.19***
Use of OCP			
Never	50 (61.0%)	17 (43.6%)	
≤ 5 years	26 (31.7%)	17 (43.6%)	
> 5 years	6 (7.3%)	3 (7.7%)	0.29**
Barrier use	64 (78.0%)	30 (76.9%)	0.89***
Abnormal pap smear	5 (6.1%)	10 (25.6%)	0.01***

* independent t-test
** chi-square with correction
*** test of proportion

The characteristics of the tumors are presented in Table 2. The mean diameter of the cervical mass in the conventional radical hysterectomy group was 2.5 cm (SD 1.4), while that in the nerve-sparing group was 2.1 cm (SD 1.5). Approximately 90 percent of the patients in both groups had invasive disease, with more than half of the cases having squamous cell histology. There were no significant differences between the nerve-sparing and the conventional technique of radical abdominal hysterectomy in terms of tumor size, stage of disease and histologic subtype of the patients included in either group.

Table 2. Tumor characteristics.

	Radical Hysterectomy (n=82)	Nerve-sparing Radical Hysterectomy (n=39)	p value
Tumor size (cm)	2.5 (SD 1.4)	2.1 (SD 1.5)	0.15*
Histology			
CIN/CIS	0	1 (2.6%)	
SCCA	43 (52.4%)	20 (54.3%)	
Cervical adenoCA	22 (26.8%)	8 (20.0%)	
Endometrial adenoCA	14 (17.1%)	10 (25.7%)	
Others	3 (3.7%)	0	0.51**
Stage of Cervical Cancer			
Pre-invasive	0	1 (3.4%)	
Micro-invasive	1 (1.5%)	1 (3.4%)	
Invasive	61(91.0%)	27 (93.2%)	
Post-RT	5 (7.5%)	0	0.18**

*independent t-test
**chi-square with correction

Comparison between the conventional and nerve-sparing procedures performed for patients with cervical carcinoma is depicted in Table 3. The mean duration of surgery was 240.2 minutes (SD 51.7) in the former, and 224.1 minutes (SD 71.6) in the latter. This difference was not statistically significant (p=0.25). The mean blood loss was 840.6 cc (SD 415.2) and 739.3 cc (SD 309.5) in the conventional and nerve-sparing radical hysterectomy, respectively. There was likewise no significant difference between the two (p=0.24). The procedures were also comparable in terms of the need for blood transfusion (p=0.65) and the number of blood products transfused (p=0.61).

Table 3. Results for cervical cancer patients.

	Radical Hysterectomy (n=68)	Nerve-sparing Radical Hysterectomy (n=29)	p value
Duration of surgery (minutes)	240.2 (SD 51.7)	224.1 (SD 71.6)	0.25*
Morbidity	8 (14.8%)	4 (14.8%)	1.00***
Estimated blood loss (mL)	840.6 (SD 415.2)	739.3 (SD 309.5)	0.24*
Need for BT	30 (57.7%)	17 (63.0%)	0.65***
Number of blood products transfused	1.9 (SD 0.7)	2.0 (SD 0.9)	0.61*
Number of days with catheter	21.0 (SD 7.0)	9.4 (SD 8.8)	0.01*
Number of days in the hospital	4.6 (SD 2.6)	4.3 (SD 1.5)	0.58*

* independent t-test
*** test of proportion

With regards to bladder function, the patients who underwent a conventional radical hysterectomy required a statistically significantly longer time for an indwelling foley catheter, with a mean of 21.0 days (SD 7.0), compared to those who underwent a nerve-sparing approach and required only a mean of 9.4 days (SD 8.8) (p=0.01).

The incidence of peri-operative morbidity was similar between the two groups (p=1.0). These included 4 cases of febrile morbidity, 3 cases of surgical site infection, a case each of bowel injury, acute pyelonephritis, and metabolic complication in the conventional radical hysterectomy. On the other hand, patients in the nerve-sparing group experienced febrile morbidity, 2 incidences of surgical site infection, and one pulmonary embolism.

Nevertheless, the length of hospital stay was comparable (p=0.58).

Meanwhile, comparison between the conventional and nerve-sparing procedures performed for patients with endometrial carcinoma is shown in Table 4. The mean duration of surgery was 251.9 minutes (SD 30.2) for the conventional technique, and 223.2 minutes (SD 69.3) for the nerve-sparing approach. This difference was not statistically significant (p=0.19). In addition, the mean blood loss was 746.4 cc (SD 316.5) in the former, and 590.0 cc (SD 242.4) in the latter, respectively. There was likewise no significant difference between the two (p=0.20). Despite this, there was note of a greater need for blood transfusion among patients who underwent the conventional radical hysterectomy (p=0.03). Nevertheless, the two procedures were still similar in terms of the number of blood products transfused (p=0.44).

Parallel to the patients with cervical carcinoma, those with endometrial carcinoma with cervical extension who underwent a nerve-sparing radical hysterectomy had a statistically significantly shorter duration of bladder recovery, requiring a mean of 8.5 days (SD 9.0) for an indwelling catheter, compared to a mean of 22.6 days (SD 5.8) for the non-nerve-sparing group (p=0.01).

Peri-operative morbidity was comparable between the two groups (p=0.94), which included 4 cases of febrile morbidity, and a case each of surgical site infection, bowel injury, obturator nerve injury, inferior vena cava injury and acute pyelonephritis among the patients who underwent the conventional radical hysterectomy. Meanwhile, those in whom a nerve-sparing approach was performed experienced febrile morbidity, surgical site infection and an inferior vena cava injury. Nevertheless, the length of hospital stay was comparable (p=0.63).

Histopathologic characteristics of the resected tissues are shown in Table 5. Almost half of the tumors from both treatment arms had more than one-third invasion of the cervical stroma. Less than 5% of cases from either group had tumor in the parametria and vaginal cuff. There was likewise no statistically significant difference between the conventional and nerve-sparing radical abdominal hysterectomy in terms of depth of cervical stromal invasion and tumor infiltration into the parametria and vaginal cuff.

Table 4. Results for endometrial cancer patients.

	Radical Hysterectomy (n=14)	Nerve-sparing Radical Hysterectomy (n=10)	p value
Duration of surgery (minutes)	251.9 (SD 30.2)	223.2 (SD 69.3)	0.19*
Morbidity	4 (30.8%)	3 (30.0%)	0.94
Estimated blood loss (mL)	746.4 (SD 316.5)	590.0 (SD 242.4)	0.20*
Need for BT	11 (84.6%)	4 (40.0%)	0.03***
Number of blood products transfused	1.6 (SD 0.9)	1.2 (SD 0.5)	0.44*
Number of days with catheter	22.6 (SD 5.8)	8.5 (SD 9.0)	0.01*
Number of days in the hospital	4.2 (SD 0.6)	4.4 (SD 1.1)	0.63*

* independent t-test
*** test of proportion

Table 5. Pathologic characteristics of the resected specimen.

	Radical Hysterectomy (n=82)	Nerve-sparing Radical Hysterectomy (n=39)	p value
Depth of invasion ≥1/3	44 (53.6%)	19 (48.7%)	0.61***
Positive vaginal cuff	4 (4.8%)	1 (2.6%)	0.56***
Positive parametria	0	2 (5.1%)	NA

*** test of proportion

Discussion

Early stage cervical carcinoma can be primarily managed adequately with either surgery or

radiotherapy with no significant difference in overall or disease-free survival.[11] The treatment of choice depends on the availability of resources, the attending oncologist, and the age and general condition of the patient.[12] In a developing country such as the Philippines, where resources are low and where radiotherapy facilities, although available, are deemed costly and unaffordable by most patients afflicted with cervical carcinoma, surgery has played a fundamental role in the primary control of the disease.

The performance of radical hysterectomy has been extensively described in literature since Wertheim introduced the procedure in the 19th century.[2] Several modifications to the original technique were adopted through the years, with the aim of improving survival rates. Considerable experience has been gained worldwide, with most oncology centers achieving five-year survival rates of approximately 90% for tumors that are confined to the cervix.[1] In view of these encouraging results, recent improvements in the technique of radical hysterectomy have been devoted to the reduction of complications associated with the procedure. Latest in these developments is the introduction of a nerve-sparing technique aimed at decreasing the incidence of postoperative bladder dysfunction without sacrificing radicality of the procedure or treatment outcomes.

Several authors have described the technique of sparing the pelvic autonomic nerves during radical hysterectomy, and evaluated the feasibility of such procedure in different parts of the world.[4,5,6,7] In the Philippines, a report on the first twenty patients for whom this approach was employed has shown that such technique was indeed feasible, and able to provide better quality of life in terms of bladder function.[10]

Feasibility, however, is not necessarily equivalent to acceptability. Although a growing body of literature has already been published, the adequacy of the procedure in terms of radicality and cure has still been questioned by others. The main concern raised by some authors is that the most lateral and distal part of the parametria might not be removed. Conflicting results on parametrial involvement have been published in the literature. Some authors claim that occult parametrial disease could occur in as high as 13-39 percent of cases.[13,14] Disaia and Creasman, however, have shown that patients with stage IB to IIA disease rarely do have lateral parametrial involvement. Kinney, et al. further demonstrated that parametrial metastases occur in only 3 percent of cervical cancer patients who underwent surgery, and that this incidence drops to zero when the tumor is 3 cm or less. In this study, microscopic examination of the resected specimens showed that the incidence of tumor infiltration into the parametria in the entire study population was 1.7 percent, demonstrating that indeed, parametrial involvement occurs in only a small number of cases and that concerns regarding potential inadequate radical parametrial resection are unfounded.

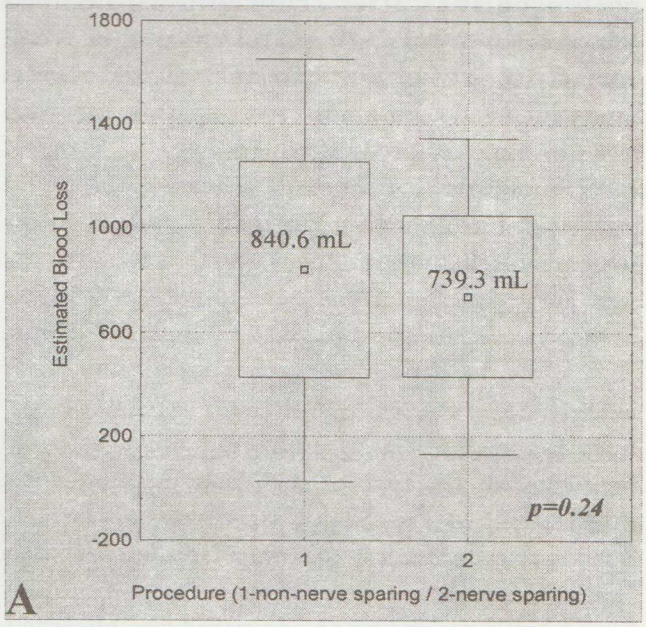
In the nerve-sparing radical hysterectomy, the level of colpectomy has been restricted to 2 cm instead of resecting the cranial half of the vagina. This step is performed in order to preserve the most distal part of the vesicovaginal branch of the inferior hypogastric plexus that courses medially along the lateral vaginal wall to the bladder. Among the 121 patients included in this study, only 5 patients demonstrated tumor involvement of the vaginal cuff with less than 2 cm of tumor-free margin. From these 5 patients, 4 underwent the conventional radical hysterectomy, while only 1 underwent the nerve-sparing approach. This difference however, is not significant ($p=0.56$). In contrast, the systematic nerve-sparing radical hysterectomy technique proposed by Sakuragi, et al. did not strictly adhere to this guideline. They obtained satisfactory results even with a length of the resected vagina ranging from 20 mm to 45 mm. In their series, they concluded that the inability to complete the nerve-sparing procedure does not seem to be affected by the length of the vagina removed. Despite this, if apprehensions exist on the possibility of an inadequate tumor-free vaginal cuff, then strict and appropriate criteria must be employed in selecting patients in whom the nerve-sparing procedure is contemplated.

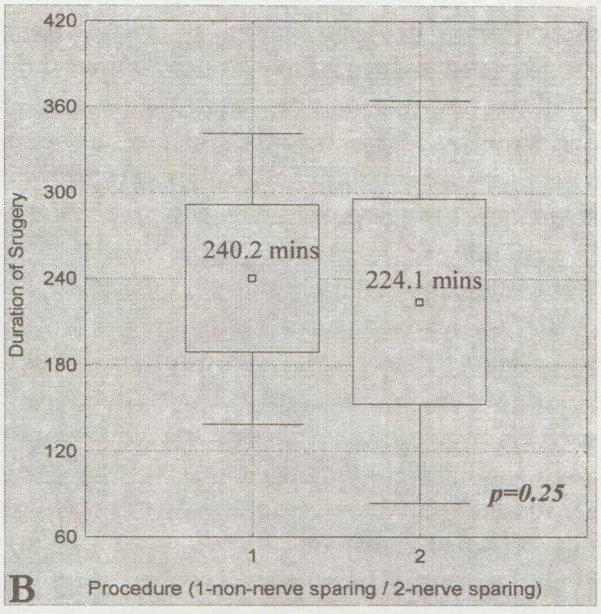
A depth of cervical stromal invasion of at least one-third was identified in about half of the study patients, with an almost equal distribution between the two treatment arms, such that no significant

difference was noted (p=0.61). This shows that either of the two procedures may be employed regardless of how deep the tumor has infiltrated into the cervical stroma. Aside from this, no statistically significant difference in tumor diameter was documented among the cases performed in either technique (p=0.15), suggesting that cervical size is not a limiting factor in the accomplishment of the nerve-sparing technique.

These parameters lend proof to the contention that the preservation of the pelvic autonomic nerves during radical hysterectomy does not compromise the radicality of the procedure since adequate tumor-free margins were obtained from the parametria and vagina, and that the procedure is still feasible regardless of tumor size and depth of cervical stromal infiltration.

What about peri-operative conditions, complications and morbidity? Table 3 and Figures 5A & 5B illustrate a comparison of the non-nerve-sparing and the nerve-sparing techniques among cervical cancer cases in terms of duration of surgery, amount of intraoperative blood loss, need for blood transfusion, as well as the number of blood products transfused. Analysis of all these parameters has shown that the two procedures are comparable. The mean duration of surgery for the non-nerve-sparing radical hysterectomy was 240.2 minutes (SD 51.7) versus a mean of 224.1 minutes (SD 71.6) in the nerve-sparing group (p=0.25). Intraoperative blood loss was likewise similar, with an average of 840.6 mL (SD 415.2) in the conventional approach, as against 739.3 mL (SD 309.5) utilizing the nerve-sparing technique (p=0.24). Corollary to this, there was no significant difference (p=0.65) in the need for blood transfusion between the two treatment arms (57.7% in the former and 63% in the latter). The mean number of blood products transfused in the traditional radical hysterectomy (1.9, SD 0.7) was almost equivalent to that in the nerve-sparing (2.0, SD 0.9) group (p=0.61). These results parallel those obtained by Raspagliesi, et al. (2006) in terms of major perioperative complications.[9] Theirs is the only published study that compared the type II and type III versus the nerve-sparing radical hysterectomy, and found that neither did the nerve-sparing technique entail a significantly longer operative time, nor a significantly higher intraoperative bleeding. Similarly, two other feasibility studies[4,5] mentioned that their nerve-sparing techniques were well within the normal range of their conventional radical hysterectomy surgery.



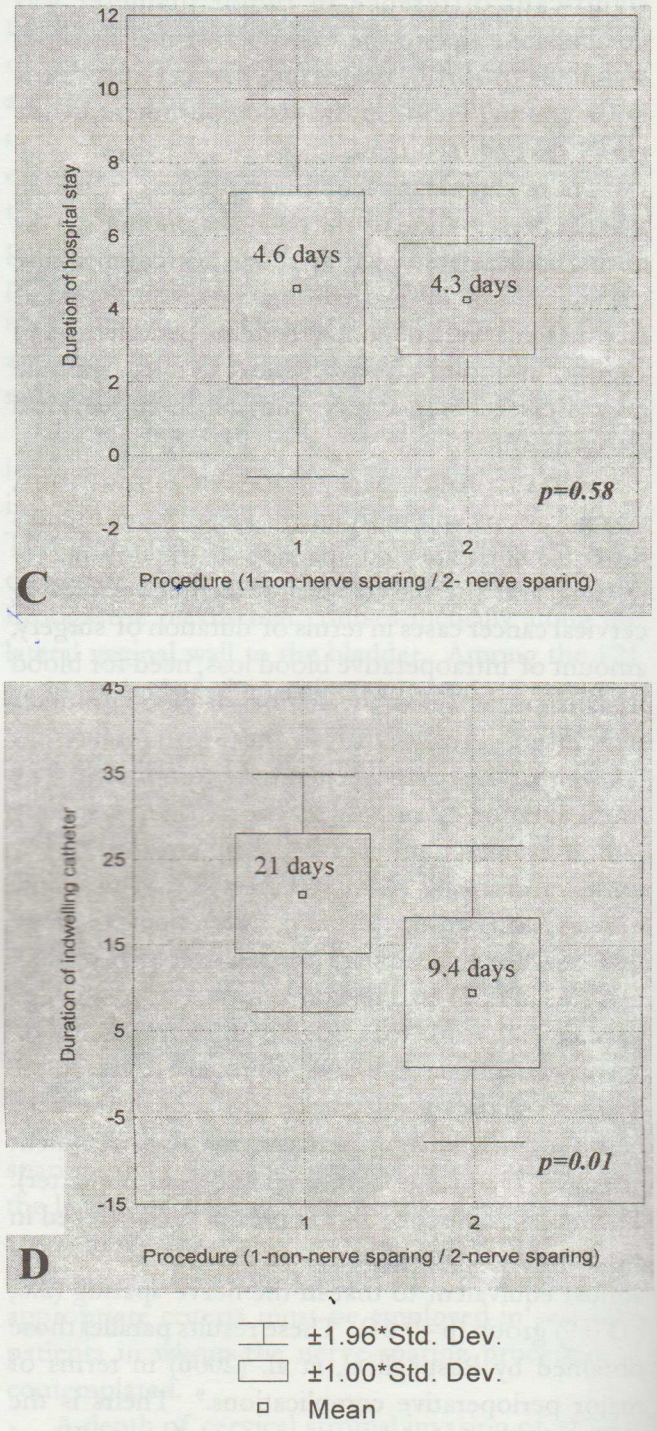


Figures 5A & 5B. Comparison of the different parameters of evaluation between non-nerve sparing and nerve sparing hysterectomy among patients with cervical cancer.

The incidence of postoperative morbidity was also demonstrated to be equivalent between the two techniques (p=1.0). Most of these complications were non-specific and infectious in nature, such as would have occurred after any type of surgical intervention. The patient who had an acute pyelonephritis after conventional radical hysterectomy was adequately managed with administration of intravenous antibiotics. The bowel injury incurred after a non-nerve-sparing approach was promptly repaired intraoperatively. Majority of the complications were easily managed, without a consequent prolongation or significant delay in the patients' discharge from the hospital (4.6 days in the non-nerve-sparing group [SD 2.6] versus 4.3 days in the nerve-sparing group [SD 1.5]) (p=0.58) (Figure 5C). Only the patient who experienced pulmonary embolism required a longer duration of hospitalization. Such phenomenon, however, could happen with any type of malignancy and is not a direct effect of the surgical procedure performed. Such is also the finding in foreign studies[4,9] where a lack of difference in the early grade 3 or 4 morbidity between the groups being compared was observed. However, the authors noted that this finding must be taken with caution since the equivalence among the different procedures may be secondary to a casual variance due to their limited sample size.

Postoperative bladder dysfunction has been consistently identified as the most common long-term complication after a radical hysterectomy, with an incidence ranging from 8 percent to 80 percent.[17] It can manifest itself as an inability to void spontaneously, urinary retention, a decreased force of stream, urinary strain, hesitancy, intermittency, a sense of residual frequency, urgency, incontinence, and nocturia.[6] The pathogenesis of such dysfunction has been said to be multifactorial and may be secondary to direct surgical trauma, subsequent perivesical fibrosis and interruption of the afferent sensory or autonomic motor nerves.[9] Such symptoms can be totally distressing to the patient and may lead to the deterioration in quality of life.

