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The Philippine Journal of Gynecologic Oncology (ISSN 2704-3045) is the peer-reviewed journal produced as a program of the Society of Gynecologic Oncologists of the Philippines (SGOP). It is published biannually by the SGOP with business and production offices at Unit 404, Manila Astral Towers, 1330 Taft Ave. cor. Padre Faura Sts., Ermita, Manila, Philippines.

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Minimally Invasive Radical Hysterectomy: Is it the end of a journey just begun?

Renee Vina G. Sicam, MD, FPOGS, FSGOP, FPSGE

Much has been said and written about the state of the minimally invasive approach to cervical cancer. Ever since the Laparoscopic Approach to Cervical Cancer (LACC) trial of Dr. Pedro Ramirez et al. was presented in March 2018, gynecologic oncologists who perform robotic or laparoscopic radical hysterectomy were compelled to reevaluate the application of this procedure. The LACC trial is a randomised non-inferiority study that compared laparoscopic or robotic radical hysterectomy against abdominal radical hysterectomy for stage IA1 with lymphovascular space invasion, IA2 and IB1 (FIGO 2009) cervical cancer. Due to the trend of higher rates of deaths in the minimally invasive surgery arm, the data and safety monitoring committee recommended closure of the study before completion of patient recruitment. Only 631 patients out of planned 740 were included and randomized to either minimally invasive surgery (319) or open surgery (312). With the available data, it was found that the minimally invasive approach was associated with lower rates of disease-free survival at 4.5 years (86.0% versus 96.5%, 95% confidence interval, -16.4 to -4.7) and overall survival as compared to open surgery (3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77 to 20.30).[1]

These results were met with both alarm and skepticism by the endoscopic community. Almost ten years had passed since the publication of the Gynecologic Oncology Group LAP2 which cemented the role of minimally invasive surgery in surgical staging of early endometrial cancer.[2] The SGO guidelines stated that minimally invasive surgery should be recommended as the standard surgical approach for endometrial cancer due to less complications and hospital stay, and comparable overall survival rates to laparotomy.[3] The Society of Gynecologic Oncology of the Philippines (SGOP) embraced this recommendation with the caveat that it should be performed in areas with surgical expertise and appropriate facilities.[4] Over the years, more and more gynecologic oncologists expanded their indications for laparoscopy from diagnosis of adnexal masses to staging of endometrial and cervical cancer. Robust experience in laparoscopy and the development of the robotic platform enabled endoscopists to overcome the steep learning curve of radical hysterectomy (RH) or trachelectomy with pelvic lymphadenectomy for cervical cancer.[5] Several published observational and retrospective studies supported the feasibility and safety of minimally invasive approach to radical hysterectomy. Thus, the findings of the LACC trial of poorer survival after laparoscopy or robotic surgery was unexpected.[6]

The strength of the LACC trial is its randomized prospective multi-center design. For quality control, each of the surgeons of the 33 institutions were required to submit outcomes of at least 10 laparoscopic or robot-assisted radical hysterectomies. The gynecologic oncologist surgeon was required to perform both open and minimally invasive RH. Surgeons were evaluated in the proficiency of their skills through a committee review of two unedited minimally invasive type III radical hysterectomy videos, to assure that only experienced endoscopists would be included in the study.[1] At the same time, a cohort study conducted by the National Cancer Institute showed that in patients with stage IA2 or IB1 cervical cancer who underwent radical hysterectomy, minimally invasive surgery had a higher 4-year mortality of 9.1% compared to 5.3% in open surgery (hazard ratio, 1.65; 95% confidence interval 1.22 to 2.22; P=0.002).[7] The impact was so great that larger cancer centers abroad reverted back to open surgery. The SGOP followed suit by not recommending minimally invasive surgery for cervical cancer in its Clinical Practice Guidelines of 2018.[4] In September 2019, the SGO updated their statement on the surgical approach to cervical cancer. Although minimally invasive radical hysterectomy was not declared as contraindicated, SGO stated that "gynecologic oncologists are encouraged to consider all available data as they counsel individual patients to determine the most appropriate surgical approach."[8] The National Comprehensive Cancer Network announced that open radical hysterectomy should be offered as the standard of care for stage IA2-IB1 cervical cancer. If the patient still wants minimally invasive surgery, an informed shared decision-making should be achieved.[9]

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She is a Clinical Associate Professor of the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology of the Philippine General Hospital. Dr. Sicam is the current Chief of the Section of Minimally Invasive Surgery, Department of Obstetrics and Gynecology of the Makati Medical Center.

On the other hand, the authors of the LACC Trial acknowledged several limitations of their study. Firstly, only 59.7% of the patients reached the 4.5-year follow-up point (median of 2.5 years) at the time of analysis, due to the alert to stop the study for safety reasons. The final publication achieved a power of 84%, meaning that the accuracy of the null hypothesis that MIS is inferior to open surgery is 84% accurate, and conversely, 16% up to chance. Secondly, the trial was not powered enough to conclude the same outcomes for patients with a low risk of recurrence, such as those with tumor size less than 2 cm, no lymphovascular space invasion, less than 10 mm stromal invasion and absence of lymph node involvement. Furthermore, though it was beyond the scope of the research, they could not explain the reason why there was poorer survival in the laparoscopy/robotic arm. The authors hypothesised that the widespread utilization of a uterine manipulator may have caused tumor spillage, or that carbon dioxide may have a biological effect on the tumor cells.[1]

Early comments on the LACC trial pointed out that the survival outcomes of the patients in the open RH arm performed extraordinarily well. Based on previously published prospective trials of open surgery in similar patient populations, the expected 3- to 5-year progression free survival is 80-95%, whereas the laparotomy arm in the LACC trial had a DFS of 96.5%. In contrast, the MIS arm had a DFS of 86%.[6] In addition, there were only 7 recurrences in 312 patients (2.2%) in the open arm, as compared to 27 (8.4%) in the MIS arm. Reported recurrence rates for abdominal radical hysterectomy vary from 9.1% and 14.3%. The authors could not account how the open arm had such a good oncologic outcome in the LACC trial whereas the MIS arm performed within what was expected.[6,10,11]

The main criticism against the LACC trial was the assumption that the surgeons performing the laparoscopic/robotic-assisted RH had sufficient skills. The Asia-Pacific Association for Gynecologic Endoscopy and Minimally Invasive Therapy (APAGE) through its published statement, questioned the evaluation and selection of the surgeons who participated in the study. APAGE asserted that the minimum requirement of 10 prior LRH or RRH and 2 surgical videos were not enough to assess the experience of the surgeon.[12] In literature, 40-50 cases of LRH are necessary to overcome the learning curve to be able to achieve optimal radicality and good oncologic outcomes.[11] The LACC trial had 631 patients operated on in a span of 9 years in 33 different centers, which can be extrapolated to only 2.1 radical hysterectomies per year per center. The low volume of surgeries reflects on the experience of the surgeon and center.[10,12] Furthermore, they argued there was no standardization of surgical techniques among the surgeons. The extent of resection of the parametria may not be uniform such that some may have performed more radical surgeries to achieve better margins while others may have not. Details on what instruments were used were lacking.[12]

While others may have abandoned LRH/RRH, some authors have recommended preventive techniques such as discontinuing the usage of a uterine manipulator, avoidance of intraabdominal colpotomy and placing the uterus in a specimen bag. Some have limited the indication of the procedure to those with tumors of less than 2cm. A recently published multicenter study of 1952 patients underwent vaginal-assisted laparoscopic radical hysterectomy (VALRH). It is a combined laparoscopic and vaginal technique without a uterine manipulator that avoids spillage and manipulation of the cervical tumor. A vaginal cuff is created and closed vaginally while developing the pre-rectal and vesico-vaginal spaces. The resection of the parametria is completed laparoscopically. The technique shows immense promise such that the 3-, 4.5-, and 10-year disease-free survival rates were 96.8%, 95.8%, and 93.1% are comparable to the open arm of the LACC.[13]

The challenge to come up with a randomized study is being spearheaded by the APAGE in the form of the MITOR Study (Minimally Invasive Therapy versus Open Radical Hysterectomy). Its primary objective is to compare the disease-free survival of patients with early-stage cervical cancer undergoing total laparoscopic/radical hysterectomy versus total abdominal hysterectomy. It aims to include only experienced surgeons, such that 100 cases of LRH are required from the surgeon and his/her center should perform 50 cases of LRH per year or a history of more than 200 cases. As of November 2019, recruitment was ongoing.[14]

As the debate rages on regarding the LACC trial, it makes us think about its implications in the local practice of minimally invasive surgery for cervical cancer. With more SGOP members becoming adept in laparoscopy and/or robotics, should we be dissuaded from performing radical hysterectomy via MIS? In 2017, the Division of Gynecologic Oncology at the Philippine General Hospital (PGH) incorporated laparoscopic surgical staging for early endometrial cancer in the fellowship training program. Out of 121 cases of endometrial cancer staging surgeries at the charity ward in 2019, 9% were performed laparoscopically.[15] We expect this number to increase as the number of faculty and fellows trained in MIS increases. Translating this to cervical cancer may not be too easy. Competence in open radical hysterectomy is an essential skill the fellows must obtain from the gynecologic oncology program. Majority of the cervical cancer patients are diagnosed in advanced stages, and only a minority of cases are eligible for primary surgery. Since the training of the fellows in open surgery must be prioritized, there are not enough clinical cases to achieve the high volume needed for the learning curve of LRH. We may rectify this by cooperating with gynecologic oncologists in other institutions to pool our cases in a context of a study. In addition, strengthening the cervical cancer screening program would allow detection of more cases of early cervical cancer suited for radical hysterectomy. Till then, it is prudent to wait for the results of future randomized controlled studies, while continuing to gain expertise in what is known to be oncologically safe. It is not the end of the MIS journey, but a moment of pause, skill acquisition and watchful waiting.

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Chemotherapy-related hematologic toxicities among elderly women with endometrial and ovarian cancer: A 10-year experience in a tertiary hospital

Maria Constancia Y. Wylengco, MD, FPOGS, DSGOP and Jericho Thaddeus P. Luna, MD, FPOGS, FSGOP

ABSTRACT

Background: Increased toxicity of antineoplastic drugs may be anticipated due to the increased vulnerability of multiple organ systems in the elderly. Decreased absorptive ability, decreased volume of distribution may also be expected, in addition to the decrease in glomerular filtration rate and hepatic drug metabolism. Having frail physiology, elderly patients are prone to complications brought about by chemotherapy.

Objective: This study aimed to determine the prevalence of, and factors associated with chemotherapy-induced hematologic toxicities among elderly women (60 years and above) diagnosed with endometrial and/or epithelial ovarian carcinoma seen at a tertiary care government hospital.

Methodology: This retrospective cohort study utilized data and patient records of patients sixty and above diagnosed with endometrial or epithelial ovarian cancer who received systemic chemotherapy from the outpatient department of the Philippine General Hospital from 2007-2016.

Data Analysis: Data processing and analysis were carried out using the software Stata 13. Descriptive statistics were used for continuous variables; frequency and percentage were used for the categorical data variables so as to provide an overview of the study population. Logistic regression was utilized in determining factors affecting presence of hematologic toxicities, while fisher exact test for association of specific toxicity and demographic variables.

Results: Seventy-nine patients aged sixty and above were included in the study, majority of whom belonged to the 60 – 64 age range, with good functional capacity. Most patients received multi-agent chemotherapy, and the mean number of chemotherapy cycles given was five cycles. A higher age group of 65 – 69 years old had a statistically significant impact on the occurrence of leukopenia (p value= 0.0386), neutropenia (p value= 0.0386), and thrombocytopenia (p value= 0.0386), but not anemia compared to those aged 60-64 years old.

Conclusion: Increasing age had a statistically significant impact on the occurrence of leukopenia, neutropenia, and thrombocytopenia. Neither performance status, cancer type, nor disease stage are significant predictors of hematologic toxicity in the elderly population.

Keywords: *Elderly, Gynecologic cancer, Systemic chemotherapy, Hematologic complications*

INTRODUCTION

With the recent advances in the treatment of cancer, there is also an increase of cancer survivors. In the United States, almost half of the survivors are more than 70 years old.[1] In addition, advanced age is also a risk factor for some types of malignancies. Unlike the general population, elderly patients have special physiologic changes that needs to be considered when initiating treatment.[2] Hepatic drug metabolism decreases by approximately thirty percent in healthy elderly individuals. Age-related changes in renal excretory function will include a decrease in the glomerular filtration rate starting at age forty. This decrease may affect drug clearance, especially of drugs which are renally excreted.[3] Increased toxicity of antineoplastic drugs may be anticipated due to the increased vulnerability of multiple organ systems with reduced functional reserve. Decreased absorptive ability, decreased volume of distribution may also be expected, in addition to the decrease in glomerular filtration rate and hepatic drug metabolism.[4]

Concurrently, they are also prone to chronic illness that may affect their treatment regimen[5]. Having frail physiology, elderly patients are prone to complications brought about by chemotherapy. These include cardiomyopathy, sepsis, mucositis, gastrointestinal and hematologic toxicities. It was also noted that in elderly patients with ovarian cancer, incidence of hospitalization after chemotherapy is high.[6] The incidence of febrile neutropenia is also increased.[7]