In this study of 97 cervical cancer patients, the length of time needed for an indwelling catheter was significantly shorter (p=0.01) among patients in whom the nerve-sparing technique was employed, with a mean duration of 9.4 days (range 3-36) in the nerve-sparing group, and a mean of 21.0 days (range

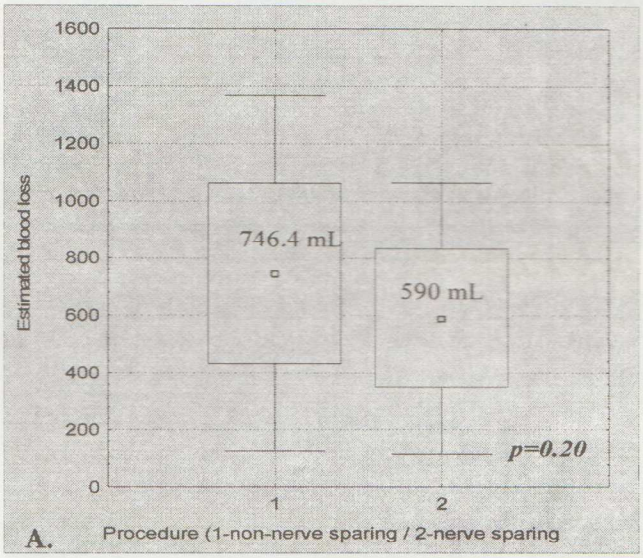


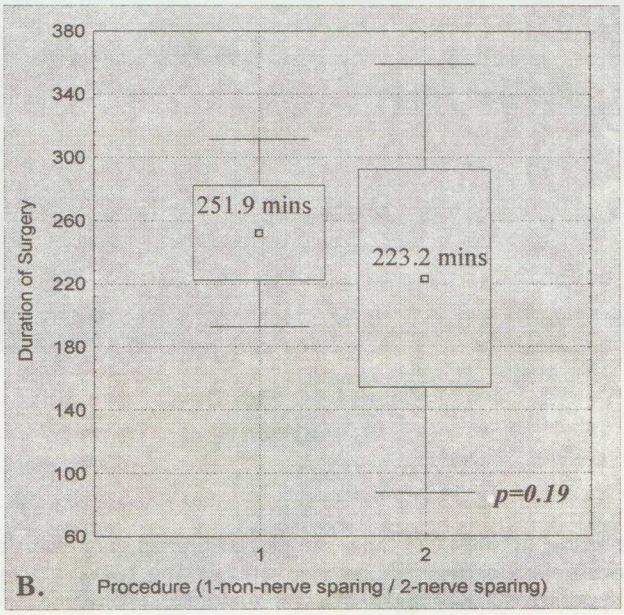
Figures 5C & 5D. Comparison of the different parameters of evaluation between non-nerve sparing and nerve sparing hysterectomy among patients with cervical cancer.

30-43) in the non-nerve-sparing group (Figure 5D). Furthermore, 57 percent of the nerve-sparing patients were discharged with normal spontaneous voiding 3-4 days from surgery. The findings of this study are in accordance with the results of Raspagliesi, et al. (2004) from whom our nerve-sparing technique was adopted.[6] In their study, 65 percent of the patients acquired recovery of spontaneous voiding by the 5th day after the operation. Only a single patient still needed self-catheterization after a month of follow-up. In another feasibility study, Charoenkwan, et al. (2006) demonstrated satisfactory return of voiding function 7 days after their nerve-sparing class III radical hysterectomy, with all patients being able to void spontaneously during the initial catheter removal.[4] In their study, a mean duration of 10.5 days (range 5-26) and 11.27 days (range 5-26) were needed before the patients' post-void residual urine became <100 mL and <50 mL respectively. Although no direct comparison was made with the non-nerve-sparing technique, a historical cohort data in their institution showed that only 66 percent of the patients who underwent the conventional radical hysterectomy were able to resume normal voiding function by the 30th day post-surgery. Additionally, about 8 percent of their patients achieved normal spontaneous voiding between 90 days to 1 year from surgery.

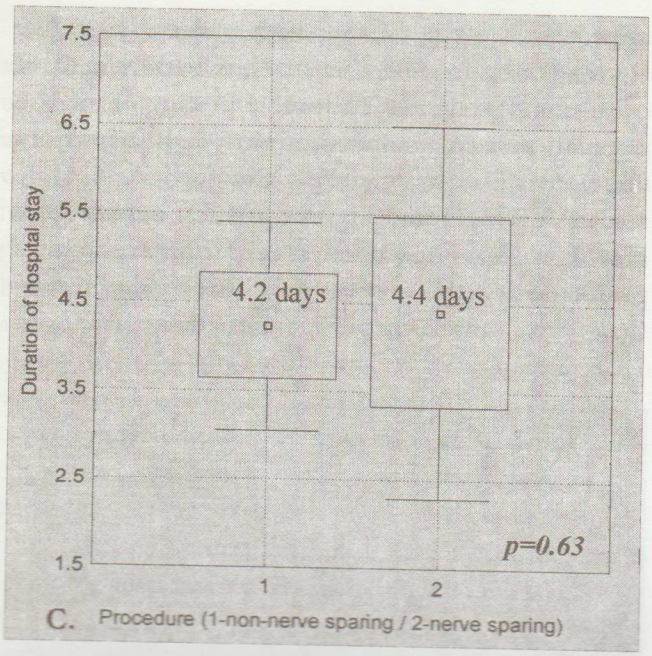
However, the results we obtained are lower than those cited in the only other published literature that directly compares the two procedures. In that series, the nerve-sparing approach was shown to be superior to the type III radical hysterectomy in terms of early bladder dysfunction. Ninety-three percent of the patients in the nerve-sparing group were discharged with spontaneous voiding, compared with 45 percent in the non-nerve-sparing group.[9] This could suggest that there is still much room to improve in the skills of the surgeons in terms of perfecting the technique of sparing the autonomic nerves in order to achieve early optimal return of bladder function.

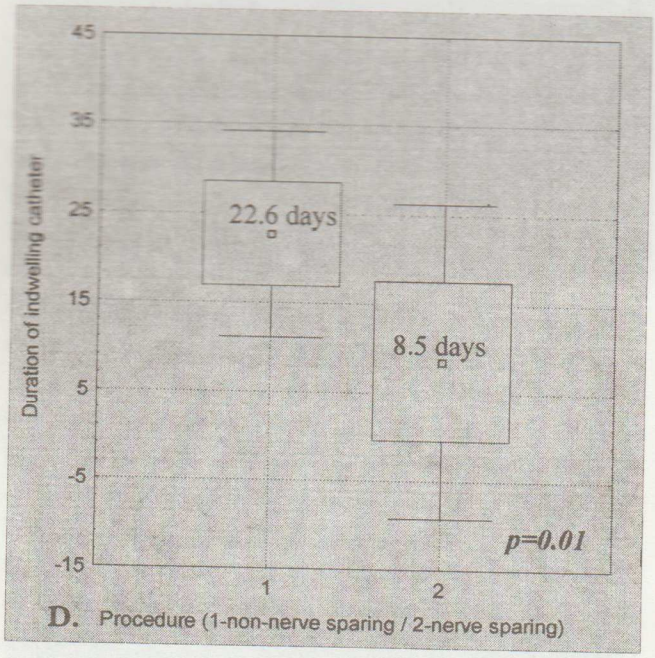
Radical hysterectomy has also been increasingly utilized as primary surgical treatment for endometrial carcinoma patients whose disease has spread into the cervix. In the Philippine setting, where radiotherapy facilities are available but not affordable, this type of surgery provides an attractive alternative option. In this study, twenty-four cases of clinical stage II endometrial cancer in the population were included, almost half of whom underwent a nerve-sparing technique. A separate analysis (Table 4 and Figures 6A-6D) between the non-nerve-sparing and nerve-sparing techniques performed on this subset of cohort yielded results that were similar as those mentioned above for our





Figures 6A & 6B. Comparison of the different parameters of evaluation between non-nerve sparing and nerve sparing hysterectomy among patients with endometrial cancer.





Figures 6C & 6D. Comparison of the different parameters of evaluation between non-nerve sparing and nerve sparing hysterectomy among patients with endometrial cancer.

cervical cancer cases, with comparable results in terms of duration of surgery (251.9 minutes versus 223.2 minutes, p=0.19), intraoperative blood loss (746.4 mL versus 590 mL, p=0.20), morbidity (30.8% versus 30%, p=0.94), and length of hospitalization (4.2 days versus 4.4 days, p=0.63). Similarly, the number of days required for an indwelling catheter (22.6 days versus 8.5 days, p=0.01) was significantly shorter in favor of the nerve-sparing radical hysterectomy. The only difference lies in a lower need for blood transfusion among the endometrial cancer patients in whom the nerve-sparing technique was employed (84.6% versus 40%, p=0.03). However, it should be noted that the amount of intraoperative blood loss was comparable between the 2 groups. This could suggest that perhaps the choice to administer blood products is subjective and quite lenient in the institution, with the decision usually originating from the anesthesiologist.

In addition, endometrial cancer patients are generally obese, and this factor could present some form of technical difficulty in the performance of the nerve-sparing technique, as suggested by Trimbos, et al. (2001) among their Western patients.[7] Although the study did not take body mass index into consideration, results have shown that such technical difficulty did not pose a hindrance in the adequate performance of the technique, and that the method of preservation of the pelvic autonomic nerves during radical hysterectomy is also feasible among endometrial cancer patients, showing superior results over the conventional approach. However, comparison with foreign literature in this aspect could not be made since the only other published literature which included endometrial cancer patients among their study population involved only a single patient.[4]

In conclusion, the technique of sparing the pelvic autonomic nerves during radical hysterectomy for early stage cervical cancer and clinical stage II endometrial cancer is comparable to the conventional method in terms of peri-operative complications and morbidity, but is superior to it in terms of return of bladder function.

However, it should be noted that several limitations to this study exist, the foremost being its retrospective nature, and is thus non-randomized. Although basically, the patients in each group were well-balanced in terms of sociodemographic and

clinical profile, including factors that could have contributed some form of difficulty in the performance of radical hysterectomy (Tables 1 and 2), theoretically, a prospective randomized trial should still be performed in order to give strength to the conclusions and further validate the results. Also, a separate analysis on the patients who received preoperative radiotherapy, or those who underwent the type II radical hysterectomy was not feasible in this study due to the limited number of cases belonging to either group, and may warrant further investigation. In addition, a urodynamic test can also be done pre- and post-operatively to completely and objectively assess bladder function among all post-radical hysterectomy patients. Furthermore, a follow-up study on the patients included in this analysis could be initiated in order to assess the impact of nerve-sparing radical hysterectomy on progression-free and overall survival rates.

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A Comparison of Different Treatment Modalities for Endometrial Carcinoma with Cervical Involvement

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Objectives: The aim of this retrospective study was to identify preoperative, operative, pathologic, and therapeutic factors that may predict the outcome of Stage II endometrial cancer and to compare the different treatment radical hysterectomy or extrafascial hysterectomy with or without radiotherapy, or primary radiotherapy followed by extrafascial hysterectomy in terms of survival. **Methods**: Ninety-seven women with surgical Stage II endometrial cancer treated at the Philippine General Hospital between January 1995 to December 2006 were reviewed. Data regarding patients' characteristics, surgical procedure, postoperative treatment and complications, and outcomes were recorded. Factors were compared using the one-way ANOVA and the Pearson chi-square tests. The over-all survival curve was constructed using the Kaplan-Meier method. **Results**: Of the 97 cases identified, 14 patients underwent Radical Hysterectomy, Bilateral Salpingooophorectomy (RHBSO) and Bilateral Pelvic Lymphadenectomy alone (15.38%) and comprised Arm I. Fourteen patients underwent Extrafascial Hysterectomy, Bilateral Salpingooophorectomy (EHBSO) and Bilateral Pelvic Lymphadenectomy alone (15.38%) and comprised Arm II, while 61 (67.03%) underwent Extrafascial Hysterectomy, Bilateral Salpingooophorectomy and Bilateral Pelvic Lymphadenectomy followed by Radiotherapy (EHBSO+RT) which comprised Arm III. Primary surgical management included an EHBSO in 84.3 percent of cases and an RHBSO in the remaining 15.7 percent of cases. Stage IIA disease was diagnosed in 34.8 percent of cases, whereas Stage IIB disease was diagnosed in the remaining 65.2 percent. No recurrences were noted in the RHBSO arm while 21.4 percent recurred in the EHBSO alone arm, and 14.7 percent recurred in the EHBSO + RT arm ($p=0.01$). Patients managed with RHBSO had improved five-year overall survival compared with those treated with EHBSO, 85.2% vs 45.3%, $p=0.01$. In those treated with EHBSO, patients treated with adjuvant radiotherapy had a 5-year overall survival rate of 57.9% compared to 38.8% in those who did not receive adjuvant radiotherapy, $p<0.01$. In comparing the 3 treatment arms, RHBSO alone showed a higher 5-year survival rate of 85.2% as compared to 57.9% in the EHBSO + RT arm and 0% in the EHBSO alone arm, and this was statistically significant ($p<0.01$). **Conclusion**: In this retrospective study of surgical Stage II endometrial cancer cases, improved survival was noted in particular with radical hysterectomy compared with extrafascial hysterectomy, with or without radiation therapy.

Endometrial carcinoma is the most common gynecologic malignancy diagnosed in women in the United States. However, in the Philippines, it only ranks 9th among the leading female cancer sites and is the 3rd most common genital tract malignancy, next to cervical and ovarian cancers[1]. Most women with endometrial cancer develop symptomatic bleeding or discharge, facilitating early diagnosis and resulting in an increased opportunity for cure. Since vaginal bleeding is an early symptom of endometrial cancer, at least 75 percent of patients present with stage I disease[2]. Prognosis for Stage 1 disease is favorable and the 5-year survival rate exceeds 90 percent.[3] However, a subset of patients has a poor outcome, including those with high-risk histology, extrauterine disease (Stages III and IV), and involvement of the uterine cervix (surgical Stage II). Stage II implies extension of the endometrial cancer to the endocervical glandular epithelium (IIA) or the cervical stroma (IIB) with negative peritoneal cytology, negative pelvic and para-aortic lymph nodes, and absence of distant metastases, according to the 1988 International Federation of Gynecology and Obstetrics (FIGO) surgical staging system.

Heyman first described cervical involvement in endometrial cancer as an adverse prognostic factor in 1941. The relative rarity of clinical Stage II disease, comprising about 10-15 percent of all endometrial carcinoma, has made its evaluation and treatment analysis difficult.[4] Stage II disease comprise only about 6.5 percent of all endometrial cancer patients seen from 1995-2006 in this tertiary hospital.[5]

Survival rates for endometrial cancer can vary widely, from 100 percent in well selected series such as small, well-differentiated, non-infiltrating and adequately surgically treated tumors to as low as 40 percent in other series with undifferentiated, deeply invading and unfavorable histotypes.[6] Survival of patients with endometrial carcinoma with cervical involvement carries a 5-year survival rate of approximately 64-86 percent.[3,6-9]

Historically, corpus cancer was treated in two ways. For the poor surgical risk patients and the elderly, primary radiotherapy is the treatment of choice. The good surgical risk patient with disease confined to the endometrial cavity was treated with intrauterine radium followed by removal of the uterus, fallopian tubes, ovaries, and vaginal apex. Studies show that 50 percent of post-irradiated hysterectomy specimens contained pathologic evidence of persistent carcinoma, and local recurrent disease was common[7]. Since the change from a clinical to a surgico-pathologic staging system in 1988, it has become increasingly common for patients with early stage endometrial cancer, even those with cervical involvement, to undergo surgery without preoperative radiotherapy. A developing belief that recurrences found in the vaginal canal after surgery were due to retrograde lymphatic dissemination rather than implantation at the time of surgery, coupled with the resurgence of radical dissection of pelvic lymphatics for cervical cancer in the 1950s, prompted adoption of the Wertheim-type hysterectomy and pelvic node dissection for treatment of corpus uteri cancer. Since the routine use of radical hysterectomy was not feasible because of its limited applicability in the elderly uterine cancer population and its high postoperative complication incidence. The combination of radiation therapy followed by conservative hysterectomy found greater usefulness and was deemed the treatment of choice. However, preoperative pelvic radiotherapy can change the histologic appearance and apparent extent of disease found at operation, and clinical assessment of cervical involvement can be inaccurate, predisposing some patients to inadequate surgical therapy or unnecessary radiotherapy. Thus, radical hysterectomy gained favor as an alternative to preoperative radiation for the following reasons: 1) It permits initial operation on patients with suspected cervical involvement; 2) It allows accurate staging of disease; and 3) It offers wide excision of the primary tumor and regional nodes.[7]

Due to its relative rarity, well-designed randomized controlled trials are difficult to conduct making the ideal management controversial. Although there is a general agreement about the usefulness of staging and primary surgery in endometrial cancer, there exist significant differences in therapeutic approach to FIGO stage II disease. Treatment options range from extrafascial hysterectomy before or after radiation therapy to primary radical hysterectomy. Several retrospective

studies have been done to compare the different treatment modalities and such reviews have indicated that each treatment plan may be a reasonable option for specific patient subsets.

The aim of this retrospective study is to compare the different treatment approaches in terms of survival after radical hysterectomy or extrafascial hysterectomy with or without radiotherapy, or primary radiotherapy followed by extrafascial hysterectomy. It is also the goal to try to identify preoperative, operative, pathologic, and therapeutic factors that may predict the outcome of Stage II endometrial cancer.

Materials and Methods

Patients with endometrial carcinoma FIGO surgical stage II disease (positive cervical involvement) on final histopathology seen at the Philippine General Hospital from January 1995 to December 2006 were included in the study. The inpatient and outpatient records were retrieved. The demographic and clinical data were recorded in a case registry form (Appendix 1) and subsequently encoded to an MS Excel database. Encoded data included patient age, gravidity, parity, past medical and family medical histories, body mass index (BMI), surgical procedure performed, intraoperative and postoperative complications, histopathologic findings, adjuvant treatment given, and disease-free duration.

Patients who met the inclusion criteria were then categorized into 4 arms according to the primary treatment received: Arm I – Radical Hysterectomy, Bilateral Salpingooophorectomy and Bilateral Pelvic Lymphadenectomy alone; Arm II – Extrafascial Hysterectomy, Bilateral Salpingooophorectomy and Bilateral Pelvic Lymphadenectomy alone; Arm III – Extrafascial Hysterectomy, Bilateral Salpingooophorectomy and Bilateral Pelvic Lymphadenectomy and Arm IV – preoperative radiotherapy followed by surgery. Radiotherapy included the following: pelvic external beam radiotherapy (EBRT), vaginal brachytherapy, extended field radiotherapy (EFRT) or any combination of the aforementioned.

Data encoded were analyzed using the one-way ANOVA and the Pearson chi-square tests. The overall survival curve was constructed using the Kaplan-Meier method. A *p value* of < 0.05 was considered statistically significant.

Results

A total of 97 patients diagnosed with endometrial carcinoma with cervical involvement seen at tertiary hospital from 1995-2006 were reviewed. Of the 97 cases identified, 20 patients underwent RHBSO but 6 were excluded since they received adjuvant radiotherapy. Therefore, 14 (15.38%) comprised Arm I. Fourteen patients (15.38%) also comprised Arm II, 61 (67.03%) comprised Arm III and 2 (2.20%) comprised Arm IV. The 2 patients who underwent preoperative radiotherapy had no evidence of disease with a mean of 70 months. Since only 2 patients underwent preoperative radiotherapy, Arm IV was not included in the final analysis anymore. Thus, comparative analysis was performed only on Arms I, II and III.