A study on elderly patients with Stage II ovarian cancer found that patients with higher tumor grade and relatively younger age were more likely to receive chemotherapy, with note of an associated 5-year mortality reduction.[8] Among patients with stages IIIC-IV ovarian cancer receiving platinum-taxane chemotherapy, patients older than 65 years of age demonstrated similar rates of initial response, platinum resistance, progression free and overall survival compared to their younger counterparts.[9] In an Italian retrospective toxicity multicentric study among elderly gynecologic malignancy patients, age did not adversely influence the ability to receive

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aggressive treatment. Hematologic toxicities were documented in 38.2% of cases (n=233 regimens), and treatment delays occurred in 16.9% of patients. Ten patients (6.8%) discontinued treatment due to hematologic toxicities.[10]

A study done by Petignat, et al in 2004 however, noted that age strongly increases ovarian cancer mortality, which may be partly explained by later diagnosis and suboptimal treatment. Older women presented with more advanced stage and were less often treated with optimal surgery and chemotherapy.[11]

Because of this observation, several studies were conducted to compare whether a full-optimal regimen versus reduced dose should be given to the elderly.[5,7,12]

In a retrospective multicenter study of elderly women with ovarian or peritoneal cancers, grade 3 to grade 4 neutropenia was higher in those who received full dose, or optimal chemotherapy regimen compared to those who received reduced doses. There was also note of delay of therapy. In addition, progression-free survival and over-all survival was comparable.[12]

Only one prospective study on the tolerability of standard dose chemotherapy regimen among patients with stage I – IV epithelial ovarian, primary peritoneal, or fallopian tube cancer was undertaken in 2011-2016 by von Gruenigen, et al. This study was not randomized but allowed physicians to choose among two chemotherapeutic regimens to implement in patients: 152 patients were given Carboplatin (AUC5) plus paclitaxel (135mg/m2) with granulocyte colony stimulating factor support every three weeks, while 60 patients were given single agent carboplatin (AUC5) on day 1 every three weeks. Findings of this study showed that baseline Instrumental Activities of Daily Living (IADL) was associated with both choice of chemotherapeutic regimen and its completion, occurrence of grade 3 toxicity, and overall survival.[13]

Several studies focused on the identification of factors in predicting the possible toxicities of cancer treatment in the elderly with the use of geriatric assessment tools. Predictive models, along with laboratory tests, and patient, tumor and treatment characteristics may be used to stratify patients as having low, intermediate, or high risk of chemotherapy toxicity. [14,15]

In the Philippines, however, chemotherapy toxicity prediction models and studies on chemotherapy completion in elderly gynecologic malignancy patients are scarce. Local guidelines on the optimal dose of chemotherapy and prevention of chemotherapeutic complications in this population are still deficient. This study aims to describe the clinicodemographic profile of elderly patients with endometrial and/or epithelial ovarian carcinoma, and the chemotherapy-associated hematologic complications in a retrospective series of patients in a tertiary healthcare institution.

OBJECTIVES

The main objective of the study was to determine the prevalence of, and factors associated with chemotherapy-induced hematologic toxicities among elderly women (60 years and above) diagnosed with endometrial and/or epithelial ovarian carcinoma seen at the Gynecologic Oncology clinic of the Cancer Institute at the University of the Philippines – Philippine General Hospital from January 2007 to December 2016.

Specific objectives of the study were as follows:

a) To describe the clinicodemographic characteristics of elderly women (60 years old and above) diagnosed with endometrial and/or epithelial ovarian carcinoma
b) To determine the prevalence of hematologic toxicities among elderly endometrial and/or epithelial ovarian cancer patients
c) To determine the association of hematologic toxicity with the following clinical characteristics:
    1. Age group
    2. Functional capacity (ECOG)
    3. Chemotherapeutic regimen
    4. Cancer type
    5. Disease stage
d) To determine the association of increasing age category and their subsequent development of hematologic toxicities during their treatment

METHODOLOGY

Study Setting

This retrospective cohort study upon approval by the Institution's Ethics Review Board utilized data and patient records from the outpatient department of the Philippine General Hospital. A list of patients for review was generated using the OPD Weekly Census of the section of Gynecologic Oncology from 2007 to 2016. Only those patients aged 60 and above, diagnosed with either endometrial or epithelial ovarian cancer necessitating adjuvant treatment in the form of systemic chemotherapy were included in the study.

Elderly patients with active bleeding (during the period when chemotherapy is to be instituted), concurrent radiotherapy, blood dyscrasias or other myelodysplastic diseases, non-epithelial ovarian cancer, or those diagnosed with malignancies other than endometrial/ovarian cancer who necessitated another line of chemotherapy, those for oral chemotherapy, and those with tumor progression necessitating second line chemotherapy were excluded.

Patient population and Medical Record Abstraction

A total of 330 patients were for inclusion in the study. Of

LABORATORY PARAMETER	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
HEMOGLOBIN (G/L)	> 110	95-109	80-94	65-79	< 65
LEUCOCYTES (10 9/L)	> 4	3.0-3.9	2.0-2.9	1.0-1.9	< 1
ABSOLUTE NEUTROPHIL COUNT (109/L)	> 1.5	1.0-1.4	0.5-0.9	<0.5	
PLATELETS (109/L)	> 100	75-99	50-74	25-49	< 25

these patients 128 charts were available for review. Forty-nine patients who were lost to follow up after the initial visit, or those who never commenced treatment were excluded. A total of 79 charts were included in this study. Subject characteristics, and data regarding their course of treatment were plotted in the data sheet prepared by the investigator. For each of the patients included, the following data were obtained: (1) Demographics: age, height, weight, body surface area and body mass index; (2) Medical co-morbidities (3) Diagnosis – stage, and cytoreductive status (zero residual disease after the initial surgery, in contrast with suboptimal cytoreduction, wherein residual tumor is still present after the initial surgery), (4) Treatment – agents, dose; (5) Hematologic response to treatment – trend in hemoglobin, leukocyte, and platelet; as well as the need for transfusions and administration of granulocyte colony stimulating factor; and lastly, (6) Treatment Status – maintained dose, delayed chemotherapy, decreased dose, or discontinued (systemic chemotherapy is usually administered in 21-day intervals. A delay of more than 7 days (≥ 28 day interval) between two cycles of chemotherapy will be considered a delay in treatment. Delays only attributable to correction of deranged hematologic parameters will be included. Dose Reductions are those reductions in the absolute dose of the chemotherapeutic agents (as stated previously) based on the projected or actual toxicities experienced by the patients (e.g. Carboplatin AUC 5-6 with Paclitaxel 155mg/m2 instead of the usual Carboplatin AUC 4 with Paclitaxel 175mg/m2)).

Hematologic toxicities were defined based on either a decrease in the hemoglobin, absolute neutrophil count, leukocytes, or platelets and such cut-offs in the determination of grading of toxicities were based on the values set by World Health Organization (shown below).

Table 1. Baseline Characteristics and its Association to Hematologic Toxicities

Baseline Characteristics	With Hematologic Toxicity	Without Hematologic Toxicity	OR	95% CI	p value
Number (Frequency)	10	69			
Age (years), mean ± sd	66.2 ± 2.5	64.5 ± 4.4	1.09	0.95 - 1.26	0.2326 ns
Age Group, n, %					
60-64	2 (20.0)	40 (58.0)		***Reference***	
65-69	7 (70.0)	19 (27.5)	7.37	1.40 - 38.90	0.0186*
70-74	1 (10.0)	7 (10.1)	2.86	0.23 - 35.91	0.4163 ns
75-79	0 (0.0)	3 (4.3)	-	-	0.9979 ns
Height (cm), mean ± sd	155.8 ± 6.6	151.8 ± 7.7	1.08	0.98 - 1.19	0.1246 ns
Weight (kg), mean ± sd	49.3 ± 8.4	54.5± 17.0	0.98	0.94 - 1.02	0.3395 ns
BSA, mean ± sd	1.5 ± 0.2	1.6 ± 0.4	0.13	0.00 - 5.30	0.2774 ns
Performance status, n, %					
ECOG 0	8 (80.0)	59 (85.5)		***Reference***	
ECOG 1	2 (20.0)	9 (13.0)			
ECOG 2	0 (0.0	1 (1.4)	1.48	0.27 - 7.98	0.6518 ns
Medical co-morbidities, n, %					
No Co-morbidity	4 (40.0)	46 (66.7)		***Reference***	
One Co-morbidity	4 (40.0)	13 (18.8)	3.54	0.78 - 16.12	0.1024 ns
Two or More Co-morbidities	2 (20.0)	10 (14.5)	2.30	0.37 - 14.38	0.3723 ns
Hypertension	5 (50.0)	20 (29.0)	2.45	0.64 - 9.40	0.1914 ns
Diabetes Mellitus	2 (20.0)	11 (15.9)	1.32	0.25 - 7.06	0.7470 ns
Type of Cancer, n, %					
Ovarian	5 (50.0)	20 (29.0)		***Reference***	
Endometrial	5 (50.0)	49 (71.0)	0.41	0.11 - 1.57	0.1914 ns
Stage of Cancer, n, %					
I,II	8 (80.0)	29 (42.0)	5.52	1.09 - 27.92	0.0390*
III,IV	2 (20.0)	40 (58.0)		***Reference***	
Chemotherapy, n, %					
Single	0 (0.0)	7 (10.1)		***Reference***	
Multiple	10 (100.0)	62 (89.9)	-	-	0.5865 ns
Cytoreductive status, n, %					
Optimally Debulked	10 (100.0)	67 (97.1)		***Reference***	
Sub-Optimally Debulked	0 (0.0)	2 (2.9)	-	-	1.0000 ns
Number of cycles, mean ± sd	5.8 ± 0.4	5.4 ± 1.0	1.53	0.83 - 2.83	0.2277ns

*significant, ns not significant
Univariate Logistic Regression

Table 2. Association of Specific Hematologic Toxicity to Age

Hematologic Toxicity	60-64 (n=42)	65-69 (n=26)	70-74 (n=8)	75-79 (n=3)	p value
Anemia	2 (4.8)	7 (26.9)	3 (12.5)	0 (0.0)	0.0535 ns
Leukopenia	0 (0.0)	4 (15.4)	0 (0.0)	0 (0.0)	0.0386*
Neutropenia	0 (0.0)	4 (15.4)	0 (0.0)	0 (0.0)	0.0386*
Thrombocytopenia	0 (0.0)	4 (15.4)	0 (0.0)	0 (0.0)	0.0386*

Table 3. Association of Specific Hematologic Toxicity to ECOG

Hematologic Toxicity	ECOG 0 (n=67)	ECOG 1 (n=11)	ECOG 2 (n=1)	p value
Anemia	8 (11.9)	2 (18.2)	0 (0.0)	0.6735 ns
Leukopenia	2 (3.0)	2 (18.2)	0 (0.0)	0.1391 ns
Neutropenia	2 (3.0)	2 (18.2)	0 (0.0)	0.1391 ns
Thrombocytopenia	2 (3.0)	2 (18.2)	0 (0.0)	0.1391 ns

Table 4. Association of Specific Hematologic Toxicity to Type of Cancer

Hematologic Toxicity	Endometrial (n=54)	Ovarian (n=25)	p value
Anemia	8 (11.9)	5 (20.0)	0.2738 ns
Leukopenia	2 (3.0)	2 (8.0)	0.5873 ns
Neutropenia	2 (3.0)	2 (8.0)	0.5873 ns
Thrombocytopenia	2 (3.0)	2 (8.0)	0.5873 ns

Table 5. Association of Specific Hematologic Toxicity to Stage of Cancer

Hematologic Toxicity	Stage I,II (n=37)	Stage III-V (n=42)	p value
Anemia	8 (21.6)	2 (4.8)	0.0394*
Leukopenia	3 (8.1)	1 (2.4)	0.3357 ns
Neutropenia	3 (8.1)	1 (2.4)	0.3357 ns
Thrombocytopenia	3 (8.1)	1 (2.4)	0.3357 ns

Data Analysis

Descriptive Statistics such as mean and standard deviation was used to present continuous variables while frequency and percentage for categorical data such as disease status, presence of hematologic toxicities (i.e. anemia, leukopenia, thrombocytopenia), and the need for GCSF injections or blood transfusion, so as to provide an overview of the study population.

Logistic regression was utilized in determining factors affecting presence of hematologic toxicities, while Fisher exact test was used for association of specific toxicity and demographic variables.

RESULTS

A total of 79 elderly cancer patients were included in the study. Majority of patients had ECOG 0 functional score, and mostly had no comorbidities. Moreover, most of the elderly had endometrial cancer and majority underwent multiple agent chemotherapy. In terms of debulking status, almost all patients were optimally debulked. Table 1 also shows that majority (90%) of our patients received multiple agent chemotherapy, and among them, 16 (20%) experienced delays in the scheduled chemotherapy administration..

The prevalence of hematologic toxicities is 12.67% (95% CI 7.02% to 21.76%). Of these, the most common hematologic toxicities turned out to be anemia (12.7%) while 5.1% of the total patients had either leukopenia, neutropenia, or thrombocytopenia. Table 1 reveals that the average age of patients with hematologic toxicities was 66 years old while the average age among those who did not experience toxicities was 65 years.