Demographic and clinical characteristics of patients included in the study are depicted in Table 1. There was no statistically significant difference in most of the demographic and clinical characteristics among the treatment arms except for the gravidity (Arm I = 4.3 $\pm$ 3.1, Arm II = 4.4 $\pm$ 3.0, Arm III = 2.3 $\pm$ 2.5, p = 0.01) and parity (Arm I = 4.0 $\pm$ 2.9, Arm II = 4.1 $\pm$ 2.9, Arm III = 2.0 $\pm$ 2.2, p = 0.01).

Primary surgical management included an Extrafascial Hysterectomy in 84.3 percent of cases and a Radical Hysterectomy in the remaining 14 (15.7%) cases. The radical hysterectomies performed were all Wertheim-Meigs abdominal hysterectomy (Type III). All patients who underwent Radical Hysterectomy had either pelvic and/or para-aortic nodal dissection and all nodes were negative. In patients who underwent Extrafascial Hysterectomy, 79 percent had pelvic and/or para-aortic nodal dissection. Stage IIA disease was diagnosed in 34.8 percent of cases, whereas Stage IIB disease was diagnosed in the remaining 65.2 percent. The mean operative time for Radical Hysterectomy is 4 hours and 30 minutes, and 2 hours and 30 minutes for

Extrafascial Hysterectomy, the difference of which is statistically significant ($p \leq 0.01$). The mean estimated blood loss for the Radical Hysterectomy group is 1,000 mL and 500 mL for Extrafascial Hysterectomy and the difference of which is also statistically significant ($p \leq 0.01$) (Table 2).

Table 1. Demographic and clinical characteristics of patients included in the study.

Characteristics	RHBSO (n=14)	EHBSO (n=14)	EHBSO + RT (n=61)	p value
Mean Age	50.6 (SD 10.5)	51.0 (SD 9.5)	49.5 (SD 10.7)	0.86*
Gravidity	4.3 (SD 3.1)	4.4 (SD 3.0)	2.3 (SD 2.5)	0.01*
Parity	4.0 (SD 2.9)	4.1 (SD 2.9)	2.0 (SD 2.2)	0.01*
Past Medical History				
HPN	2 (14.3%)	6 (42.9%)	15 (24.6%)	
DM	2 (14.3%)	1 (7.1%)	3 (4.9%)	
Others	3 (21.4%)	0	5 (8.2%)	0.25**
Family Medical History				
HPN	1 (7.1%)	5 (35.7%)	23 (37.7%)	
DM	3 (21.4%)	1 (7.1%)	6 (9.8%)	
Others	5 (35.7%)	2 (14.3%)	15 (24.6%)	0.40**
Smoking	2 (14.3%)	0	5 (8.2%)	0.30*
OCP Use	2 (14.3%)	1 (7.1%)	10 (16.4%)	0.54*
Weight	61.2 (SD 8.9)	58.1 (SD 9.0)	60.5 (SD 11.7)	0.73*
Height	1.5 (SD 0.1)	1.5 (SD 0.1)	1.5 (SD 0.1)	0.17*
BMI	25.3 (SD 3.1)	25.7 (SD 5.3)	25.6 (SD 4.7)	0.97*
Systolic blood pressure	124.3 (SD 12.2)	127.8 (SD 9.7)	126.4 (SD 14.7)	0.78*
Diastolic blood pressure	76.4 (SD 8.4)	82.1 (SD 9.7)	76.2 (SD 9.0)	0.08*
Chief Complaint				
Vaginal bleeding	12 (85.8%)	10 (71.4%)	39 (63.9%)	
Vaginal discharge	1 (7.1%)	0	7 (11.5%)	
Menstrual irregularity	1 (7.1%)	3 (21.4%)	14 (22.9%)	
Hypogastric pain	0	1 (7.1%)	1 (1.6%)	0.26**

*One-way ANOVA
**Pearson chi-square

Table 2. Procedural differences done among patients included in the study.

Characteristics	RHBSO (n=14)	EHBSO (n=14)	EHBSO + RT (n=61)	p value
OR Time	274.3 (SD 23.1)	156.4 (SD 24.1)	164.3 (SD 30.8)	<0.01
Estimated Blood Loss	1,021.4 (SD 257.7)	478.6 (SD 125.1)	508.2 (SD 117.3)	<0.01
Complications				
Present	0	0	0	
Absent	14 (100.0%)	41 (100.0%)	61 (100.0%)	—

*One-way ANOVA
**Pearson chi-square

The majority of endometrial cancer specimens demonstrated less than 50% myometrial invasion (52.8%) and were of the endometrioid type (92.1%). The histopathologic characteristics such as grade, histologic type, myometrial invasion, cervical glandular or stromal involvement were not statistically significant across the treatment arms (Table 3).

Table 3. Surgico-pathologic characteristics of patients included in the study.

Characteristics	RHBSO (n=14)	EHBSO (n=14)	EHBSO + RT (n=61)	p value
Grade				
1	6 (42.9%)	7 (50.0%)	29 (48.3%)	
2	6 (42.9%)	4 (28.6%)	23 (38.3%)	
3	2 (14.2%)	3 (21.4%)	8 (13.3%)	0.33**
Histologic Type				
Endometrial carcinoma	12 (85.8%)	13 (92.9%)	57 (93.4%)	
Adenosquamous	1 (7.1%)	0	3 (4.9%)	
Clear cell	1 (7.1%)	0	1 (1.6%)	
Papillary serous	0	1 (7.1%)	0	0.22**
Myometrial Involvement				
Superficial	0	0	5 (8.2%)	
Less than 50%	8 (57.1%)	8 (57.1%)	31 (50.8%)	
More than 50%	6 (42.9%)	6 (42.8%)	25 (41.0%)	0.65**
Cervical Involvement				
Glands	6 (42.9%)	6 (42.9%)	19 (31.5%)	
Stroma	8 (57.1%)	8 (57.1%)	42 (68.9%)	0.56**
LVSI				
Positive	2 (14.3%)	2 (14.3%)	2 (3.3%)	
Negative	2 (14.3%)	3 (21.4%)	11 (18.0%)	
Not assessed	10 (71.4%)	9 (64.3%)	48 (78.7%)	0.40**

**Pearson chi-square

At a median follow up of 16 months, twelve patients (13.5%) had experienced disease recurrence and these patients all belonged to the Extrafascial Hysterectomy ± RT arms. Also, 7 patients (7.87%) had experienced radiation complications namely radiation proctitis. Five-year overall survival rate was 53.5% (Figure 1) for the entire group. Most of the demographic and clinical characteristics evaluated failed to predict patient outcome. However, patients managed with Radical Hysterectomy had improved five-year overall survival rates compared with those treated with Extrafascial Hysterectomy at 85.2% vs 45.3% ($p=0.01$), respectively (Figure 2). In those treated with Extrafascial Hysterectomy, patients treated with adjuvant radiotherapy had a 5-year overall survival rate of 57.9% compared to 38.8% ($p < 0.01$) in those who did not receive adjuvant radiotherapy (Figure 3). In comparing the 3 treatment arms, Radical Hysterectomy alone showed a higher 5-year survival rate of 85.2% as compared to 57.9% in the Extrafascial Hysterectomy + RT arm and 0% in the Extrafascial Hysterectomy alone arm ($p<0.01$) (Figure 4).

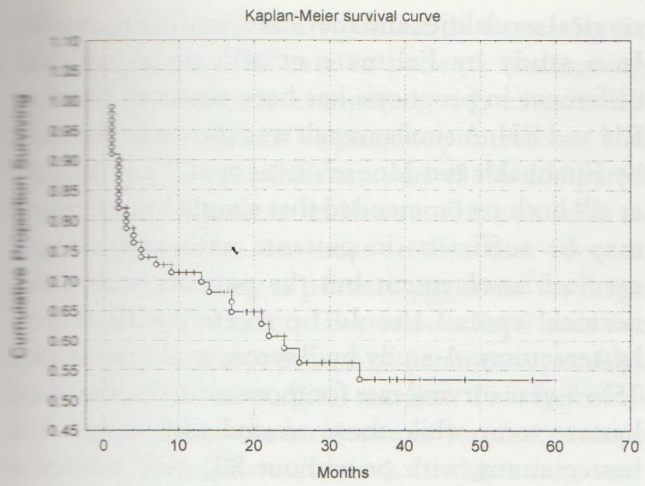

Figure 1. Overall survival curve for all patients included in the study.

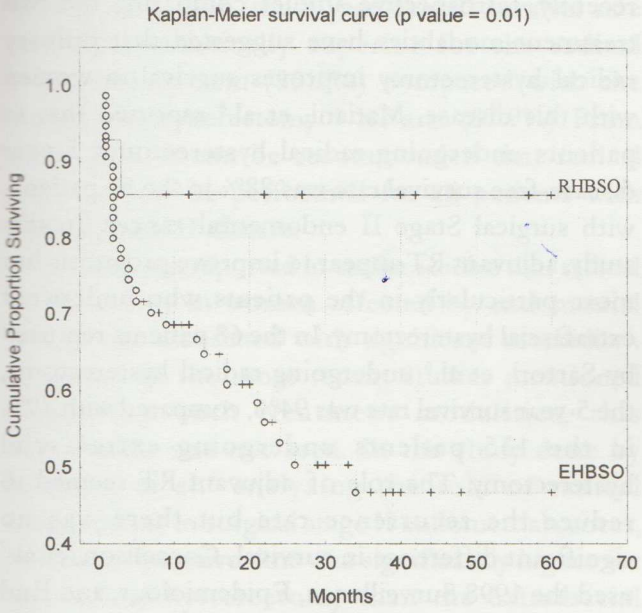

Figure 2. Comparison of survival curve between RHBSO and EHBSO.

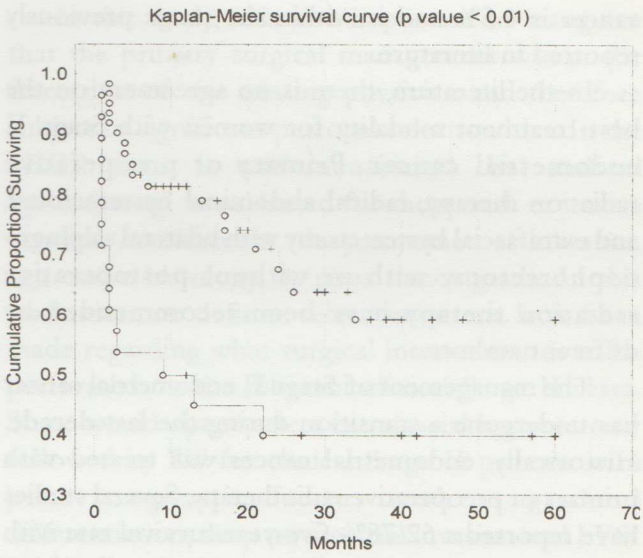

Figure 3. Comparison of survival curve between RT and no RT.

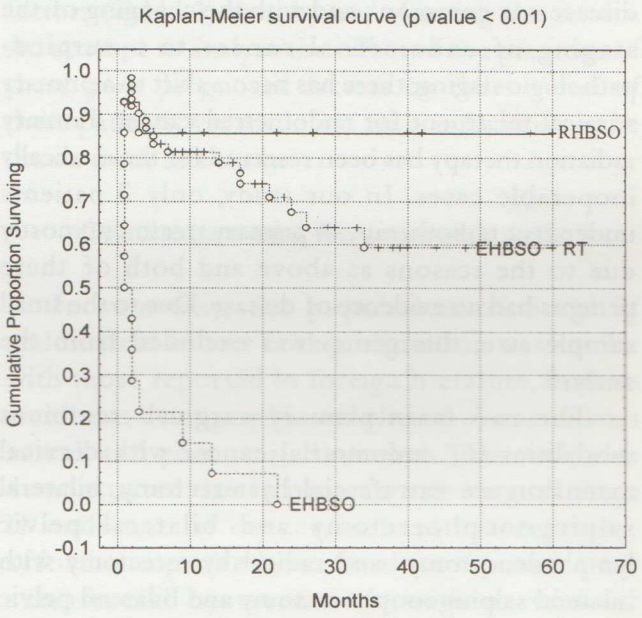

Figure 4. Survival curve per procedure and effect of RT among patients included in the study.

Discussion

Extension of endometrial cancer to the cervix has been recognized as a poor prognostic factor by Heyman, et al. in 1941 but FIGO only incorporated cervical involvement into its staging system and designated cervical involvement as Stage II in 1961. In 1988, FIGO redefined stage of disease on the basis of surgico-pathologic criteria.

The percentage of women with Stage II endometrial cancer reported in several studies ranges from 5-15%.[2-3,6,8-10] In the present study, the percentage of women with Stage II endometrial

cancer is 6.5% and is within the range previously reported in literature.

In the literature, there is no agreement on the best treatment modality for women with Stage II endometrial cancer. Primary or preoperative radiation therapy, radical abdominal hysterectomy, and extrafascial hysterectomy with bilateral salpingo-oophorectomy with or without postoperative radiation therapy have been recommended by different authors.

The management of Stage II endometrial cancer has undergone a transition during the last decade. Historically, endometrial cancer was treated with primary or preoperative radiotherapy. Several studies have reported a 62-78% five-year survival rate with this treatment modality.[11] However, studies have shown that 50 percent of post-irradiated hysterectomy specimens contained pathologic evidence of persistent carcinoma, and local recurrent disease was common[7], and with the changing of the staging of endometrial cancer to a surgico-pathologic staging, there has been a shift to a primary surgical treatment for endometrial cancer. Primary radiation therapy has been reserved for the medically inoperable cases. In our study, only 2 patients underwent radiotherapy as primary treatment mostly due to the reasons as above and both of these patients had no evidence of disease. Due to the small sample size, this group was excluded from the analysis.

The two main primary surgical treatment modalities for endometrial cancer with cervical extension are extrafascial hysterectomy, bilateral salpingooophorectomy and bilateral pelvic lymphadenectomy and radical hysterectomy with bilateral salpingooophorectomy and bilateral pelvic lymphadenectomy. This may be followed by adjuvant radiotherapy depending on the presence of poor prognostic factors. Both of these modalities resulted in a 64-86% five-year survival rate. In this study, extrafascial hysterectomy was performed in 84.3 percent of cases and radical hysterectomy was performed in the remaining 15.7 percent of cases. Of those who underwent Extrafascial Hysterectomy, majority (63.54%) had adjuvant radiotherapy.

Several studies have compared the prognosis of patients with Stage II disease treated with the two surgical modalities and they have conflicting results. In a study by Feltmate et al[12], no significant difference in prognosis has been reported between RH and EH. A similar result was shown in the study by Eltabbakh and Moore[2]. Elia, et al.[13] and Tamura et al[14] both recommended that simple hysterectomy may be sufficient in patients with microscopic cervical involvement but the patients with gross cervical spread should be treated with radical hysterectomy. A study by Boente, et al.[4] reported a 75% 5-year survival rate for those treated with radical hysterectomy while those treated with extrafascial hysterectomy, with or without RT, only showed a 42% 5-year survival rate. Ayhan, et al.[10] also showed a slightly higher survival rate for patients who underwent radical hysterectomy as compared to extrafascial hysterectomy, plus adjuvant RT, but the difference did not reach statistical significance. More recently, retrospective studies comparing the two treatment modalities have suggested that primary radical hysterectomy improves survival in women with this disease. Mariani, et al.[8] reported that in patients undergoing radical hysterectomy, 5-year disease-free survival rate was 88% in the 57 patients with surgical Stage II endometrial cancer. In this study, adjuvant RT appear to improve prognosis but more particularly in the patients who underwent extrafascial hysterectomy. In the 68 patients reported by Sartori, et al.[6] undergoing radical hysterectomy, the 5-year survival rate was 94%, compared with 79% in the 135 patients undergoing extrafascial hysterectomy. The role of adjuvant RT seemed to reduce the recurrence rate but there was no significant difference in survival. Cornelison, et al.[7] used the 1998 Surveillance, Epidemiology, and End Results (SEER) data to determine that the 5-year overall survival rate in 377 patients with surgical Stage II endometrial cancer undergoing radical hysterectomy was 93%, compared with 84% in those undergoing extrafascial hysterectomy, bilateral salpingooophorectomy. Survival for patients who received combination radiation and surgery as primary therapy was 82.77% with extrafascial hysterectomy and 88.02% with radical hysterectomy. The addition of radiation therapy did not carry a significant effect on the overall survival in both treatment modalities. The results of the study by

Galvin, et al.[3] showed a significantly better 5-year disease free survival rate in patients undergoing radical hysterectomy compared with extrafascial hysterectomy, bilateral salpingooophorectomy and bilateral pelvic lymphadenectomy (94% compared with 76%). Adjuvant radiation did not lead to improved survival. In most studies that favored radical hysterectomy as primary treatment for Stage II endometrial cancer, they rationalized that for radical hysterectomy removal of parametria provides more adequate free surgical margins. This approach may have reduced the incidence of local recurrence and possibly improve survival. In this study, very similar results were demonstrated with a significantly better 5-year overall survival rate for the radical hysterectomy arm (85.2%) compared with the extrafascial hysterectomy arm (45.3%). With the addition of adjuvant RT for the extrafascial hysterectomy arm, the 5-year overall survival rate was still statistically superior for the radical hysterectomy arm (85.2%) compared with the extrafascial hysterectomy + RT arm (57.9%). From these data, it can be recommended that radical hysterectomy be performed for all patients with clinical Stage II disease.

It has been reported in earlier studies that radical hysterectomy in women affected by endometrial cancer was associated with significant morbidity[6]. However, in the more recent studies mentioned comparing both treatment modalities, this observation was not seen. In the study done by Mariani, et al.[8] analyzing the role of radical hysterectomy in surgical stage II endometrial cancer, the mean operative time was significantly higher for the radical hysterectomy than the extrafascial hysterectomy group but the mean operative blood loss did not differ statistically between the two groups. This observation is similar to the present study with respect to the mean operative time. However, there is a significantly increased operative blood loss in the radical hysterectomy arm in this study. This could be attributed to the fact that radical hysterectomy was performed by the fellows in training in this institution. There was no increased postoperative complication rate among patients treated with radical hysterectomy compared with those treated with extrafascial hysterectomy.

In this study, it is also important to recognize that the primary surgical management was at the discretion of the treating physician and therefore subject to significant personal selection bias. In the SEER data, it was mentioned that radical hysterectomy was selected for those with extensive cervical involvement, deep myometrial invasion, aggressive histology, or poor tumor grade. In this institution, no definite selection criteria have been made regarding what surgical intervention is to be performed on the different clinical Stage II cases. Some would opt to select extrafascial hysterectomy followed by RT for clinical Stage II patients with poor prognostic factors such as grade 3 differentiation, deep myometrial invasion and LVSI thereby increasing the observed survival of those treated by radical hysterectomy alone. However, the different treatment arms showed homogeneity in terms of the presence of these poor prognostic factors (Table 3) thereby not affecting the results. An attempt to analyze the effect of the presence of these poor prognostic factors on the survival of these patients was made but no conclusions can be drawn from this study.

Conclusions and Recommendations

In summary, the population of Stage II endometrial cancer in this institution was similar with those reported in foreign literature, both in incidence, demographic and clinical characteristics as well as 5-year over-all survival. This study also demonstrated that in patients with surgical Stage II endometrial cancer, radical hysterectomy affords improved survival compared with extrafascial hysterectomy, with or without adjuvant radiotherapy, similar to foreign literature. It is therefore recommended that when cervical involvement is known or highly suspected, radical hysterectomy, bilateral salpingooophorectomy and bilateral pelvic lymphadenectomy be considered as the surgical treatment of choice, if not medically contraindicated. Especially in developing countries such as ours, where radiation facilities are sparse and not accessible to the majority, primary surgery in the form of radical hysterectomy, bilateral salpingooophorectomy and

bilateral pelvic lymphadenectomy would be a better alternative.

Given the retrospective nature of this study, the data collected were based only on the medical records retrieved and may be subject to certain biases. Therefore, a prospective evaluation of radical hysterectomy compared with extrafascial hysterectomy for the management of Stage II endometrial carcinoma would provide better recommendations. However, as was stated in several studies, because of the relatively low incidence of Stage II endometrial cancer, it is highly unlikely that such a study be performed. As such, most of the retrospective data may serve as the basis by which surgical management of patients with clinical Stage II endometrial cancer is determined.

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HPV-Associated Multicenter Intraepithelial Neoplasia: Simultaneously - Occurring CIN, VAIN and VIN in a Young Woman*

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This paper presents a case of a 26-year old G2P2 (2002) with a history of persistent HPV infection and multicentric metachronous intraepithelial neoplasia of the lower genital tract. She was diagnosed with Cervical Intraepithelial Neoplasia II (CIN II), Vaginal Intraepithelial Neoplasia III (VAIN III) and Vulvar Intraepithelial Neoplasia III (VIN III) after undergoing a Large Loop Excision of the Transformation Zone (LLETZ), a colposcopically-guided vaginal biopsy, and excision biopsy of vulvar lesion, respectively. She subsequently underwent Total Abdominal Hysterectomy, Upper Vaginectomy and Cauterization of vulvar lesions as definitive management. HPV Type 16 was the specific virus responsible for all these lesions.

Multicentric disease of the lower genital tract is rare. The presence of multicentric lesions poses a dilemma as to whether they are a result of multiclonal HPV infection or monoclonal HPV infection. This report illustrates the possible pathogenesis of multicentric intraepithelial neoplasia of the lower genital tract and discusses the present and future management of such a condition.

Key words: Multicentric disease, Human papillomavirus infection

The Human Papillomavirus (HPV) has been documented to be the etiology of Cervical Intraepithelial Neoplasia (CIN) and cervical cancer in 99.7 percent of cases.[19] It is also widely believed that HPV is the causative organism responsible for most cases of Vaginal Intraepithelial Neoplasia (VAIN) and Vulvar Intraepithelial Neoplasia (VIN). These intraepithelial lesions are almost always seen separately in women afflicted with the disease. Due to the possible similar etiology, it is theoretically plausible to observe two or three of these lesions in just one individual. This is termed Multicentric Intraepithelial Neoplasia of the lower genital tract - a sequelae of the Field Defect Theory of persistent HPV infection.

Multicentric Intraepithelial Neoplasia of the lower genital tract is widely accepted to be associated with persistent HPV infection. The average incidence of multicentricity is 0.0396 percent as studied by Menguellet, et al. 2005.[3] Local data on its incidence is scarce.

Persistent HPV infection, which is defined as presence of one HPV type two or more times in a period of several months to a year, is essential in the progression of this viral infection to pre-malignant lesions.

* First Place Winner, 2007 SGOP Fellows' and Residents' Interesting Case Contest, September 1, 2007.

This report presents a case of persistent HPV infection and multicentric intraepithelial neoplasia of the lower genital tract in a 26-year old woman.

The Case

K.N. is a 26-year old Filipina, presently residing in Japan, G2P2 (2002), who was admitted for the management of cervical, vaginal and vulvar neoplasia.

Six years prior to admission (PTA), she had 8 admissions for cauterization of genital warts (condyloma acuminata) under the care of a private gynecologist. Subsequent follow-ups were irregular as she married and migrated to Japan.

Four years PTA, she consulted her gynecologist and subsequently underwent cervical conization of cervical intraepithelial neoplasia (CIN). Repeat Pap smear after 1 year revealed atypical squamous cells of undetermined significance (ASCUS), probably low grade squamous intraepithelial lesion (LGSIL). She consulted a gynecologic oncologist where Human Papillomavirus (HPV) DNA testing done revealed positive for high-risk types. Colposcopy was advised but she did not comply as she returned to Japan.

Two years PTA, she returned to Manila for evaluation of vaginal spotting. She was evaluated to be 26 weeks' pregnant at that time. She underwent colposcopy where a polypoid hemorrhagic mass (3 cm x 2 cm with a 1 cm pedicle) was seen protruding from the external os. No other abnormal colposcopic findings were observed. Biopsy of the mass revealed endometrial polyp with decidual change. Patient was advised colposcopy every 3 months during this pregnancy and repeat colposcopy 6 weeks postpartum. However, she again returned to Japan where no colposcopy was performed during the remaining antenatal period. She delivered a full term live baby boy at term by primary low transverse cesarean section (indication unknown to patient).

One year PTA, she had a repeat HPV DNA test which still revealed (+) for high-risk types. Colposcopy was done revealing thick acetowhite epithelium with punctuations from 12 to 6 o'clock position extending into the endocervical canal. Due to the unsatisfactory colposcopic examination, she underwent loop electrosurgical excision procedure (LEEP) (Figure 1) where histopathology showed CIN 1 with HPV-associated changes. LEEP margins were negative for CIN. She was advised close follow up with her physician in Japan but again she did not comply.

Figure 1. The cervix after LEEP (Loop Electrosurgical Excision Procedure).

Three months PTA, she returned to her gynecologic oncologist who repeated the colposcopy. This revealed multifocal thick acetowhite epithelium on the entire transformation zone of the cervix, with extension to the left lateral vaginal wall (Figure 2). Vulvar inspection likewise showed hyperpigmented areas on the labia majora and minora (Figure 3). HPV DNA testing using vaginal scrapings from the left lateral vaginal wall was done revealing (+) for high-risk types. She was advised excision and ablative surgery but returned only after 2 months for the said procedure.

One month PTA, she underwent excision and electrocautery of vulvar lesions, large loop excision of the transformation zone (LLETZ), vaginal wall biopsy, and electrocautery of vaginal lesions. The postoperative course was unremarkable and she was discharged the next day. Histopathology revealed: CIN II with HPV-associated changes (Figures 4 and 5). VAIN III with HPV-associated changes (Figures 6 and 7); VIN III (Figures 8 and 9). Due to poor

compliance for follow-up, she was thus advised definitive surgery.

Past medical and family histories were unremarkable.

Personal and social history revealed the patient to be a non-smoker, non-alcoholic beverage drinker. She had her first coitus at the age of 15, with a total of 3 partners. Her first 2 partners were casual acquaintances. Her present partner (and father of her 2 children) is her Japanese husband, a businessman who she claims to have had casual sex with commercial sex workers. She had history of oral contraceptive pill use for 3 months.

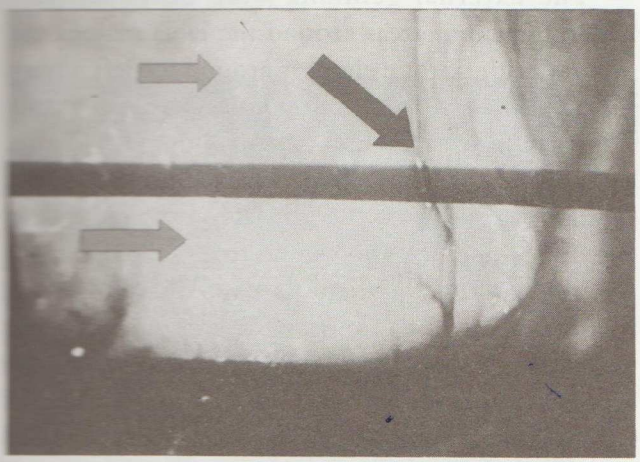

Figure 2. Multifocal thick, acetowhite epithelium on the ectocervix (green arrow) with extension to the left lateral vaginal wall (blue arrow).

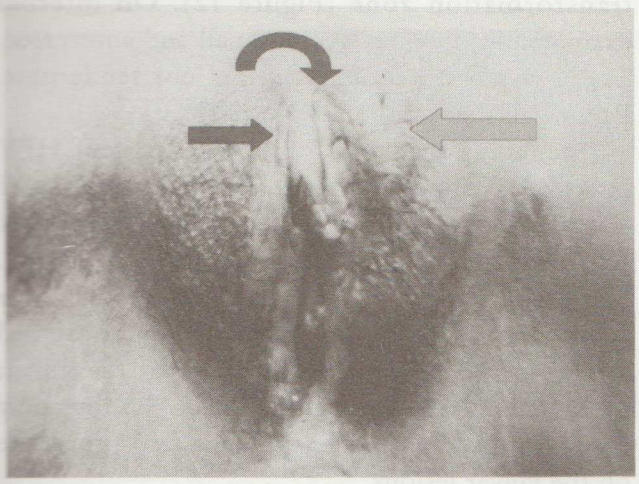

Figure 3. External genitalia with hyperpigmented areas around the labia majora and minora (red arrow), with fibrotic changes around the left labia majora (yellow arrow).

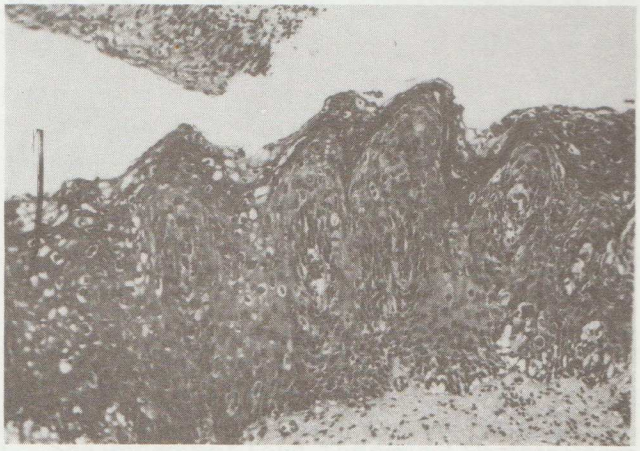

Figure 4. Section of the cervix showing 2/3 of the epithelium demonstrating high cellularity, immaturity and vertical orientation of cells.

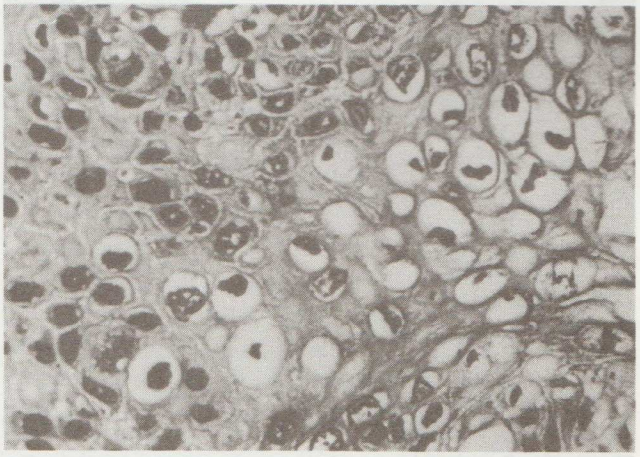

Figure 5. High magnification of the cervix showing koilocytosis and cells demonstrating nuclear atypia, nuclear halo, and increased nuclear to cytoplasmic ratio.

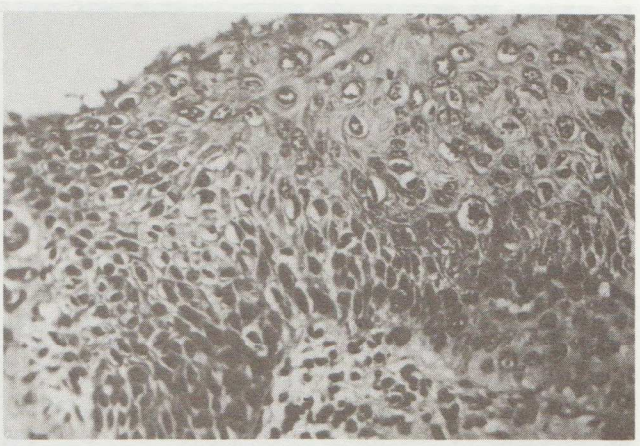

Figure 6. Section of the vagina showing almost the entire epithelium to have immature cells, irregular nuclei, and disorderly pattern.

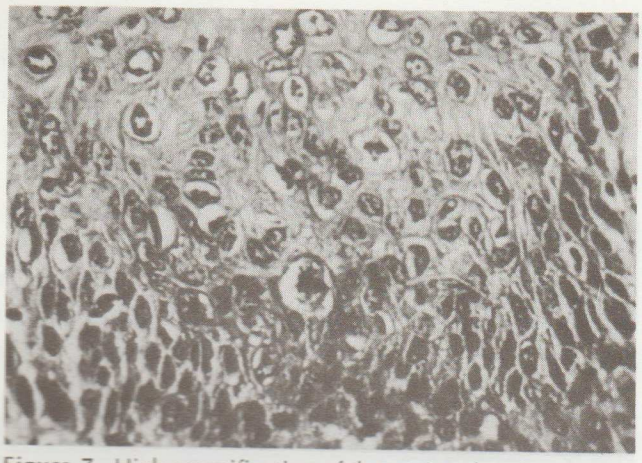

Figure 7. High magnification of the vagina showing areas of koilocytosis with disorganization of cells, hyperchromatic nuclei and mitotic activity.

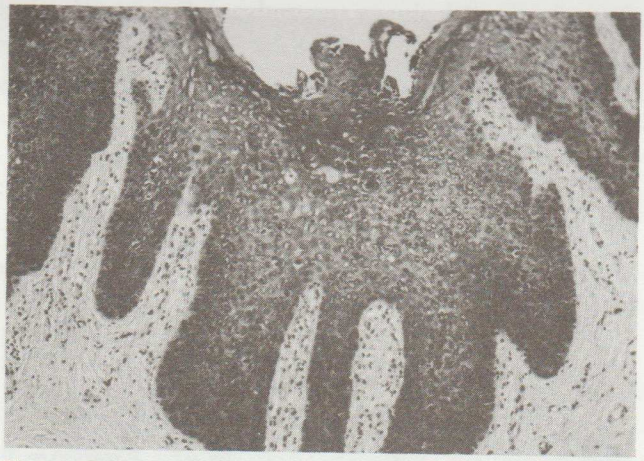

Figure 8. Excision biopsy of the vulva revealing abnormal cells, increased mitotic activity, with abnormal mitotic figures extending almost through the entire epithelium.

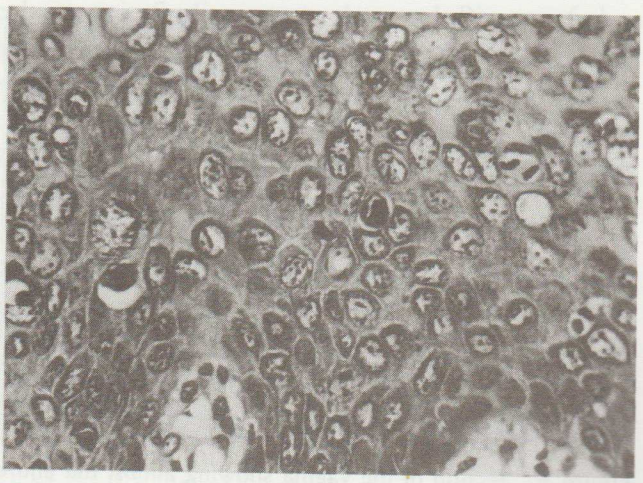

Figure 9. Higher magnification of the vulva revealing severe nuclear atypia.

She had her menarche at the age of 12, subsequent menses occurring every 28-30 days, lasting for 3 days with moderate flow.

The patient is a G2P2 (2002). All pregnancies were carried to term with no complications. Her first pregnancy was a Full Term Spontaneous Vaginal Delivery (FTSVD) and her last pregnancy ended in a primary Low Transverse Cesarean Section (LTCS).

Review of systems was unremarkable.

On admission, she was conscious, coherent, ambulatory, not in cardiorespiratory distress with stable vital signs. Systemic physical examination findings were essentially normal. Significant findings centered on her pelvis.

The external genitalia were noted to have hyperpigmented areas around the labia majora and minora, with fibrotic changes around the left labium majus, adjacent to the previous excision biopsy (Figure 3). On speculum examination with the aid of a colposcope, the vagina was smooth with an erythematous area at the left lateral vaginal wall at the upper third of the vagina from 1 to 5 o'clock positions (site of previous cautery). On visual inspection of the vagina with acetic acid, thick acetowhite epithelium was observed lateral to the said erythematous area (Figure 10). Application of Lugol's iodine solution (Schiller's Test) revealed multiple areas of non-staining at the left forniceal area (Figure 11). The cervix had circumferential erythematous areas around the external os with small areas of thin acetowhite epithelium at the transformation zone (Figure 12). On internal examination, the corpus was small and anteverted. There was neither adnexal mass nor tenderness. Parametria were smooth and pliable.

Our admitting impression was: Persistent HPV infection with Cervical Intraepithelial Neoplasia II (CIN II); Vaginal Intraepithelial Neoplasia III (VAIN III); Vulvar Intraepithelial Neoplasia III (VIN III). She was advised total abdominal hysterectomy, upper vaginectomy and simple vulvectomy. She consented to the first 2 procedures but refused the vulvar procedure (for "aesthetic" reasons). She thus only consented to an ablative (cauterization) procedure on the vulvar lesions.

On the 2nd hospital day, she underwent the contemplated procedures. Intraoperative findings

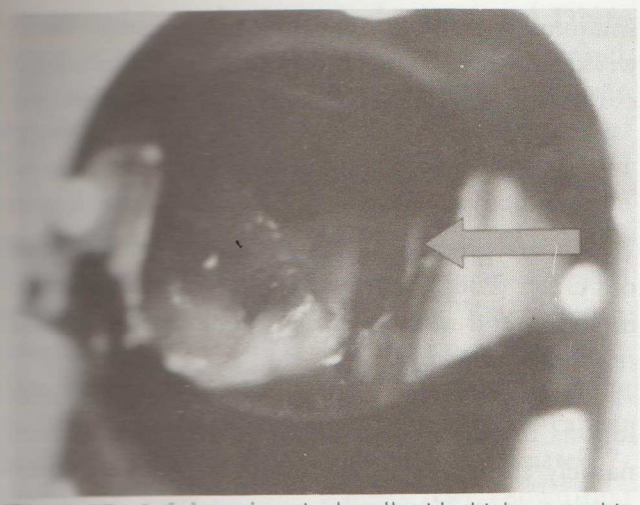

Figure 10. Left lateral vaginal wall with thick acetowhite epithelium (yellow arrow).

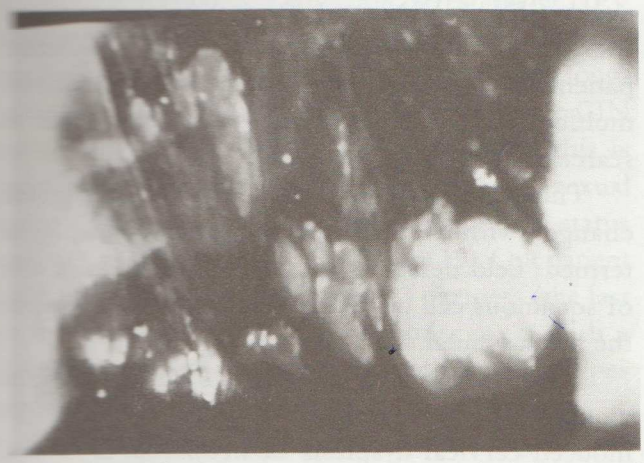

Figure 11. Multiple areas of non-staining at the left forniceal area after application of Lugol's iodine solution (Schiller's Test).

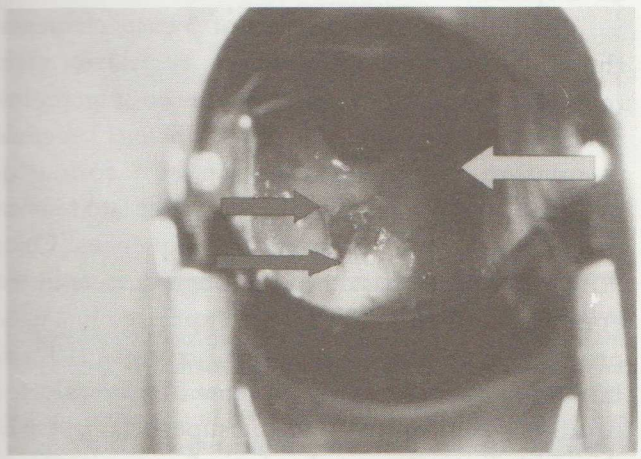

Figure 12. Cervix with circumferential erythematous area around the external os (yellow arrow) with small areas of thin acetowhitening at the transformation zone (blue arrow).

revealed the following: The external genitalia, vagina and cervix had the lesions previously described. The uterus was symmetrical measuring 5 cm x 4 cm x 4 cm with a smooth serosal surface. On cut section, the endometrium was smooth and thin while the myometrium was homogeneously thickened with no lesions (Figure 13). The cervix had erythematous areas but no masses (Figure 14). The vaginal cuff had patchy areas of brown-black discoloration (Figure 15). The rest of the pelvic and abdominal organs had smooth surfaces and were grossly normal.