Age was significantly associated with the presence of hematologic toxicity, where women from the age group of 65 to 69 years old were 7.37 times more likely to have hematologic toxicities as compared to women 60-64 years old. Likewise, cancer stage also turned out to be a significant factor where results reveal that stage I or II patients were 5.52 times more likely to have hematologic toxicities as compared to those who had stage III, IV disease. No other factors turned out to be significant.

Table 2 shows that the presence of anemia was not significantly different among the four different age groups, but presence of Leukopenia, Neutropenia or Thrombocytopenia was significantly higher among those aged 65 to 69 years old (p=.0386).

Table 3 shows that ECOG performance status was not significantly associated among each hematologic toxicity type. Table 4 also reveals that the presence of each hematologic toxicity was not significantly different between those endometrial or ovarian cancer.

Table 5 shows that presence of leukopenia, neutropenia or thrombocytopenia was not significantly different between

cancer stages. On the other hand, anemia was significantly higher among those whose stage is I or II (21.6%) as compared to only 4.8% among Stage III to V.

DISCUSSION

This study adds to the small body of literature available on the clinical and demographic characteristics of elderly women undergoing chemotherapy – the hematologic effects of chemotherapy as well as the tolerance of these women to withstand chemotherapy. The data suggests that neither increasing age, performance status, cancer type, nor disease stage are significant predictors of hematologic toxicity in the elderly population.

Findings in this study are in contrast with the findings in the study of Choi, et al in 2008, which reviewed 133 patients with malignancies who underwent systemic chemotherapy. (16) In their study, almost half of their population received single agent chemotherapy, of which, carboplatin was the most common. Among those who received combination treatment, carboplatin and paclitaxel were the most common combination. In this study, 20 percent (n=16) of those on multiple agent chemotherapy had a delay in the continuation of the second cycle of chemotherapy, compared to none among those who had single agent chemotherapy. This can be expected since the use of multiple agents increases the likelihood of toxicities, most especially in a vulnerable elderly population.

It was also reflected in this study that a higher age group of 65-69 years old as compared to the 60-64 years old had a statistically significant impact on the occurrence of leukopenia, neutropenia, and thrombocytopenia, but not anemia. It is important to note, however, that there were only eleven patients belonging to the higher age cutoff of 70 years old, which could have affected the analysis of the prevalence of hematologic toxicities in this population. This is in contrast with the findings in the retrospective study done by Eisenhauer, et al in 2007, wherein their finding was that more than the age, the performance status of patients undergoing chemotherapy was the more predictive determinant of the elderly patients' ability to tolerate standard chemotherapy. Instead of using age as a categorical cutoff for treatment decisions, focus should be on the functional capacity and the medical co-morbidities of these elderly population in determining whether or not standard treatment may be given. In that same study, more elderly patients were presumably started on lower carboplatin doses due to concern of increased toxicity (9). In their population of elderly patients with stage IIIC-IV ovarian cancer, chemotherapy dose adjustments were necessary in 27 percent of patients more than 65 years old. Mostly, this was due to myelosuppression, and for poor performance status in this population. (9) Similar findings were noted in the study of Gronlund, et al. in 2001, wherein they concluded that performance status, rather than age per se, should be the primary consideration in the treatment of ovarian cancer among elderly patients. (17) Performance status was not a predictor of toxicity in the present study, but this may be because there were only a few patients with ECOG 2 scores. A larger sample size may be best able to show such an association.

The study utilized a retrospective design, with a relatively small population, and the heterogeneity of the cases and the selection bias as to the chemotherapy regimen to be given to patients, brought about by limitations in the financial capability of the patients.

The study analysed mostly patients who received both carboplatin and paclitaxel, and thus, cannot totally account for the hematologic toxicities of the different systemic chemotherapeutic regimens in elderly patients. The choice of chemotherapeutic drugs for the patients were at times affected by their financial capability.

As in any other study, a prospective, though observational, study with a larger sample population would best be able to detect the interplay of patient factors and the toxicities brought about by chemotherapy in the elderly.

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Tumor size as independent prognostic factor in stage IA endometrioid endometrial adenocarcinoma

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ABSTRACT

Objective: To evaluate the effect of tumor size on the rate of recurrence among patients with stage IA endometrioid endometrial cancer.

Methodology: This is a 10-year retrospective cohort study. Patients diagnosed with endometrioid endometrial adenocarcinoma stage IA managed surgically (peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingooophorectomy with bilateral pelvic lymph node dissection, with paraaortic lymph node sampling) were included. Data extracted from the outpatient department weekly census of the Philippine General Hospital between January 1, 2008 to August 31, 2018 were obtained. Tumor size, clinico-pathologic factors, incidence of tumor recurrence were determined.

Data Analysis: Data analysis was carried out using Stata 14. Descriptive statistics such as mean, median, standard deviation were used for numerical data variables, while frequency and percentage were used for categorical variables. Kaplan-Meier method was used to determine survival curves between the 2 tumor size groups. A P-value of < 0.05 was significant.

Results: Included in the study were 286 patients whose ages ranged from 22 to 76 years. Eleven patients (3.8%) had tumor recurrence. Tumor size was not significantly associated with increased risk of tumor recurrence.

Conclusion: Data suggests that tumor size in itself did not increase tumor recurrence.

Keywords: Tumor size, endometrial cancer, recurrence, prognostic factor

INTRODUCTION

Endometrial adenocarcinoma is the fourth most common cancer among women worldwide, and the most commonly diagnosed gynecologic cancer in the United States.[1] In the Philippines, uterine cancer is the 3rd most common gynecologic malignancy. About 2,451 cases and 565 deaths are expected to occur each year due to uterine cancer.[2] The overall 5-year survival rate worldwide was 82%.[3] Most of the diagnosed endometrial cancers are confined to the uterus (stage I).[4]

Management for all stages of endometrial cancer according to the FIGO (International Federation of Gynecology and Obstetrics) and the Society of Gynecologic Oncology of the Philippines (SGOP) remains to be primarily surgical in the form of peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, paraaortic lymph node sampling.[5]

After surgery, it is important to stratify patients with stage I endometrial cancer using the Mayo Risk Stratification Criteria shown below (Table 1). This defines low risk group as those with grade 1 or 2 endometrioid adenocarcinoma with less than 50% myometrial invasion; intermediate risk as those with comprising of endometrioid histology, grade 1 or 2 tumor with less than 50% myometrial invasion and with tumor size of more than 2 cm or tumor with less than 50% myometrial invasion and grade 3, and high risk as those with stage IB with grade 3 endometrioid adenocarcinoma, stage II with grade 3 endometrioid adenocarcinoma.