She underwent Total Abdominal Hysterectomy, Upper Vaginectomy, Electrocautery of Vulvar Lesions (Figure 16).

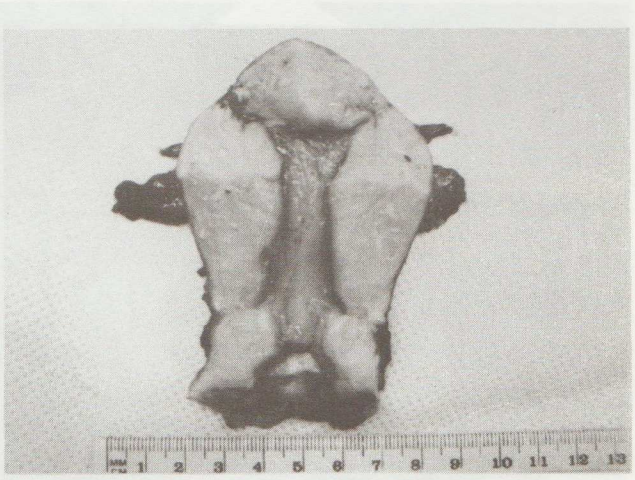

Figure 13. Endometrium smooth and thin and myometrium homogenously thickened with no lesions.

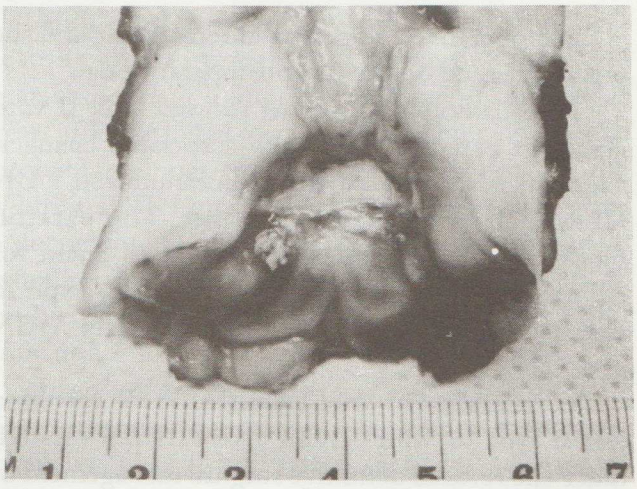

Figure 14. Cervix with erythematous areas but no masses.

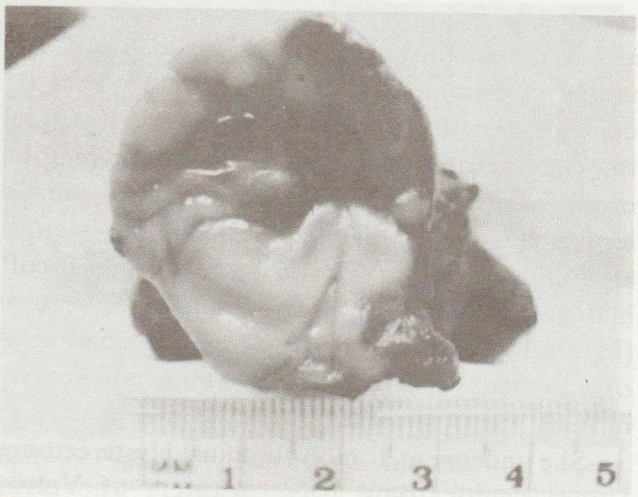

Figure 15. Vaginal cuff with areas of brown-black discoloration.

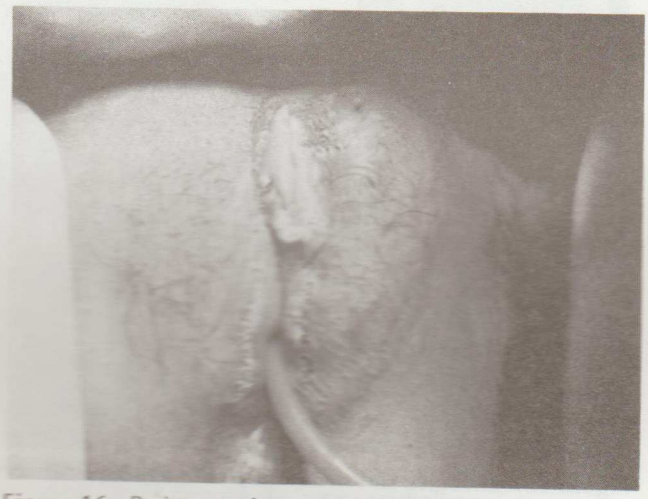

Figure 16. Perineum after cauterization of vulvar lesions.

Postoperative course was unremarkable and she was discharged on the 3rd postoperative day.

Histopathological report showed CIN II with glandular extension and HPV-associated changes, adenomyosis, proliferative endometrium and VAIN III with HPV-associated changes. The paraffin blocks of the three areas were sent to Spain for determination of specific HPV type. HPV type 16 was the specific type isolated from the CIN, VAIN and VIN.

Final Diagnosis was: Persistent HPV Infection (HPV Type 16) with CIN II, VAIN III and VIN III. Since she refused definitive surgical management of the VIN III, she was advised application of Imiquimod (Aldara) over the vulvar lesions thrice weekly for 4 months. Moreover, vaginal cytologic evaluation every 4 months was impressed upon her.

Discussion

We are presented with a rare case of a 26-year old G2P2 (2002), with a history of persistent HPV infection and multicentric intraepithelial neoplasia of the lower genital tract.

Multicentricity is defined by intraepithelial lesions in two or three areas of the genital tract, namely the cervix, vagina and vulva. In a study conducted by Menguellet, et al. in 2005, 44 of 998 (4.4%) patients referred for CIN presented with multicentric lesions - 91 percent presented with either CIN + VIN, or CIN + VAIN; 9 percent presented with 3 sites of genital dysplasia.[1] Affected patients had a mean age of 36.8 years. Local data on multicentric disease of the lower genital tract is scarce and primarily anecdotal.

The tendency to develop multiple pre-malignant changes within the lower genital tract has been termed 'field defect.' It denotes the increased risk of squamous cell neoplasia arising from any site in the lower genital tract.[2]

Majority of vulvar and vaginal lesions arise in women who have a history of high-risk HPV-induced cervical dysplasia or neoplasia. It is well accepted that persistent infection with high-risk HPV (HR-HPV) types is required for the development of such lesions.[3,4,5]

The HPV genome consists of 3 basic elements: the non-coding region which regulates viral replication and transcription; the coding region which consists of the early (E) and late (L) regions in relation to gene production in a course of infection; and the ends of the early and late regions that connect to the non-coding sequences. Once HPV reaches the basal cells through defects in the epithelial surface, E regions are expressed in a non-productive, episomal state. The L regions (L1 and L2) code for viral capsid proteins. As the affected squamous cells move up to the superficial layers of the epithelium, thousands of viral copies replicate and viral capsid structures are expressed in the nuclei of mature squamous cells. After viral DNA is

integrated into the human chromosomal DNA, [illegible] of viral DNA in the late region are disrupted. This eliminates the normal expression of certain regulatory genes which lead to over-expression of E6 and E7. E6 and E7 bind to the p53 and retinoblastoma genes, respectively which are the gatekeepers of cell cycle regulation.

The key steps in cervical carcinogenesis consist of development of HPV infection, HPV persistence, progression to precancer, and invasion (Figure 17). The modal time between HPV infection occurring in the late teens or early twenties and pre-cancer peaking around 30 years of age, is approximately 7-10 years[6,19,20] (Figure 18). Studies have shown that although up to 40 percent of women are infected with HR-HPV, fewer than 10 percent of women develop persistent HPV infection.[7] Presumably, HPV is cleared completely by host cell-mediated immune system, is self-limited, or is suppressed into long-term latency.[6] Progression of HPV infection to CIN occurs only in 20 percent of women and this is primarily dependent on the patient's age, sexual activity, presence of HR-HPV, her immune status and her smoking history[6,8,9,19] (Figure 19). Our patient is 26 years of age, had a total of 3 partners (the last of whom she claims to be promiscuous) with a documented history of infection with high-risk types of HPV.

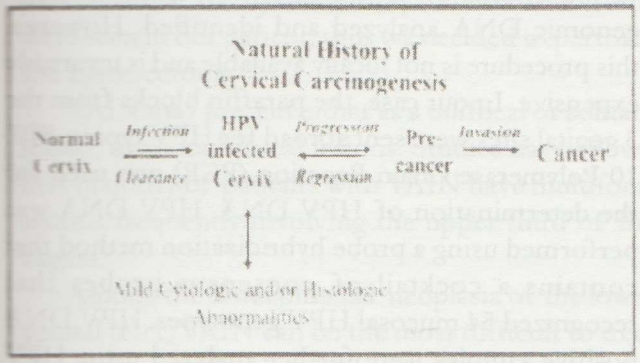

Figure 17. An epidemiologic model of cervical carcinogenesis. The major steps in cervical carcinogenesis are the presence of human papillomavirus (HPV) infection (offset by viral clearance) to progression to pre-cancer (sometimes offset by regression of pre-cancer) to development of cancer by invasion. The persistence of oncogenic HPV types is necessary for progression and invasion. HPV infection is frequently but not necessarily associated with cytologic and histologic abnormalities.

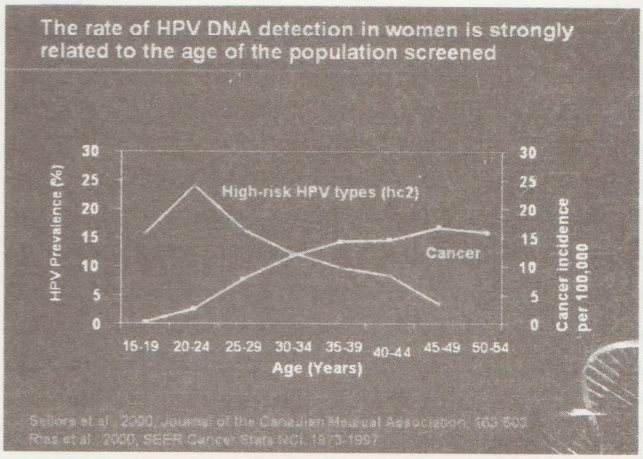

Figure 18. Model time between HPV infection and development of pre-cancerous lesion.

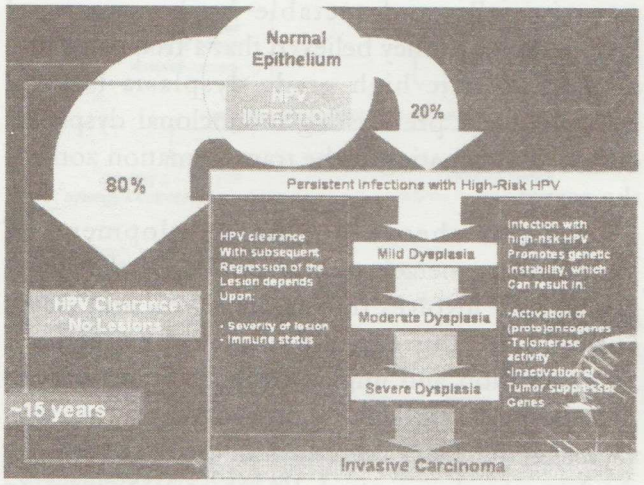

Figure 19. Natural course of HPV infection.

Multicentric lesions are either synchronous - lesions that appear at the same time, or metachronous - lesions that appear up to several years after the initial cervical lesion. Our patient most probably belongs to the latter group because the VAIN and VIN appeared approximately 4 years after a documented CIN. However, a significant issue is whether the multicentric lesions were a result of multiclonal HPV infection or monoclonal HPV infection.

In a study by Vinokurova, et al.[7], the site of HPV DNA integration may be used as a marker of clonality. They hypothesized that the existence of both synchronous and metachronous lesions

suggests that several independent local infective events induce development of multiclonal dysplastic lesions at distinct anatomic sites. Alternatively, the multicentric lesions might all originate from a distinct cell population that was infected and transformed by the HR-HPV before being disseminated. In the later scenario, all lesions would be expected to be derived from one initially transformed clone. Their study revealed that the viral genome integration sites in multifocal, metachronic vaginal or vulvar lesions were the same as that in the pre-existing cervical lesion, suggesting a common clonal origin. With these findings, the authors speculated that subsequent lesions could have been derived from quiescent dysplastic HPV-transformed cells that were disseminated early during carcinogenesis but were initially undetectable by conventional histopathology. They believed that a frequent cause of multicentric high grade dysplasia is local spreading of a pre-existing monoclonal dysplastic cell clone originating at the transformation zone of the cervix.[7]

Another theory on the development of multicentric, metachronous lesions of the lower genital tract involves trauma on vaginal and vulvar epithelium during a surgical procedure. Dissemination and implantation of pre-cancerous cells during cervical biopsy procedures on "injured" vaginal and/or vulvar epithelium could account for the later development of VAIN or VIN from an initial CIN.[10]

The vulva is considered to be an independent anatomical site. High-risk HPV DNA has been shown to be predominantly present in multifocal VIN lesions in more than 90% of cases, whereas monofocal lesions were HPV-negative in the majority of the cases. This supports the hypothesis of two etiologically different subset of patients: one which is HPV-positive presenting in younger women with multifocal VIN and multicentric dysplasia of the lower genital tract, and another in older women with a tendency towards an HPV-negative monofocal VIN lesion without the presence or history of multicentric dysplastic disease.[11] Our patient is young with multifocal VIN lesions and multicentric dysplasia. Though her VIN lesions were not accompanied by histologic findings suggestive of HPV, it is noteworthy to remember that HPV infection is frequently but not necessarily associated with cytologic and histologic abnormalities.[6] Local continuous or discontinuous intraepithelial spread appears to be the most likely mechanism.[7] Another possibility is that the VIN lesions which were present in the patient may have a low viral load without microscopically-evident changes as opposed to VIN lesions with high viral load and microscopically evident changes.[6] In our patient's case, HPV-associated VIN was confirmed when specific HPV typing was performed revealing HPV Type 16.

Further study has shown that among treated patients whose primary cervical lesions were of the high grade type, the initial recurrence in the vagina was always a high grade lesion (VAIN III or Invasive Carcinoma). It was reported that the grade of vaginal abnormality was equal to or even more severe than that of the original lesion on the cervix. This finding further suggests that vaginal and vulvar lesions represent the local progression of pre-existing cervical lesions.[7] In our patient, the cervical lesion (CIN II) was initially manifested, followed by higher grade vaginal and vulvar lesions (VAIN III and VIN III). This presentation may further boost our suggestion of a monoclonal type of HPV infection.

The ideal method to resolve the dilemma whether the multicentric lesions present in our patient were caused by monoclonal HPV infection or multiclonal HPV infection is to have the total genomic DNA analyzed and identified. However, this procedure is not locally available and is invariably expensive. In our case, the paraffin blocks from the 3 genital sites were sent abroad for HPV typing. SPF 10 Polymerase Chain Reaction (PCR) was used for the determination of HPV DNA. HPV DNA was performed using a probe hybridization method that contains a cocktail of consensus probes that recognized 54 mucosal HPV genotypes. HPV DNA positive samples were further analyzed using HPV SPF 10-LIPA (version 1), a reverse hybridization technique that detects 25 high risk and low risk HPV types. All 3 genital sites of our patient with pre-invasive lesions revealed HPV Type 16.

At present, management of multicentric disease of the lower genital tract remains to be a challenge. Definitive management of these lesions involves

individual treatment modalities for each individual lesion. The major objectives are the eradication of the pre-malignant lesion in each involved area, monitoring of possible recurrence and prevention of disease progression.

CIN, VAIN and VIN, individually and collectively, are managed based on the age of the patient, the severity of each and all of the lesions, and her desire to maintain reproductive, sexual and aesthetic functions. Conservative procedures, ranging from ablative to excisional modalities, are usually adequate in the management of these lesions in young women desirous of maintaining their fertility. However, more definitive treatments such as hysterectomy, vaginectomy, and vulvectomy can be considered in special or extreme situations.

CIN II or III is preferably treated with excisional modalities such as cold-knife cone biopsy, LEEP/ LLETZ, and laser conization. However, ablation (using cryotherapy, CO_2 laser ablation and electrofulguration) of the entire transformation zone is an acceptable treatment modality.[12] (Figure 20) According to the ASCCP (American Society of Colposcopy and Cervical Pathology) Guidelines in the management of CIN, there is no role for hysterectomy, even in cases of CIN III/CIS. However, recurrent or persistent CIN despite adequate conservative measures and an anticipated poor compliance for follow-up may justify that performance of hysterectomy. These conditions were seen in our patient; thus we decided to perform the hysterectomy.

VAIN may present either as a unifocal or solitary lesion, or as multifocal lesions. Studies have shown that majority of patients with VAIN have multifocal lesions frequently involving the upper third of the vagina.[3,13]

Among the intraepithelial neoplasia of the lower genital tract, VAIN can be the most difficult to treat due to its multifocality, high risk of recurrence and inaccessible location of some lesions after hysterectomy or radiotherapy. Major therapeutic modalities for VAIN III include surgery and/or ablative procedures. Local excision or partial vaginectomy is usually sufficient for unifocal or isolated lesions but frequently, total vaginectomy is the only recourse for multifocal lesions involving the entire vaginal tract. Ablative procedures, on the other hand, may include electrocautery, cryotherapy, CO_2 laser, topical application of 5-fluorouracil (5-FU), and surface irradiation (using interstitial or cylinder brachytherapy). Though the use of chemotherapeutic agents and radiotherapy is usually reserved for invasive disease and may be considered as "overkill" treatments for a pre-cancerous condition, their application for high grade VAIN has been accepted because of its ease of administration and its reported efficacy.

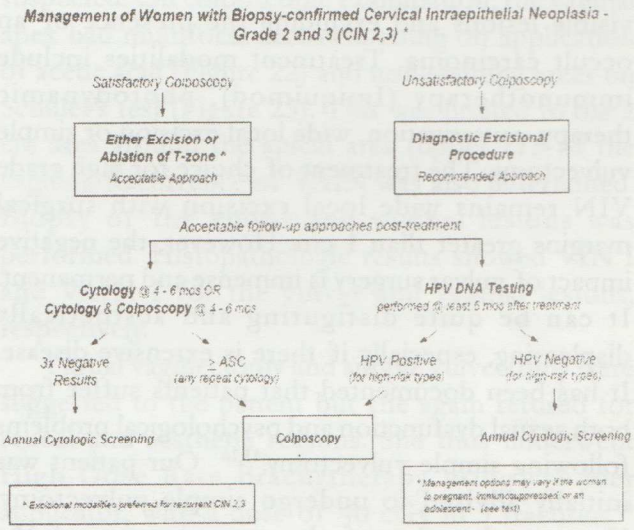

Figure 20. ASCCP Treatment algorithm for management of women with CIN II and III.

Topical 5-FU is thought to be the ideal method for multifocal VAIN and recurrences seem to be prevented with repeated usage. However, it is sometimes associated with hypersensitivity reactions, vaginal burning and vulvar irritation. In unifocal or multifocal lesions, surgical excision has the advantage of providing a surgical specimen to assess the possibility of invasive disease and to check the resection margins for metastatic lesions. Partial vaginectomy has been shown to have the highest cure rate. Recurrence rate of VAIN was highest with 5-FU application and lowest with partial vaginectomy (59% and 0%, respectively).[3,14] Our patient had multifocal VAIN with majority of lesions located in the upper third of the vagina adjacent to

the cervix. We thus decided to perform an upper vaginectomy. Technical difficulties though surrounded the performance of this procedure and we were only able to excise ~2 cm of the upper vagina. To compensate for this limitation, we fulgurated (using an electrocautery) the vaginal epithelium within 2 cm from the vaginal stump. Two weeks post-operative, colposcopy with application of acetic acid and Lugol's iodine solution over the entire vaginal vault did not reveal any acetowhite epithelium and non-iodine staining areas, respectively.