The SGOP recommends that for the low risk group, adjuvant treatment is not warranted. In the intermediate risk group, vaginal brachytherapy is recommended.[5,6] According to American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO), vaginal brachytherapy as adjuvant therapy may be considered in patients with tumor less than 50% myometrial invasion, grade 1 or grade 2 and lymph nodes were negative for tumor metastasis but with higher-risk features, such as age more than 60 years and/or positive lymphovascular space invasion (LVSI).[6]

Histologic type, tumor grade, depth of myometrial invasion, cervical invasion, adnexal involvement, peritoneal spread, positive peritoneal fluid cytology, presence of LVSI, tumor ploidy and hormone receptor status have all been identified as

Table 1. Risk Stratification Criteria 5

Low Risk Stage IA, Grade 1 or 2, tumor size <2cm
Intermediate Risk Stage IA, Grade 1 or 2, tumor size >2cm Stage IA, Grade 3 Stage IB, Grade 1 and 2 Stage II, Grade 1 and Grade 2
High Risk Stage IB, Grade 3 Stage II, Grade 3

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important independent prognostic factors.[7,8,9] Although tumor size has not been established as an independent prognostic factor, some studies have identified tumor size as potentially being associated with increased risk of distant[10-14] and local[15] recurrence. Mahdi, et. al reported that tumor size of more than 5 cm was a predictor of lower disease-specific survival but with no difference in outcome between tumor size of more than 2 to 5 cm and less than or equal to 2 cm.[11]

While the SGOP clinical practice guidelines recommend giving adjuvant treatment for endometrial cancer stage IA, grade 1-2 cases with tumor size more than 2 cm, there is still much debate among gynecologic oncologists as to whether adjuvant therapy is indeed warranted on the basis of tumor size alone. Therefore, this study was conducted to determine the role of tumor size as an independent prognostic factor in determining the need for adjuvant therapy.

OBJECTIVES

The main objective was to determine the effect of tumor size on the rate of recurrence among patients diagnosed with stage IA endometrioid endometrial adenocarcinoma.

Specific Objectives

1. To describe the clinico-pathologic characteristics of patients with stage IA endometrioid endometrial adenocarcinoma.
2. To describe the adjuvant treatment given to patients with stage IA endometrioid endometrial adenocarcinoma after primary surgery and after diagnosis of recurrence
3. To determine the recurrence rate of patients with endometrial cancer based on tumor size and on other poor prognostic factors: (i.e. grade, LVSI).
4. To compare the effect of pelvic EBRT vs. brachytherapy vs. no adjuvant treatment on the rate of recurrence among patients diagnosed stage IA endometrioid endometrial adenocarcinoma.

MATERIALS AND METHODS

Study Setting

Institutional review board approval was obtained prior to initiation of the study. This was a 10- year retrospective cohort study including all cases of stage IA endometrioid endometrial adenocarcinoma seen from January 1, 2008 to August 31, 2018 generated using the outpatient weekly census in a single tertiary government hospital who underwent peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingo-oophorectomy, pelvic lymph node dissection, with paraaortic lymph node sampling, with or without adjuvant treatment.

Selection criteria included stage IA endometrioid endometrial adenocarcinoma following the 2009 FIGO staging system for endometrial cancer. All cases diagnosed under the 1998 FIGO staging for endometrial cancer were re-staged using the 2009 FIGO staging system based on the available histopathologic report. Architectural grading was based on the degree of glandular differentiation in accordance to the FIGO guidelines. LVSI was present when tumor cells were within or attached to the wall of a capillary-like space. Tumor size was determined by the maximum dimension of the tumor as reported by the pathologist. Primary surgical management were performed by gynecologic oncologist. Postoperative adjuvant treatment consisted of external beam radiation therapy and/or vaginal brachytherapy or systemic chemotherapy depending on the assessment of the attending gynecologic oncologists. Patients excluded were those with serous, clear cell or sarcomatous histology, those with synchronous tumors, and patients diagnosed with another cancer before the diagnosis of endometrial cancer. Patients with FIGO stage IB to IV, clinically staged using FIGO 1971, who received pelvic radiation and/or chemotherapy prior to surgery and with incomplete data were also excluded.

Local recurrence was defined as recurrence localized to the vagina, vaginal vault or pelvic sidewall determined by physical examination or imaging studies. Locoregional recurrence sites were at the pelvic and/or paraaortic lymph nodes, pelvic peritoneum or pelvic viscera while distant sites includes the liver, lung, bone, brain and omentum.

Patient population and Medical Record Abstraction

From January 1, 2008 through August 31, 2018, 373 patients were eligible for review. All data from patients' charts, intraoperative reports and histopathologic reports were manually encoded into an electronic spread sheet file and were collated and checked periodically for consistency and completeness. For each of the patients included, the following data were extracted: (1) Demographics: age, height, weight, body mass index (BMI); (2) Surgeon, procedure performed, stage, histologic type, tumor grade, tumor size based on final histopathologic report, status of LVSI, number of pelvic and paraaortic lymph nodes harvested. (3) types of adjuvant therapy, if any, and outcome. (4) onset (from time of surgery, in months) and location of recurrence and (5) treatment given for tumor recurrence.

Data Analysis

Data processing and analysis were carried out using the software Stata 14. The Kaplan-Meier method was used to determine survival curves between the 2 tumor size groups. Statistical analysis was performed using univariate and multivariate Cox analyses to determine which prognostic variable significantly predicted recurrence. The crude and unadjusted hazard ratios, standard errors, p-values, and 95% confidence intervals were provided. A p-value of less than 0.05 was considered significant for all tests.

RESULTS

From January 1, 2008 through August 31, 2018, 373 patients were eligible for review. There were 50 patients (13.40%) with missing data for tumor size, 31 patients (8.31%) who were lost to follow-up, 4 (1.07%) whose pelvic and paraaortic lymph nodes were not counted, and 2 (0.53%) whose final histopathologic report only showed hyperplasia.

A total of 286 eligible patients were included in the study with an average age of 51.4 years (median 52 years, range 22- 76 years), and average BMI of 27.3 kg/m2 (median

Table 2. Clinical and pathologic characteristics of patients with endometrioid adenocarcinoma (n=286)

Variable	Frequency (%)	Mean (SD)	Median, p50	Min, Max
Age in years	-	51.4 (9.4)	52	22,76
Stage at diagnosis IA (FIGO 2009) IA (before 2009) IB (before 2009)	 250 (87.4) 6 (2.1) 30 (10.5)	-	-	-
BMI (kg/m2)	-	27.3 (5.4)	26.9	13.3, 47.1
Tumor size <2 cm >2 cm	 91 (31.8) 227 (68.2)	3.7 (2.3)	3	0, 12.5
Grade 1 2 3	 160 (56.1) 112 (39.3) 13 (4.6)	-	-	-
LVSI (-) (+)	 255 (89.1) 31 (10.9)	-	-	-
Total pelvic lymph nodes	-	16.7 (8.3)	16	0, 57
Total paraaortic lymph nodes	-	2.2 (2.6)	1	0, 19
Adjuvant treatment None Yes	 231 (80.8) 55 (19.2)	-	-	-
Recurrence None Yes	 275 (96.1) 11 (3.9)	-	-	-

BMI, body mass index; LVSI, lymphovascular space invasion

26.9 kg/m2, ranged from 13.3 to 47.1 kg/m2). The average tumor size was 3.7 cm with a range of 0-12.5 cm. Pelvic and paraaortic lymphadenectomy was performed in all patients. Average number of harvested pelvic lymph nodes was 16.7 nodes (median 16, range 0-57), while the average number of paraaortic lymph nodes was 2.2 nodes (median 1, range 0-19). Fifty-five patients (19.2%) received adjuvant treatment and 231 patients (89.1%) did not. Clinical and pathologic characteristics of these patients are summarized in Table 2.