VIN III is treated with the aim of removing all visible lesions and excluding the presence of an occult carcinoma. Treatment modalities include immunotherapy (Imiquimod), photodynamic therapy, cauterization, wide local excision or simple vulvectomy. The treatment of choice for high grade VIN remains wide local excision with surgical margins greater than 1 cm. However, the negative impact of vulvar surgery is immense and permanent. It can be quite disfiguring and aesthetically displeasing, especially if there is extensive disease. It has been documented that patients suffer from both sexual dysfunction and psychological problems following simple vulvectomy.[15,16] Our patient was initially advised to undergo simple vulvectomy. However, because of the extensiveness of the dissection (which would have included the clitoral area) and her desire to maintain a "normal-appearing" perineum for sexual and aesthetic purposes, she refused the contemplated surgery. As an alternative, she underwent cauterization of the vulvar lesions and was later advised to apply Imiquimod (Aldara) for four months.

The present goal of management is to eradicate the lesion rather than eliminate the HPV infection. Future therapies will be directly or indirectly antiviral, targeting HPV protein functions, boosting ability of the immune system to resolve infection or induce apoptosis indirectly in HPV infected cells.[17,18] With increasing evidence of chronic and persistent HPV infection as the stimulus for growth and proliferation of these lesions, anti-viral treatment modalities (such as the HPV vaccines), immunotherapy and gene therapy may start to play a role in its future management. Commercially-produced HPV vaccines have already been approved for use in the prevention of this viral infection in the hope that cervical neoplasia and cancer may be eradicated soon after. It is envisioned that with universal HPV vaccination, HPV-induced infections in the lower genital tract and their sequelae will be a thing of the past, much like the eradication of the smallpox virus in the late 1970's and early 1980's.

The American College of Obstetricians and Gynecologists (ACOG) recommends that women who had a hysterectomy for treatment of CIN III or carcinoma-in-situ undergo vaginal cytology with or without colposcopy every 4-6 months until 3 documented, consecutive and technically satisfactory normal or negative vaginal cytology tests and no abnormal or positive cytology tests within a 36-month period following hysterectomy are obtained. Thereafter, cytologic screening proceeds in an annual manner.[10]

Multicentric disease has a recurrence rate of approximately 43 percent.[1] It has a higher recurrence rate when individually compared with CIN, VAIN and VIN (Figure 21). Multicentricity in itself and persistent HPV infection are risk factors for recurrence. Though HPV DNA testing was designed mainly for detection of HPV in the cervix, this could still be utilized in the detection of the virus from the vaginal epithelium. Aside from the plastic cytobrush provided with the kit, the use of the cervical brush with its more rigid bristles may increase the chance of recovering adequate cells from the vaginal epithelium. This diagnostic procedure was performed on the patient's vaginal lesions 3 months prior to admission yielding positive results for high risk HPV types. This proves that HPV DNA testing can be utilized even on the vagina. The presence of persistent HPV infection within the vagina can thus be documented and this modality will be utilized by the patient's attending gynecologist in future follow-ups.

There is no current data as to the progression to carcinoma of multicentric disease. Among the 3 anatomical sites, CIN has the highest rate of progression.[2,3,16] In our patient, the choice of definitive management was total abdominal hysterectomy with upper vaginectomy and simple vulvectomy. This "radical" procedure was suggested

to a very young woman because of fear of progression of her lesions to malignancy due to her poor compliance for follow-up and surveillance. She refuses to consult a gynecologist/gynecologic oncologist in Japan because of her personal distrust in them coupled with the language barrier that prevented effective communication between her and her physician. She agreed to the first two procedures but opted for a more conservative and "visually-pleasing" vulvar procedure. Presently, she is living in Japan and is advised follow-up whenever she returns to Manila.

	CIN II	VAIN III	VIN III	Multicentric
Age Group	20 -30	35 +/- 17	46	36.8
Incidence	2.8 - 5%	0.2- 0.3/ 100,000	0.0021%	9%
Progression to CA	22%	2%	6.5%	Unknown
Recurrence	5 - 35%	33%	10 - 50%	43.5%
Management	Excision or Ablation (CIN II, III)	Upper vaginectomy	Excisional Modalities	Combination of management

Comprehensive Gynecology, 2001
Dodge, 2001
Seters, 2005
Menguellet et al, 2005

Conclusion

We are presented with a rare case of multicentric metachronous intraepithelial neoplasia of the lower genital tract in a 26-year old patient. She presented with a history of persistent HPV infection. She underwent total abdominal hysterectomy, upper vaginectomy and biopsy and electrocautery of vulvar lesions. Final diagnosis was persistent HPV infection with CIN II, VAIN III and VIN III. These simultaneous lesions were a result of monoclonal high risk-HPV infection (HPV Type 16).

Multicentric disease of the lower genital tract is treated by excisional or ablative methods, with CIN, VAIN, and VIN considered as separate lesions. HPV-induced intraepithelial neoplasia of the lower genital tract may hopefully be eradicated with the development and universal administration of the HPV vaccine. Hopefully in the future, HPV-induced pre-invasive lesions (and subsequently, cervical carcinoma) may be a thing of the past.

Medical Updates on the Patient

KN followed up with her attending gynecologic oncologist in February 2007. She was asymptomatic. On examination of the perineum, there were hyperpigmented areas again on the labia majora, adjacent to the clitoris. Though they were smaller in diameter and less in number, recurrence of VIN was suspected. On colposcopic examination, the vaginal apex had multifocal acetowhitening on application of acetic acid (Figure 22) and non-staining areas on Schiller's test (Figure 23). This was limited to the 2 cm area around the apical area (upper 2/3 of the vagina). Recurrence of VAIN was also entertained. Biopsy of the vulvar and vaginal lesions was performed. Histopathologic results showed VIN I and VAIN I for the vulvar and vaginal lesions, respectively.

Partial vaginectomy and simple vulvectomy were suggested to the patient but she again refused for sexual and aesthetic reasons. She thus underwent High-Dose Rate Brachytherapy using cylinder applicator, with a dose of 40 cGy in 5 fractions.[21] This was given weekly from February to March 2007. She tolerated the treatments well and no adverse

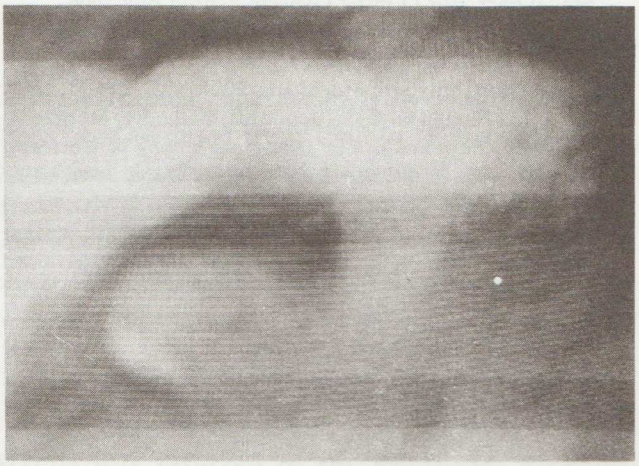

Figure 22. Multifocal areas of acetowhitening at vaginal apex after application of acetic acid (February 2007).

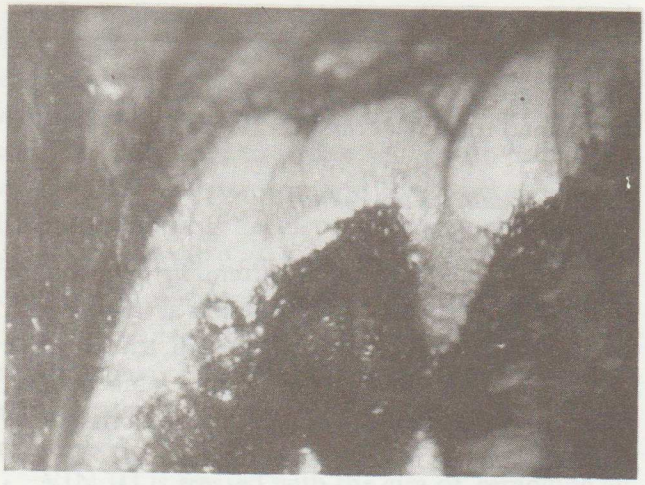

Figure 23. Non-staining areas at vaginal apex after application of Lugol's iodine solution (February 2007).

acute radiation effects were observed. She was also advised re-application of Imiquimod to the vulvar lesions for four months.

Re-examination in May 2007 showed smaller and less hyperpigmented lesions on the vulva and no acetowhitening at the vaginal vault. Liquid-based cytology of vaginal scrapings revealed no evidence of intraepithelial neoplasia. She was advised to continue the Imiquimod for another 2 months. She promised to follow-up in August or September 2007.

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Placental Site Trophoblastic Tumor with Increased Serum Beta Chorionic Gonadotropin: A Case Report and Review of Literature

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Placental Site Trophoblastic Tumor (PSTT) is one of the rarest forms of Gestational Trophoblastic Neoplasia (GTN). It is composed of neoplastic implantation site intermediate trophoblastic cells which produce human placental lactogen or hPL. In contrast to other forms of gestational trophoblastic neoplasia (GTN), PSTT produces low levels of beta βhCG and is not as responsive to chemotherapy. Therefore, surgical resection is the main therapy for this tumor. In this paper, a case of a 41 year old G2P1 (1011) who presented with on and off vaginal bleeding roughly a year after evacuation of a hydatidiform mole is presented. Serum beta human chorionic gonadotropin (βhCG) determination yielded elevated titers. Hysterectomy was performed due to persistence of the bleeding. Examination of the specimen revealed placental site trophoblastic tumor. Immunohistochemical staining of the specimen using hPL was positive for PSTT confirming the histopathologic result. Multi-agent chemotherapy using Etoposide, Methotrexate, Actinomycin, Cyclophosphamide and Oncovin (EMACO) was promptly initiated following the diagnosis resulting in a good response. The antecedent hydatidiform mole along with the markedly elevated levels of serum BhCG made this case different from the other reported PSTT cases.

Key words: Placental site trophoblastic tumor, gestational trophoblastic neoplasia, human placental lactogen, human chorionic gonadotropin

Placental site trophoblastic tumor or PSTT is a rare form of gestational trophoblastic disease (GTD), accounting for 3.1 per 1000 to 2 per 100 of all trophoblastic diseases.[1,2] Presentation of this tumor varies, ranging from benign lesions confined in the uterus in 90 percent of cases to highly aggressive, malignant disease with widespread metastases in 10 percent of cases.[5] The first case of malignant PSTT reported in the Philippines was in 1986. The patient died before completion of chemotherapy.[3] In the Section of Trophoblastic Disease of the Philippine General Hospital, four histologically confirmed PSTT cases were admitted from 1988 to 1998 with varying outcomes. We now report an unusual case of PSTT presenting with high beta hCG titers, treated successfully by hysterectomy and multiagent chemotherapy using the EMACO regimen.

The Case

LM, a 41 year old, G2P1 (1011) from Santa Ana, Manila was referred to the Philippine General

Hospital (PGH) last October 8, 2001 for further management of placental site trophoblastic tumor. Her past medical history, family medical history, personal, social and sexual histories are non-contributory.

The patient's first pregnancy in 1997 was carried to term and delivered by spontaneous vaginal delivery with no complication. Her second pregnancy in 2000 was a complete hydatidiform mole for which she underwent suction curettage. She was given methotrexate chemoprophylaxis post-operatively. Serum βhCG monitoring after the suction curettage was done which showed decreasing values from 43.93 to 24.88mIU/ml. Patient was advised to start oral contraceptive pills and to continue serum βhCG monitoring. However, the patient was lost to follow-up.

Four months prior to admission (roughly a year following evacuation of the molar pregnancy), the patient experienced on and off vaginal bleeding using 2-3 pads/day. An ultrasound done during consult with an obstetrician-gynecologist revealed hydatidiform mole. Serum βhCG taken at this time was 472.28 mIU/ml. Serial βhCG monitoring was advised but patient did not comply due to financial constraints.

Two months prior to admission, due to persistence of vaginal bleeding, patient sought consult with another obstetrician-gynecologist. Laboratory examinations were done. Serum βhCG at this point increased to 1,760 mIU/ml. Chest x-ray was normal. Repeat transvaginal ultrasound showed hydatidiform mole with no invasion noted. Patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (THBSO) due to persistent vaginal bleeding. Intra-operative findings revealed a small uterus with a smooth intact serosa. Cut section showed placenta-like tissue with hemorrhage at the fundal area. No myometrial invasion was noted. Bilateral adnexae were grossly normal. The postoperative course was uneventful. She was discharged improved on the third post-operative day and was advised serial βhCG monitoring. Histopathologic diagnosis showed "placental site trophoblastic tumor, chronic cervicitis and 2 small intramural leiomyoma" (Figure 1).

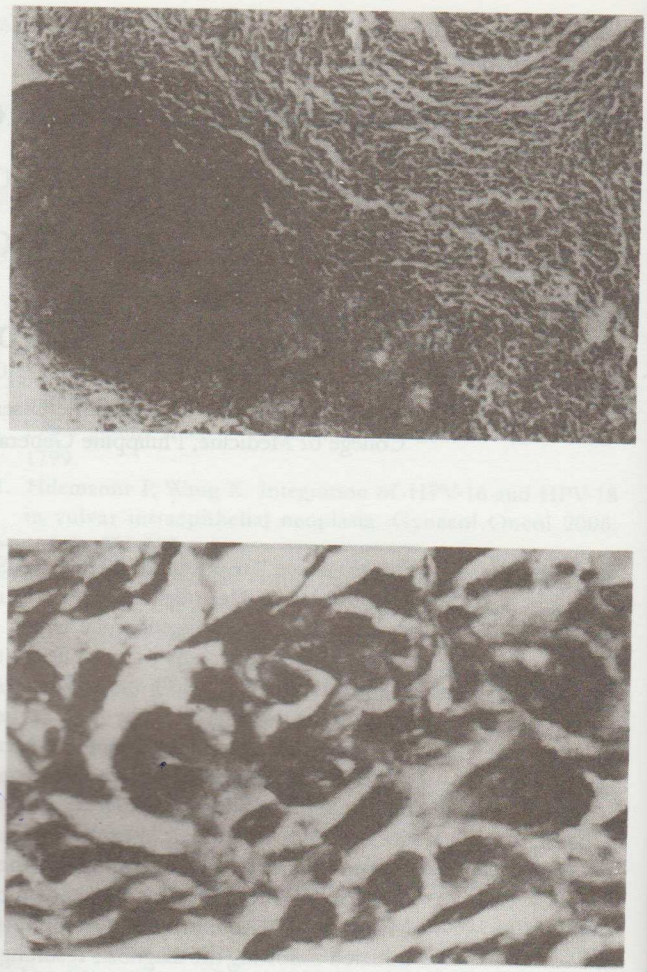

Figure 1. PSTT on H and E stain.

One week following the surgery, the patient noted a gradually enlarging vaginal mass associated with vaginal spotting. However, no consultation was done.

About 24 days prior to admission (24 days after hysterectomy), patient noted profuse bleeding from the vaginal mass prompting consult with another obstetrician-gynecologist. On speculum examination, the vaginal stump was intact with no granulation tissues. However, a 2.5 cm x 2.0 cm friable, necrotic mass was seen at the anterior vaginal wall near the urethra. Suturing of the area surrounding the mass as well as vaginal packing were done for hemostasis. Iron supplement and antifibrinolytic were given. Weekly βhCG monitoring using radioimmunoassay was done, showing a rising pattern, from 23,572 mIu/ml to 968,500 mIu/ml.

Patient was then referred to the Philippine General Hospital for further evaluation and management.

Exactly 47 days after her hysterectomy, patient was admitted at PGH for further management. Her vital signs were stable with essentially normal systemic physical examination findings. Pelvic examination revealed a 6 cm x 3 cm friable, bluish and necrotic mass surrounding the urethra with no active bleeding. The vaginal vault was intact and smooth. The uterus was surgically absent. No adnexal mass or tenderness was noted.

Admitting impression was placental site trophoblastic tumor with vaginal metastases; previous suction curettage for complete hydatidiform mole (Chinese General Hospital, September 23, 2000); previous methotrexate chemoprophylaxis; previous THBSO (Chinese General Hospital, August 23, 2001).

Immunohistochemical staining using human placental lactogen was done which showed a strong positive reaction (Figure 2). Serum βhCG on admission was 968,500 mIU/ml. Chest x-ray showed multiple pulmonary nodules, the largest of which measured 3.0 cm x 3.0 cm. Cranial CT scan showed no brain metastases. Holoabdominal ultrasound showed cholelithiasis and fatty liver changes. Her complete blood count, renal, liver and thyroid function tests were all within normal limits. Using the FIGO 2000 Staging and Risk Scoring System, the patient was classified as stage III with risk score of 14 (Tables 1 & 2).

Patient was immediately started on multiagent chemotherapy using the EMACO regimen. After five cycles of EMACO, serum βhCG went down to normal level. She received an additional three consolidation therapies thereafter (Figure 3). The vaginal mass resolved after the 4th cycle of chemotherapy. Repeat chest x-ray after the last chemotherapy showed resolution of pulmonary masses. Patient has been disease free 63 months following successful treatment of her PSTT.

Table 1. FIGO 2000 staging system.

STAGE I	Disease confined to the uterus
STAGE II	Disease extends to outside the uterus but confined to the genital organs
STAGE III	*Pulmonary metastases*
STAGE IV	Metastases to other sites

Italized staging is that of the index patient.

Table 2. FIGO 2000 risk scoring system.

Prognostic Factors	SCORE 0	1	2	4
Age (years)	<40	**≥ 40**		
Antecedent Pregnancy	**Mole**	Abortion	Term	
Pregnancy Interval (months)	< 4	4 to <7	7 to ≤ 12	≥ 12
Beta hCG Titer (mIU/ml)	<1,000	1000 - <10,000	10,000- <100,000	**>100,00**
Largest tumor, including the uterine tumor	<3	3 to <5	≥ 5	
Site of metastases	**Vagina, lungs**	Spleen, kidney	GI tract	Liver, Brain
Number of metastases		1-4	5-8	>8
Prior chemotherapy			**Single agent**	2 or more agents

Highlighted factors are those of the index patient.

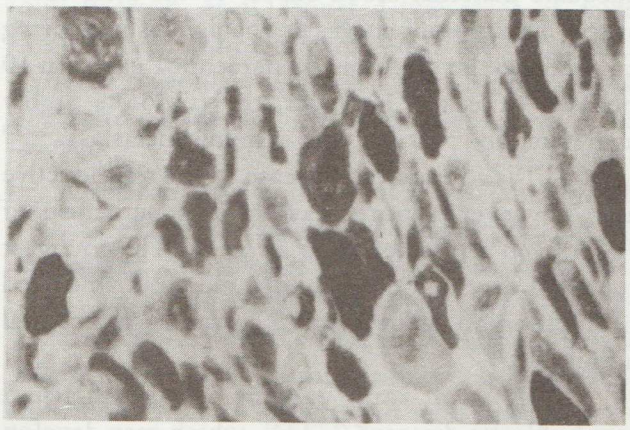

Figure 2. PSTT on immunostain.

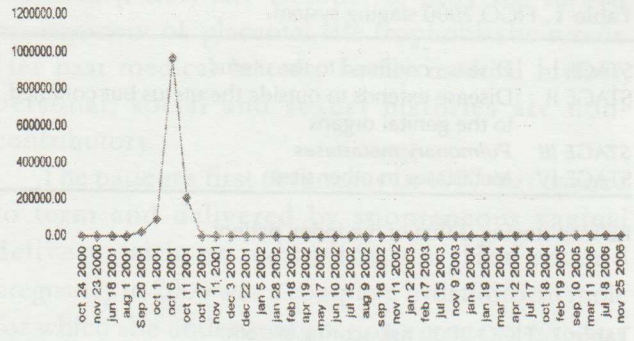

Figure 3. Graph showing decrease in βhCG titer during treatment.

Discussion

Gestational Trophoblastic Disease (GTD) includes a spectrum of conditions, all arising from placental tissue. The villous forms of GTD include partial and complete hydatidiform mole as well as invasive mole. The nonvillous forms consist of the placental site nodule, exaggerated placental site, placental site trophoblastic tumor (PSTT), choriocarcinoma and epithelioid trophoblastic tumor (ETT).

Placental site trophoblastic tumors (PSTT) are neoplastic lesions derived from the intermediate trophoblast cell lineage.[1] Normally, these intermediate trophoblast differentiate from the cytotrophoblast shell, which emanates from the anchoring villi of the basal plate of the placenta. Their natural history is infilration into the endometrium, myometrium and spiral arteries, thereby anchoring the placenta to the uterus and ensuring an adequate maternal blood supply to the intervillous space.[4] This tumor behaves in a benign fashion, being confined to the uterus, in 90 percent of cases. In 10 percent of cases, however, the tumor is highly aggressive and presents with systemic metastases.[5,6,7,8]

PSTT is considered a disease of the reproductive age. However, reports have shown detection of PSTT even up to the age of 66 years.[9] The youngest reported case was the 4 month old child who died of multiorgan failure within 5 weeks of hospital admission.[10]

PSTT is a rare variant of gestational trophoblastic diseases (GTD), which may develop from an antecedent normal pregnancy, abortion, ectopic pregnancy or after either a complete or partial mole.[11] In a report by Papadopoulus, et al. 2002, 53 percent of cases followed a term pregnancy while 21 percent of cases followed a molar pregnancy.[2] The interval between the occurrence of PSTT and the antecedent gestational event varies from several weeks up to 15 years.[6] Patients usually present with irregular vaginal bleeding, sometimes following a period of amenorrhea.[7,8] Vaginal bleeding however, is not considered a pathognomonic sign in PSTT since patients with the other forms of GTD may present with this symptom. PSTT can also manifest with galactorrhea, virilization, nephrotic syndrome, polycythemia and cutaneous metastases.[11] Unlike other malignant forms of GTD, PSTT is often more slow growing, and tends to spread locally through the uterus. It can involve the lymph nodes before metastasizing elsewhere. Metastases occur more commonly in the vagina and lungs as seen in the case presented. The other sites of metastases include the liver, gastrointestinal tract, bladder, ovary, omentum, diaphragm, spleen, pancreas and bone marrow.[5]

In the case presented, the patient is a 41 years old G2P1 (1011) who presented with irregular vaginal bleeding a year following a suction curettage for a hydatidiform mole. On admission, metastatic work-up revealed spread of disease to the lungs and the vagina.

On transvaginal sonography, placental site trophoblastic tumors commonly present as a posterior wall uterine mass having tiny cystic structures, thought to represent dilated vessels because of the flow void sign identified on magnetic resonance imaging (MRI).[12] They may also appear as a heterogenous, hyperechoic mass with multiple cystic spaces within the myometrium of an enlarged uterus.[13] However, these features alone do not allow distinction from other forms of gestational trophoblastic disease (GTD). On Doppler, both hypovascular and hypervascular forms of the disease have been described in the presence or absence of cystic masses. Again, none of these features are diagnostic of PSTT.[12] Therefore, the main role of imaging diagnosis of PSTT is to confirm the

presence of the mass and to assess the vascularity of the tumor.

PSTT may present grossly as a diffuse nodular enlargement of the myometrium or it maybe microscopic in size. Most of the tumor masses appear well circumscribed but may occasionally be ill defined. The lesion may also be polypoid and project into the uterine cavity or it may invade the myometrium. Cut surface of the tumor is mostly yellow or tan, soft, granular and contains areas of hemorrhage and necrosis.[1]

On microscopic examination, PSTT is composed predominantly of mononuclear cells with an abundance of cystoplasm and does not contain chorionic villi. It often shows sheet of polyhedral, rounded or occasionally spindle-shaped intermediate trophoblastic cells that dissect between individual myometrial fibers and bundles at the periphery.[1] The cytoplasm is predominantly amphophilic in 50 percent, eosinophilic in 44 percent and clear in 6 percent of cases.[14] Fibrinoid material, similar to that associated with extravillous trophoblast in the placenta may be found within blood vessel walls and surrounding groups of cells in 90 percent of cases and is particularly characteristic of PSTT.

Immunohistochemical studies with PSTT often reveal extensive staining for human placental lactogen (hPL).[15] Human placental lactogen is a glycoprotein that is produced by synctial and intermediate trophoblasts in the normal placenta. Since PSTT is composed mainly of intermediate trophoblastic cells large quantities of hPL[11] is produced thus explaining the diffuse positivity to hPL and focal positivity to hCG. (Figure 2) This test is confirmatory of presence of PSTT.

The characteristic microscopic features and immunohistochemical pattern of PSTT were seen in this case. The histopathologic findings were reviewed by 3 different pathologists confirming the findings of PSTT. The tumor cells invaded the myometrium and showed pleomorphic spindly nuclei, dark staining and the vessel walls were invaded by tumor. Abundant fibrin was seen and the tumor was monomorphic. Immunohistochemical staining with hPL showed positive immunoreactivity thus confirming the diagnosis of PSTT.

Human chorionic gonadotrophin (hCG) is the tumor marker of choice for patients with GTD. In PSTT, however, the serum level of βhCG is not reflective of the tumor burden nor with the malignant behavior of this disease. PSTT commonly present with low beta hCG titer despite a large and widespread disease. In a study done at the Caring Cross Hospital,[2] the range of βhCG at the diagnosis was 0-58,000mIu/ml wherein 79 percent have levels of <1000 and 58 percent have levels <500 mIu/ml. Thus, hCG appears to have no predictive value in assessing patients with PSTT and that the disease may still progress even if the levels are not elevated.[5] However, according to the latest research conducted by Cole, et al.[20], hCG free β-sub-unit was noted to be a reliable tumor marker of PSTT. Thus, this justifies the continued use of serum βhCG as a tumor marker for PSTT. In the case presented, the βhCG initially was low ranging from 43.93 to 968,500 mlu/ml prior to the hysterectomy. Such a low titer coupled with a large mass is compatible with the classic presentation of PSTT. However, on follow-up and with the appearance of the vaginal metastasis, beta hCG rose to as high as 968,500mIu/ml. Such presentation is not commonly seen in cases of PSTT and may be due to a possible focal area in the uterus which contained syncytiotrophoblast-like cells which were not sampled during biopsy. Given the short interval from the hysterectomy and the appearance of vaginal and lung metastases, the aggressive behavior found in choriocarcinoma is compatible with the presentation of the index patient. Thus, the possible simultaneous occurrence of a PSTT and choriocarcinoma cannot be ruled out. Baergen, et al. reported two cases of mixed PSTT and choriocarcinoma wherein rare syncytitrophoblast-like cells were found, but the biphasic pattern of choriocarcinoma was seen focally.

Differential diagnosis of PSTT include the normal exaggerated placental site reaction, the rare epithelioid trophoblastic tumor or the early onset choriocarcinoma.[1] The most reliable histologic feature favoring PSTT over the normal exaggerated placental site is the histologic impression of a mass lesion rather than a scattering of individually invasive cells.[4] The normal implantation site has rarely more

than 2 intermediate trophoblastic cells in direct contact with one another as seen in normal exaggerated placental site. In PSTT, clusters and aggregates of intermediate trophoblast are seen. The rare epithelioid trophoblastic tumor (ETT) resembles the monomorphic growth pattern of PSTT, however, the cells of ETT are smaller and display less nuclear pleomorphism. ETT grows in a nodular fashion compared with the infiltrative pattern of PSTT.[18] Unlike PSTT, ETT can present with elevated serum βhCG. In the case presented, a focal area may have contained ETT, which may have been missed out by the pathologist due to its rarity. The possible occurrence of ETT may be proven through immunohistochemical staining using cytokeratins (CK7, AE1/AE3, CAM 5). Unfortunately, these were not done. PSTT can be differentiated from choriocarcinoma through the characteristic biphasic pattern or admixture of cytotrophoblast and syncytiotrophoblast associated with copius hemorrhage seen in cases of choriocarcinoma.[1] Likewise, it lacks the typical vascular palisading and fibrinoid reaction seen in PSTT.

Once the diagnosis of PSTT is established, metastatic work up is done to evaluate the extent of the disease. Diagnostic examinations include transvaginal and whole abdomen ultrasound, chest x-ray. Chest CT scan is done after a normal chest x-ray while a cranial CT scan is done after an aggregate of 3 cm lung masses are detected.

In managing cases with nonmetastatic PSTT, conservative therapy by giving combination chemotherapy without hysterectomy maybe an option for patients desirous of pregnancy.[19] Local excision by hysterotomy with close follow-up of serum βhCG levels, pelvic examination and radiologic imaging such as MRI may also be done.[19] Machtinger, et al. in 2004, reported that the combination of operative hysteroscopy and chemotherapy in women with localized disease, who want to preserve their fertility, can be a possible treatment option in highly selected patients.[16] However, hysterectomy is still the primary mode of therapy if further childbearing is not desired.[2]

In managing cases with metastatic PSTT, hysterectomy plus multiagent chemotherapy using EMACO has shown promising results. The first line of chemotherapeutic regimen should be EMA/CO as reports have shown complete response with this regimen.[17] During the 1990's, response to chemotherapy was variable. However, recent studies have shown that the EMACO[5] can be used satisfactorily. Similar to the other forms of GTD, the use of consolidation courses or clean up courses has been incorporated as part of treatment plan. As in our index patient, the administration of EMACO with 3 clean up courses showed continued normal results further emphasizing the importance of clean up courses in adequately removing all viable trophoblastic tissues no longer detected by the available assays. The administration of granulocyte colony stimulating factor (GCSF) can prevent treatment delays which may arise following intensive administration of multiagent chemotherapy.

Salvage chemotherapy with Etoposide, Cisplatin/Etoposide, Methotrexate, Dactinomycin (EP/EMA) maybe used for treatment failure with EMACO. Other alternative salvage treatments include BEP (Bleomycin, Etoposide and Cisplatin) and VIP (Etoposide, Ifosfamide and Cisplatin).[14] Finkler reported that radiation therapy may also play a role in metastatic cases.[16]

In the index patient, the interval from antecedent pregnancy of one year and the combination treatment of surgery and chemotherapy all provided good results. These are indicators of good prognosis similar to what is reported in literature. It was reported that surgery and chemotherapy would give a 100 percent remission rate.[2] However, recurrences would still develop in over 30 percent of cases.[19] About 5 percent of early stage PSTT will have recurrence while 70 percent of stage III and 90 percent of stage IV will have recurrence. The overall survival for patients with disease limited to genital tract in 94 percent as compared with 33 percent for those patients with metastases. Poor prognosis was signficantly associated with higher stage, metastases, long pregnancy interval, high mitotic rate and high serum hCG level.[14] The patient has been disease free since completion of her treatment 63 months ago.

Follow-up of patients with PSTT includes serial βhCG monitoring, regular physical examination,

chest x-ray, and pelvic ultrasound to detect recurrence.

Summary

Presented was a 41 year old, multipara with a previous molar pregnancy. She presented with vaginal bleeding where she underwent hysterectomy with result of the rare placental site trophoblastic tumor. This disease needs histopathologic diagnosis unlike the other forms of GTN. This disease should be one of the differential diagnoses when presented with low serum βhCG in the presence of a large intrauterine mass with or without metastases. Further immunohistochemical staining with the use of human Placental Lactogen (hPL) can confirm the diagnosis of PSTT as was done in our index patient. The use of multiagent chemotherapy such as Etoposide, Methotrexate, Actinomycin, Cyclophosphamide and Oncovin (EMACO) has provided normal serum βhCG levels indicating remission. Thus, surgery coupled with timely chemotherapy can be good treatment options for the rare PSTT.

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The Surgical Staging of Endometrial Cancer: A Personal Experience

Luciano S.J. Sotto, MD*

From 1998 to November 2006, 140 consecutive private patients with a diagnosis of endometrial cancer were explored. Pelvic peritoneal fluid sample was taken for cytology. Complete abdominal and pelvic exploration and assessment were done, followed by total hysterectomy bilateral salpingooophorectomy and bilateral pelvic node dissection. In eleven patients, radical hysterectomy, bilateral salpingooophorectomy and bilateral pelvic node dissection was done. The incidence of lymph node metastasis was 9.56%. The stage distribution was as follows: stage I, 72.86% (102 pts), stage II, 12.14% (17 pts), stage III, 11.43%, (16 pts) and stage IV, 3.57% (5 pts). One fourth of the patients (22%) received postoperative pelvic radiotherapy. One hundred twenty two patients qualified for a three year follow up. The disease free survival rate of stage I was 88.3%; stage II, 75%; stage III, 56.3%, and stage IV, 0% for an overall rate of 80.16%. The 3 year follow up rate in this series was 93%. There was one surgical mortality and two serious complications from radiation therapy. In conclusion, surgical staging of endometrial cancer is more accurate, easy to do, and markedly reduces and rationalizes the use of radiotherapy. The 3 year survival rate is very respectable.

Cancer of the endometrium or uterine corpus is the most common gynecological malignancy in the United States of America and other developed countries of the west. In the Philippines, it is the third most common gynecological cancer. Until 1988, staging of endometrial cancer was clinical. Fractional curettage, uterine depth, pelvic and rectal examinations were the major components of the clinical staging. The successful feasibility study by Boronow, Creasman, DiSaia, and Morrow on endometrial cancer led to a massive staging study by the Gynecologic Oncology Group (GOG 033). Between 1977 and 1983, nearly 1200 patients with endometrial cancer were entered in these studies. Seventeen abstracts and publications resulted from this work and the findings led to the revision in the FIGO staging for endometrial cancer in 1988. This was published in 1988 in Obstetrics and Gynecology, (the green journal) which is the official journal of the American College of Obstetricians & Gynecologists. The section of Gynecologic Oncology of the PGH adopted the suggested protocol with some minor modifications which we felt were more applicable to our setting.

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The Proposed Guidelines

All patients with a diagnosis of endometrial cancer shall be staged surgically, except those who are poor surgical risks. The diagnostic procedures maybe any one of the following: conventional D & C, fractional curettage and endometrial biopsy.

The surgical staging technique was as follows:

1. Midline suprapubic incision.
2. Peritoneal fluid sampling (pelvic) or peritoneal washings.
3. Inspection and palpation of the abdomen and pelvis.
4. Total hysterectomy and bilateral salpingo-oophorectomy.
5. Bilateral pelvic node palpation, sampling or dissection.

We in PGH decided on routine pelvic node dissection.

The histological report will determine the stage of the cancer.

The surgical stages are as follows:

STAGE I The cancer is confined to the uterine corpus.
- IA. the cancer is limited to the endometrium.
- IB. myometrial invasion is less than 50%.
- IC. myometrial invasion is more than 50%.

STAGE II. The cancer involves the cervix.
- IIA. cervical glands only.
- IIB. cervical glands and stroma.

STAGE IIIA. the tumor invades the serosa, and/or adnexae, and/or positive peritoneal cytology.
- IIIB. vaginal metastasis.
- IIIC. metastasis to the pelvic and/or paraaortic nodes.

STAGE IVA. the tumor invades the bladder or rectal mucosa.
- IVB. distant metastasis, including intra-abdominal and/or inguinal nodes.

All the sub-stages bear the numbers 1, 2, or 3, indicating the histological grade of the tumor (Gr. 1, well differentiated; 2, moderately differentiated; and 3, poorly differentiated). Some patients shall receive postoperative treatment, depending on the risk factors present. In the protocol that we prepared, we identified the different factors that were at high risk for recurrence, and these were;

1. Poorly differentiated tumors, Grade 3.
2. Stage II tumors if only total hysterectomy was done.
3. Deep myometrial invasion.
4. All stage III tumors (positive nodes, positive cytology, adnexae and parametria.)
5. Stage IV

The postoperative treatments prescribed were as follows:

1. External beam radiotherapy.
2. Complete pelvic radiation, (paraaortic radiation in some cases).
3. Chemotherapy
4. Hormone therapy

This Series

From 1988 to November 2006, (an 18 year period), one hundred forty patients (140) with endometrial cancer were surgically staged and treated. This represented 100% of all the untreated cases seen in this author's clinic.

Age Incidence

The youngest patient was 32 year old and the oldest, 82.

Nine patients were 40 years old and younger. Sixty-one percent were 51 years old and older. Endometrial cancer is a disease of older women.

Table 1. Age distribution.

40 and Below	9	6.4%
41 - 50	44	31.4%
51 - 60	47	33.6%
61 - 70	24	17.1%
71 plus	15	10.7%

Parity

Forty six patients (32.9%) were nulliparous, and 47 (33.6%) had a parity of 1-3.

Table 2. Obstetrical history.

Nulliparous		46	32.9%
Parity	1-3	47	33.6%
	4-6	35	25.0%
	7 plus	10	7.2%
	Unknown	2	0.3%

Overweight and Obesity

Sixty four patients or 45.7% were overweight

Diabetes Mellitus

This was seen in 26 patients or 18.6%.

Diagnostic Procedures

Prior to 1988, fractional curettage was required in the clinical staging of endometrial cancer. The 1988 surgical staging did not require this anymore. In this series, majority of the patients (75 or 53.5%) underwent conventional D & C and a little more than one third (37.14%) had fractional curettage. There were 8 patients whose diagnosis was established at the time of surgery. In five of these, the main indication was myoma. When the uterus was opened, there was an obvious cancer. In one patient, frozen section was requested. The indication for surgery on one patient was endometriosis, but her chief complaint was postmenopausal bleeding. In all these patients we proceeded to bilateral pelvic node dissection after the hysterectomy. (Table 3)

Table 3. Diagnostic procedures.

Fract. D & C	52	37.14%
D & C	75	53.57%
Endo biopsy	5	3.5%
At surgery	8	5.7%

Two patients were explored for possible ovarian newgrowth. They had ascitis and abdominal masses. The tumor turned out to be primary endometrial malignancy. (Table 3)

Histological Types

Based on the histology of the surgical specimens, 134 (95.71%) had an endometrioid type of adenocarcinoma. There were three patients with clear cell carcinoma and three with papillary serous carcinoma. (Table 4).

Table 4. Histological types.

Adenocarcinoma	134	95.71%
Clear cell CA	3	
Papillary serous CA	3	

Histologic Grade of Adenocarcinoma

Sixty percent had a well differentiated adenocarcinoma, Grade 1. In 28 percent, the tumor grade was 2, or moderately differentiated, and in 12 percent, poorly differentiated, or Grade 3 (Table 5).

Table 5. Histological grade.

Well Differentiated	(Gr. 1)	82	59.85%
Moderately Differentiated	(Gr. 2)	39	28.46%
Poorly Differentiated	(Gr. 3)	16	11.67%
Total		127	
Papillary serous CA		3	

Pelvic Nodes

One hundred twenty three (87.85%) patients had negative pelvic nodes. These included six patients whose pelvic nodes were evaluated by palpation. There were 13 (9.56%) with metastasis to the pelvic nodes. The average number of pelvic nodes harvested was 6 to 8. This is lower than the number of nodes in radical hysterectomy for cervical cancer. (Table 6)

Table 6. Pelvic node metastasis.

Negative for CA	123	(6 by Palp.)
Positive for CA	13	(9.56%)
Not evaluated	4	

Pelvic Peritoneal Fluid Cytology

One hundred thirty six patients had pelvic peritoneal fluid sampled, and 8 (5.9%) were positive for malignant cells. They were then placed under stage III A. (Table 7)

Table 7. Pelvic peritoneal fluid.