A total of 11 patients experienced tumor recurrence. Four patients received adjuvant therapy after the surgery: 2 patients received pelvic external beam radiation and 2 patients received Carboplatin (AUC5)- Paclitaxel (175mg/m2). Average onset of tumor recurrence was 4.2 months (median 2 months, range 2-78 months) after completion of primary surgery for patients who did not receive adjuvant treatment and after completion of adjuvant treatment for those patients who underwent adjuvant therapy. Four patients (36.4%) had locoregional recurrences while 2 patients (18.2%) had both distant and locoregional recurrence. Three patients (27.3%) experienced distant recurrence and 2 patients (18.2%) only had local recurrence. Characteristics of patients with tumor recurrence are summarized in Table 3.

The unadjusted Cox Proportional Hazards Regression Analysis is shown in Table 4.

In Figure 1, log-rank test showed no significant difference between ≤ 2cm and > 2cm tumor size in terms of recurrence rates (p-value=0.3428).

DISCUSSION

The standard of care of endometrial cancer is surgery. Patients included in this study were completely staged to determine the true extent of the disease.

Histologic type, tumor grade, depth of myometrial invasion, cervical invasion, adnexal involvement, peritoneal spread, positive peritoneal fluid cytology, presence of LVSI, tumor ploidy and hormone receptor status have all been identified as important independent prognostic factors.[7,8,9] Tumor size, on the other hand, has not been established as an independent prognostic factor. Most of the literature reported on the incidence of lymph node metastasis.

In this study, 31.8% (91 of 286 patients) had tumor size of < 2 cm and 68.2% (227 of 286 patients) had tumor size >2cm. Tumor recurrence occurred in 11 patients. Two patients had tumor size of < 2cm while 9 patients had >2cm. However, it was not significantly associated with tumor recurrence (HR 1.11, 95% CI 0.895-1.398, p=0.325). Mariani et. al reported that tumor size was not a significant predictor of vaginal relapse (P>0.05) in patients with stage I endometrial cancer managed with hysterectomy.[16] Tumor size was also not part of the reported prognostic factors in endometrial cancer.[17] However, the outcome of this study are in contrast with the findings of Mariani et. al that for primary tumor of < 2 cm when compared with tumor size of > 2 cm, disease-related survival (P=0.003) and recurrence-free survival (P=0.03) were significantly different.[8] Some studies have likewise identified tumor size as potentially being associated with risk of local[15]

Table 3. Characteristics of patients had tumor recurrence (n=11)

n	Age at diagnosis (years	BMI (kg/m2	Tumor size (cm)	Tumor Grade	LVSI	Total pelvic lymph nodes	Total paraaortic lymph nodes	Adjuvant treatment	Onset of recurrence (months	Location of recurrence	Treatment given
1	66	26	7	2	Negative	23	5	Pelvic EBRT (treatment duration 54 days)	7	Lumbar vertebrae	Cisplatin-Doxorubicin for 6 cycles
2	57	19.5	4	2	Negative	15	2	None	12	Vagina	Pelvic EBRT with Brachytherapy
3	48	24.2	2.1	1	Negative	18	2	None	78	Pelvic lymph nodes	Carboplatin-Paclitaxel for 6 cycles
4	61	25.8	5	1	Negative	27	3	None	72	Right inguinal lymph node, pelvic lymph nodes	Carboplatin-Paclitaxel for 6 cycles
5	56	19.7	5	2	Positive	7	0	Pelvic EBRT (treatment duration 49 days)	5	Lungs	Carboplatin-Paclitaxel for 6 cycles
6	61	44	7	2	Negative	14	0	None	9	Lungs, pelvic lymph nodes	Carboplatin-Paclitaxel for 6 cycles
7	65	19.9	2	2	Negative	18	4	None	14	Vaginal stump	Pelvic EBRT with Brachytherapy
8	59	42.4	4	1	Negative	16	0	None	22	Pelvic lymph nodes	Carboplatin-Paclitaxel for 6 cycles
9	57	22.4	4.6	2	Positive	18	0	Carboplatin-Paclitaxel 6 cycles	4	Pelvic bone	RT to pelvic bone, Pegylated liposomal doxorubicin for 6 cycles, Zoledronic acid for 6 cycles
10	50	17.8	2	2	Positive	17	5	Carboplatin-Paclitaxel 6 cycles	2	Pelvic lymph nodes	Pelvic EBRT
11	46	27.3	4	2	Negative	5	0	None	57	Lungs, pelvic lymph nodes	Carboplatin-Paclitaxel for 6 cycles

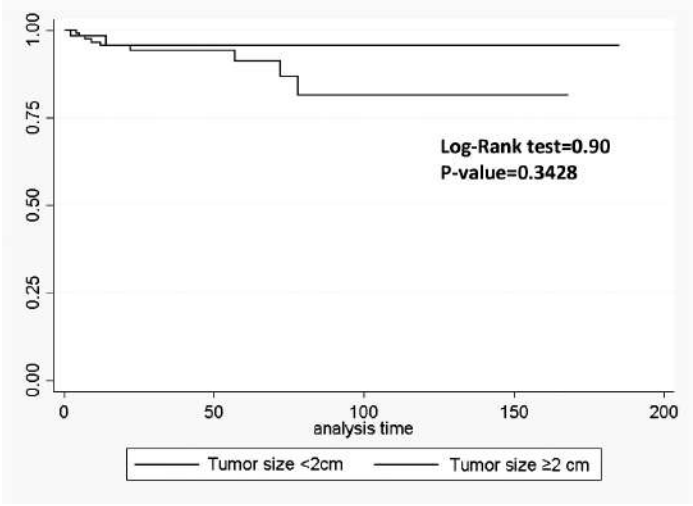

Figure 1. Kaplan-Meier Survival Estimates for Recurrence by Tumor Size

recurrence and distant recurrence.[10-14] As reported by Sozzi et al, tumor size of more than 2.5 cm predicts a higher rate of local recurrence (P<0.001, HR=18.2, P=0.005) and a lower local recurrence-free survival and recurrence-free survival (P<0.0001) in patients with low risk category endometrioid endometrial cancer.[15]