Negative	128	
Postive	8	5.9%
Not done	4	

Tumor Size

The size of the tumor was measured and this can be seen in table 8. Almost one third had tumor measuring more than 4 cm and filling the endometrial cavity. There were nineteen specimens that did not show any residual tumor. (Table 8)

Table 8. Tumor size.

	Residual	
No tumor	19	13.57%
Less than 2 cm	29	20.71%
2 - 4 cm	49	35.0%
Over 4 cm	35	25.0%
Whole cavity	8	5.71%

Myometrial Invasion

It is an accepted fact the depth of myometrial invasion influences the prognosis of endometrial cancer. In this series, myometrial invasion was absent in 31 (22.1%) patients. This included those with no residual cancer in the surgical specimen, but had positive preoperative biopsies. Seventy (50%) had myometrial invasion of less than 50 percent and 39 (27.9%) had more than 50% myometrial invasion. (Table 9)

Table 9. Myometrial invasion.

No invasion	31	22.1%
Less than 50%	70	50.0%
More than 50%	39	27.9%

Cervical Involvement

Tumor invasion of the cervix, be it gland or stroma or both, places the stage at II. In the early part of this series, we persisted in doing fractional curettage because our preferred treatment for such cases was, and still is, radical hysterectomy and bilateral pelvic node dissection. This explains the number of radical hysterectomy in this series. The incidence of cervical involvement in this series was 29 percent. Some of these patients were actually stage III lesions with cervical tumors as well (Table 10)

Table 10. Cervical involvement.

With cervical involvement	29%
Without cervical involvement	71%

Operative Procedure

A large majority (87.14%) underwent total hysterectomy, bilateral salpingooophorectomy, and bilateral pelvic node dissection. Eleven patients (7.85%) had radical hysterectomy, BSO and bilateral pelvic node dissection. Seven (5%) had total hysterectomy and BSO only. (Table 11)

Table 11. Operative procedures.

Total Hyst. BSO, BLND	122	87.14%
Rad. Hyst. BSO, BLND	11	7.85%
Total Hyst. BSO	7	5.0%

Stage Distribution

One hundred two patients (72.86%) were classified as having stage I disease; 17 stage II cancer; 16, stage III and 5, stage IV. A large majority, almost three fourths had their tumor confined to the uterine corpus. (Table 12)

Table 12. Surgical stage distribution.

Stage I	102	72.86%
Stage II	17	12.14%
Stage III	16	11.4%
Stage IV	5	3.5%

The following tables show the substage distribution.

Table 13. Sub stage distribution.

Stage/Substage	Number	Percent
I A	26	25.4
B	58	56.8
C	18	16.8
Total	102	72.86
II A	6	
B	11	
Total	17	12.14
III A	4	
B	0	
C	12	
Total	16	11.43
IVA	0	
B	5	3.57

Table 14. Substage and tumor grade.

Stage/Substage	Number	Percent
I A 1	23	17.03
B 2	3	2.2
A 3	0	
Total	26	19.25
I A 1	37	27.4
B 2	16	11.85
B 3	5	3.7
Total	58	42.96
I C 1	8	5.9
C 2	6	4.4
C 3	4	3.7
Total	18	14.0
II A 1	4	2.9
A 2	2	1.4
Total	6	4.4
II B 1	4	2.9
B 2	5	3.7
B 3	2	1.4
Total	11	8.14
III A 1	0	
A 2	1	
A 3	2	
Total	3	2.2
III B 1	0	
B 2	0	
B 3	0	
III C 1	6	4.4
C 2	6	4.4
C 3	1	0.8
Total	13	9.6

Postoperative Treatment

Based on the protocol on surgical staging of 1988, 36 patients (25.7%) had additional treatment. These were the patients who had one or more risk factors for recurrence. Thirty one out of 36 received radiotherapy, alone or in combination with chemotherapy. (Table 15)

Prior to the surgical staging classification of 1988, the standard treatment of endometrial cancer consisted of intracavitary radium followed by total hysterectomy six weeks later. This was universally practiced. Only a few centers used surgery alone. In 1957, at the Roswell Park Cancer Center in Buffalo

New York, I was in charge of a randomized study between intracavitary radium plus hysterectomy and surgery alone. When the study matured, there was no difference in the survival rate between the two modalities. The results of this study was published in Surgery, Gynecology & Obstetrics (SGO) in 1971. When I started in PGH in 1961, primary surgery became our policy. Of course at that time, we were not equipped to give intracavitary radiation. We didn't have any radiation facilities in PGH then.

Table 15. Postoperative treatment.

No treatment	104	74.3%
EBRT	19	
Complete R.T.	9	22.4%
RT plus Chemo	3	
Chemo only	5	3.5%

In this series, the use of radiotherapy was limited to less than one fourth of the total number of patients. These were the patients who had high risk factors for recurrence.

Results of Treatment

This report will describe the condition of the patients treated 3 years after treatment. I will use the old terminologies such as NED (no evidence of disease clinically), DD (died of disease), DOC (died of other causes), LOST TO FOLLOW UP, and alive with disease (AWD). The more common terminologies at present are, DFS (Disease Free survival), PFS (Progression Free Survival), OS (Overall Survival) and SD (Stable Disease).

One hundred twenty two patients treated had a follow up of at least 3 years. I had a good follow up at 3 years, but after this period, most patients did not come for check up anymore.

Eighty six patients belonged to stage I and 76 (88.37%) were alive with no evidence of disease 3 years after treatment. Sixteen patients with stage II lesion were treated and of these, 12 (75%) were alive with no evidence of cancer clinically. The survival of patients with stage III disease was 56.3%, (9/16). All five patients with stage IV cancer died within one year of treatment. The overall 3 year survival rate was 80.16% (97/122). A total of 15 patients died of cancer, within 3 years of their treatment. Eight patients were lost to follow up and one patiend died of hypertensive heart disease. There was one mortality. (Table 16)

Table 16. Three year disease free survival rate.

Stage	Number	Med/DFS	Percentage
I	86	76	88.37
II	16	12	75.0
III	16	9	56.3
IV	4	0	0
Total	122	97	80.16
	Died of cancer	15	12
	Lost to follow up	8	
	Doc	1	
	Sur.. mort.	1	

There were patients who were deemed at high risk for recurrence. Of 27 patients treated, 20 (74.07%) were alive and well at 3 years.

Mortality and Complications

There was one surgical mortality in this series. This was a 32 year old single patient, obese, with uncontrolled diabetes and hypertensive heart disease that took the cardiologist 3 weeks to give clearance for surgery. There was no problem during the surgery. Eight hours after surgery, this author made his rounds. She was awake and her vital signs were normal. I talked to her, and told her she could turn from side to side. We had a short conversation and by all indications she was alright. Around 30 minutes later, according to the mother, she developed seizures and lost consciousness. It looked live a CVA. CT scan of the brain later on revealed diffuse brain findings. She did not recover from this anymore. There were two patients who developed severe rectal complications following

radiation. One developed rectovaginal fistula and another developed rectal ulcer with repeated episodes of rectal bleeding that required repeated blood transfusions. The patients with rectal fistula had a colostomy. Both patients were alive and well 3 years after treatment.

There was no serious complication that could be blamed on the bilateral pelvic node dissection.

Comments

The superiority of surgical staging over the clinical staging of endometrial cancer is universally accepted. The Roman numerals indicate the anatomical extent of the tumor. The capital letters suggest the biological aggressiveness of the tumor, such as myometrial invasion, cervical involvement, extrauterine and lymph node metastases, as well as distant metastases. The numbers 1, 2, and 3, indicate the histological grade of the tumor. At a glance, each stage and substage under which a certain patient is assigned or classified, tell us the extent of the tumor as well as the possible prognosis. It also tells us whether or not, a particular patient will require post operative treatment.

The surgical staging is comprehensive, all embracing, practical and easy to duplicate. However, it is still far from being perfect. There are still some questions that need to be answered, such as,

1. Should paraaortic node dissection be done routinely on all cases, or should it be limited to those with positive pelvic nodes?
   Direct metastasis to the paraaortic nodes is supposed to be quite rare. What are the risks involved in paraaortic node dissection? What are the complications of paraaortic radiation? Should this be necessary following paraaortic node sugery?
2. As regards postoperative adjuvant treatment, we are limited to radiotherapy. I believe more randomized studies are needed.
3. Do we have effective chemotherapy agents for endometrial cancer?
4. What is the real role of hormone therapy in this disease?

The personal series that I have just presented is small in number, and not randomized. It is a cohort of patients staged and managed under the original protocol with some minor modifications. The three year disease-free survival rate to me is quite good, especially with the stages I & II disease, and even the stage III lesions.

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Keynote Address*

Augusto M. Manalo, MD**

Thank you, Dr. Limson. Thank you for your very kind introduction. I could not help but feel a furtive tear in my eye when you said that perhaps the reason why I am very passionate about things is my being born in an idyllic barrio in Batangas. That is very true. If I should be born again, I would choose to be born in the same place, where the sun always shone with a warm though somewhat melancholy glow, and every sound, from the chirping of the birds to the roar of the thunder seemed like music to my ears.

Dr. Efren J. Domingo, President of the Society of Gynecologic Oncologists of the Philippines, Dr. Gil S. Gonzalez, President of the Philippine Society for Cervical Pathology and Colposcopy, Dr. Lourdes B. Capito, President of the Philippine Society for the Study of Trophoblastic Diseases, other officers and Past Presidents of the three societies, Dr. Rey H. de los Reyes, Vice President of the Society of Gynecologic Oncologists of the Philippines and Overall Chairman of the Organizing Committee for this Convention, Dr. Suzanne Garland and Dr. Diane Harper, our very distinguished speakers from across the seas, Colleagues, Ladies and Gentlemen:

I am deeply honored, and humbled, that I should be asked to address our most esteemed colleagues, and share with them my personal and professional philosophies, including what I think each of us can do to help build a healthy nation that we all want to have. It would be like talking to a group of very intimate friends. Many of you have recently graduated from fellowship and residency training programs with me as one of your mentors. Many of you have been co-faculty member in these training programs. Having been President of two other organizations, the Philippine Obstetrical and Gynecological Society and the Philippine Society of Oncologists, I have invited many of you to our various committees and have worked intimately with you. Indeed, you have all touched my life more than you will ever know.

It has been about seven years now since we stepped into the twenty first century. We are still striving to attain excellence in our specialties. We still find ourselves torn between the strong and often conflicting forces of globalization and the value that we, in our formative years, have sworn to uphold-nationalism.

With the rapid and almost unbelievable advances in science and technology, particularly information technology, national boundaries have started to crumble and we find ourselves looking at an almost limitless horizon. I hope that in the vast expanse, we can still see the distant islands that constitute the rest of our country.

As we pride in our ability to integrate recent concepts and philosophies, our ability to adopt recent technologies and, of course, our potential to contribute significantly to international good, we should not forget the millions of Filipinos, particularly in our distant regions for whom our organizations also exist.

Perhaps, right now, in an isolated village in the Mountain Province, a woman is bleeding profusely from an undiagnosed cancer of the cervix. She has not had the benefit of a Papanicolau smear, or even an internal examination.

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** Professor Emeritus, College of Medicine, University of the Philippine Manila; Past President, Society of Gynecologic Oncologists of the Philippines.

Perhaps, right now, in an almost inaccessible island in Mindanao, a woman is writhing in pain, at the same time clutching a mass in her lower abdomen. The mass has been present for several months, but completely ignored because of the absence of health care provider in her vicinity.

Perhaps, right now, in the slums of Metro Manila, in a shanty beneath the imposing buildings, or along the railroad tracks, or by the banks of the estero, not very far away from the health centers, a woman is giving birth to what her lay attendants consider as wonder of all wonders - hydatidiform mole. She has not had the benefit of even one or two prenatal examinations.

Who among us would not be touched by the scenarios which I have just described? They are only examples of the grim realities of our nation's present state of health, a state of health that is fired by poverty and inaccessibility of health care facilities. Who among us would not, even once in a while, want to sacrifice his conveniences and even put himself at risk, to be able to reach out to these people? Those of us who work in charity hospitals may feel less guilty, but then we only serve those who can afford to come to the hospital. The cries of these people, mostly from far away places, will continue to reach us, will continue to haunt us, like the mournful sounds of distant drums.

I am reminded of the writings of John Donne, writings that have provided inspiration for Ernest Hemingway's celebrated novel, "For Whom the Bell Tolls." To paraphrase him, "No man is an island, entire in itself. Every man is part of the continent. Every man is part of another man because they are both parts of creation. If a man dies, you cannot say, even to yourself, that you are not responsible for his death. So why should you grieve for him? The truth is, when he dies, a part of you dies with him. You become a lesser man. Therefore, in your quiet evenings, when you hear the mournful sounds of the bell, do not send to know for whom the bell tolls; it tolls for thee."

In 1997, in my Baldomero Roxas Memorial Lecture before the Philippine Obstetrical and Gynecological Society, I raised the following questions:

1. What kind of health care delivery system must we help design?
2. What kind of residents and fellows must we graduate?
3. What reforms in medical education must we try to effect?
4. What researches must we initiate and preferentially support?

I am sure that many of you will notice that most of the things that I am saying now are just repetitions of things that I have said before, in previous lectures, in previous years. I find it very necessary to do this because I still believe that someday, the messages would fall on more receptive ears.

This deplorable state of health in our regions has also been the finding in the Regional Workshops of the Asia Oceania Federation of Obstetrics and Gynecology and the Philippine Obstetrical and Gynecological Society, of which I was privileged to be the National Coordinator. These were undertaken from 1995 to 1997. In these workshops, we invited, as participants, all levels of health care providers as well as representatives from the communities, the recipients of health care. In many communities, some of which could only be reached by foot, the problems identified seemed insurmountable and the solution suggested sounded more like wistful dreams.

While we may not have created a significant dent in the health care delivery system in the regions that we visited, we have truly become sensitized to the health problems of these regions. So are the participants from the major cities and towns. These participants can now work with passion in their communities.

Focusing on women's cancer, which is the main concern of our organizations, our present situation is indeed very disheartening. We have learned that out of our total national budget, only two percent is allocated for health. This is mostly channeled to other health priorities like control of communicable diseases, safe motherhood and promotion of children's health. What is left for cancer control?

Focusing specifically on cancer of the cervix which is our leading gynecologic cancer, it has been estimated that in year 2005, 7,277 new cases would

be discovered and 3,807 deaths from the malignancy would occur. These are the grim figures from the Philippine Cancer Facts and Estimates. These figures have not significantly changed in the past several decades, considering that much progress has already been made in many developed countries in terms of prevention, early diagnosis and effective treatment.

Most of the cases seen are in the late stages: stage IIb to stage IV. Considering that adequate treatment facilities are available only in a few tertiary care hospitals, cancer of the cervix has indeed become a killer disease among Filipino women.

It is most unfortunate that the victims of this disease are generally women of low socioeconomic status who can hardly meet the cost of screening, diagnosis and treatment.

The burden of this disease cannot be expressed only in terms of incidence and mortality figures. We have to consider also the economic burden brought about by the high cost of diagnosis and treatment and the loss of earnings while the afflicted women are undergoing treatment. Above all, we should not fail to consider the social burden. Since these women are generally multiparous, many children are deprived of the tender, loving maternal care while their mothers are undergoing treatment. More so if the treatment fails and these mothers die.

Past efforts to control cancer of the cervix in the Philippines have been very ineffective. Our screening programs have targeted perhaps less than 10% of our susceptible women. We have depended mainly on the Papanicolaou smear, the results of which, in many regions, have taken eternities to become available.

It is a comforting thought that we have now become aware of a nationally relevant and cost effective screening method. Knowing the limitations of the Papanicolaou smear which is highly dependent on good infrastructure, we are now advocating visual inspection of the cervix with the aid of acetic acid, particularly in areas where the Papanicolaou smear is not available or not practical. We are also advocating the single-visit approach.

We are also supporting, very enthusiastically, vaccination of our women, particularly the young ones, against the human papilloma virus, the essential cause of cancer of the cervix. Although the program is still in its infancy, it has been well received, and endorsed, not only by gynecologists but also by pediatricians. In fact, in our program for today, we have devoted almost one whole day for the topic. We are only waiting for the health information to completely cascade to our poor and illiterate women, and make the services accessible and affordable to them, before we can pressure our government to make it mandatory.

Recently, the Philippines joined the Asia Oceania Research Organization on Genital Infection and Neoplasia (AOGIN), an organization which brings together clinicians and scientists who will work hand in hand with all health care providers, particularly those who deal with women's health. Areas of concern include continuous assessment of the cervical cancer burden in Asian countries, cervical cancer prevention and screening, natural history, immunology and molecular biology of HPV and HPV vaccine updates. The last International Conference held in Cebu City was indeed a milestone in our efforts to decrease significantly the incidence of cancer of the cervix in our country, as well as in the rest of Asia and Oceania.

Also recently, the Cervical Cancer Prevention Network (CECAP) was established at the Cancer Institute of the UP-PGH Medical Center. Funded by JHPIEGO and strongly supported by the Department of Health, it is an alliance of organizations from both the private and public sectors with a vision of a cervical cancer free Philippines. Its program for cervical cancer prevention and control is very comprehensive: from professional as well as lay cancer education, enhancement of the capabilities of all health care providers involved, prevention, screening, early diagnosis, treatment and rehabilitation.

Needless to say, the Department of Health, through the National Center for Disease Prevention and Control, has doubled its efforts to help eradicate cancer of the cervix in our country and is working in close collaboration with the CECAP. This is in addition to its previous Administrative Order endorsing the use of visual inspection with the use of acetic acid in cervical cancer screening.

If the interest and capability of all those involved can be sustained, I believe that in about 10 year's time, the incidence of cancer of the cervix will significantly decrease and its stage distribution will significantly improve.

In spite of all these developments, I still seem to see a cloud of doom hovering menacingly over us. Years from now, who is to undertake these programs? Although reproductive health care is multidisciplinary, multisectoral and multilevel, the burden of responsibility and the task of implementation still rests upon the shoulders of the physician.

As early as now, we are already beginning to feel the exodus of some well-trained physicians. Many of the fresh graduates of medical schools and graduates of residency programs have shifted to another profession because of the attraction of more lucrative positions abroad. Others are leaving us because they cannot stand anymore the spectre of hunger and disease, graft and corruption, lawlessness and terrorism in our surroundings. Promises of a better life are heard only just before election time. However, this much I can say: no matter how you look at the problems of our country, abandonment is certainly not the solution.

One very important human value seems to have been lost-the value of gratitude-gratitude to the country which provided the venue for our medical education and training, gratitude to the local mentors who have given their quality time, the best years of their lives, to mould us into men and women that we are now, and most of all, gratitude to our patients, our clinical material whom we have extensively used, and sometimes abused, during our training.

Somehow, through these clouds of doom I can still see some rays of hope. You are these rays of hope. If you are not determined to stay in our country, why should you bother to attend a local medical convention such as this?

Many of you have recently graduated from residency and fellowship training programs. A few of you are still in these programs. I hope that these programs have not only made you academically and clinically competent physicians but have also sensitized you enough to the needs of our people. I hope that these programs have taught you that serving our people, particularly the poor and those in need, is not only an obligation but a privilege, a very good opportunity to put meaning into your training.

Some of you may choose to be connected to a university hospital. You can exert more influence there, on your students and on your resident trainees. If, in spite of your busy schedule, you can still find time to walk through "the road not taken", to borrow the words of Robert Frost, "the less trodden roads" of organized and sustained community service, you may find, at the end of this road, a picture of healthy and happy people which, at this time, has still remained as a very elusive dream.

If, once in a while you can be tormented by your inability to reach out to our people; if, once in a while you can find it in your heart to weep over the poverty, the poor health and the loneliness of our people, I can truly say that:

Maybe you are the reason why many of us have spent the best years of our lives being involved with residency and fellowship training programs.

Maybe you are the reason why we have never stopped trying to improve those programs.

Maybe you are the reason why we can walk with joy into the twilight of our careers, because we know, we know fully, that there will be you to continue what we have failed to do - to take good care of our people.