The decision to administer adjuvant treatment in our cohort of patients with stage IA endometrioid endometrial cancer was based on the SGOP treatment guidelines. Most of these cases had either the presence of LVSI or a tumor grade of 3.[5]

In their study, Mariani et. al identified grade 3 tumor and LVSI as predictors of vaginal recurrence (P<0.05) among patients with stage I endometrial cancer who did not receive any adjuvant treatment after surgery.[16] In our study, tumor grade 2 increased the likelihood of tumor recurrence 4.32 times when compared to tumor grade 1 (95% CI=1.125-16.56, p=0.033). Grade 3 tumor was not evaluated in our setting since patients who had tumor recurrence are with grade 1 and 2 differentiation. Most of the reported literature lumped the tumor grades 1 and 2 together apart from tumor grade 3. In the SGOP guidelines, grade 1 and 2 tumors in stage IA endometrial cancer are categorized as low risk while patients with grade 3 tumor in stage IA endometrial cancer is categorized as high intermediate.

LVSI was also evaluated in endometrial endometrioid adenocarcinoma and was determined as an independent predictor of distant recurrence.[18] In this study, the presence of LVSI almost tripled the risk of tumor recurrence, although it was not statistically significant (HR 2.91, 95% CI 0.770-10.98, p=0.115). The possible explanation of this is probably due to small sample size. Other predictors of tumor recurrence are: age, BMI, harvested pelvic and paraaortic lymph nodes as seen in Table 3.

Adjuvant treatment was given for 4 patients after surgery. It seems that it increased the risk of tumor recurrence (HR 1.84, CI 0.533-6.330, p=0.336). This might be due to the presence of LVSI in 3 out 4 of patients given adjuvant treatment.

Limitation of this study utilized a retrospective design with a small population of patients who had tumor recurrence.

Table 4. Unadjusted Cox Proportional Hazards Regression Analysis of patients who had Tumor Recurrence (n=11)

Variable	Recurrence Rate	HR	Standard Error	95% CI	p-value
Tumor size*					
<2 cm	2 (2.2%)				
>2 cm	9 (4.0%)	1.11	0.127	0.895-1.398	0.325
Age in years	-	1.06	0.039	0.988-1.141	0.101
Grade					
1	3 (1.9%)	Ref	-	-	-
2	8 (7.1%)	4.32	2.961	1.125-16.56	0.033
3	0 (0.0%)	-	-	-	-
BMI	-	0.994	0.056	0.891-1.109	0.918
LVSI					
(-)	8 (3.1%)	Ref	-	-	-
(+)	3 (9.7%)	2.91	1.97	0.770-10.98	0.115
Total pelvic lymph nodes	-	1.00	0.033	0.939-1.070	0.940
Total paraaortic lymph nodes	-	0.988	0.135	0.757-1.291	0.932
Adjuvant					
None	7 (3.0%)	Ref	-	-	-
Yes	4 (7.3%)	1.84	1.16	0.533-6.330	0.336

* Analyzed as continuous variable

BMI, body mass index; LVSI, lymphovascular space invasion

Slide review was done in the institution by pathologists but no central pathology done by designated pathologists. The tumor size was determined by means of measuring the largest tumor diameter without considering the tumor volume, diffuse spread and specific location of the tumor.

CONCLUSION

While patients with tumor size > 2 cm had a higher frequency of tumor recurrence, this factor was not found to be significantly associated with an increased risk for local or distant recurrence. Tumor size did not prove to be an independent prognostic factor for recurrence among patients with Stage IA endometrial endometrioid adenocarcinoma.

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Clinical profile and survival outcomes of Filipino women with uterine sarcoma: A 10-year retrospective cohort study in a tertiary government hospital

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ABSTRACT

Background: Uterine sarcoma is a rare kind of gynecologic cancer. This study aimed to determine the prevalence of uterine sarcoma subtypes, their clinical and demographic characteristics, as well as their outcomes.

Methods: This is a retrospective cohort study of patients diagnosed with uterine sarcoma from January 2008-December 2014. Demographic data were obtained and Kaplan Meier survival curves used to estimate overall survival (OS) and progression free survival (PFS). Multivariate analysis using Cox regression analysis was used to determine the association of PFS and OS with clinically important prognostic factors.

Results: A total of 87 patients diagnosed with uterine sarcoma had median progression free survival of 4 months and median overall survival of 36 months. Histologic subtype, age, tumor size, adjuvant treatment with radiotherapy and chemotherapy showed no significant association with disease progression (p=0.05). It was, however, observed that surgical approach (p= 0.004) and disease stage (p=0.038) were significantly associated with disease progression.

Conclusions: The observed 3-year PFS was 41.5% and OS was 61.4%. The median progression free survival was 4 months and median overall survival was 36 months. Multivariate analysis showed that lack of complete surgical staging and advanced stages of the disease were significant predictors of disease progression.

Keywords: *uterine sarcoma, overall survival, progression free survival*

INTRODUCTION

Uterine sarcoma is a rare form of uterine malignancy that arises from the myometrium or connective tissue. It comprises about 1-3% of all gynecologic malignancies and accounts for 4-9% of all uterine cancers in the United States.[1,2] Incidence and prevalence data are, however, lacking in the Philippines.

The rarity of uterine sarcoma, coupled with its aggressive and lethal clinical course, explains why there is relatively limited amount of literature regarding the disease. In the Philippines, there is still no data on the clinical demographic profile of patients diagnosed with uterine sarcoma. There is also paucity of information on overall survival and progression free survival of patients with uterine sarcoma, as well as the relevant risk factors associated with the disease. This study, therefore, aims to contribute knowledge in these areas by conducting a 10-year retrospective cohort study of patients seen in a tertiary government hospital.

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OBJECTIVES

The study determined the clinical and demographic characteristics, as well as outcomes of Filipino patients diagnosed with uterine sarcoma. The specific objectives were to determine the:

1. prevalence of uterine sarcoma subtypes seen in the institution.
2. recurrence rate of the disease.
3. clinico-demographic profile of patients with uterine sarcoma.
4. survival rates, progression free survival (PFS), and overall survival (OS) of patients with different tumor histology.
5. association of patient's clinical characteristics with PFS and OS.
6. association of patient's clinical characteristics with lymphovascular space involvement.

METHODOLOGY

This is a retrospective cohort study involving all Filipino patients diagnosed with uterine sarcoma (Leiomyosarcoma, Adenosarcoma, ESS, Undifferentiated, Carcinosarcoma / MMMT) treated at a tertiary government hospital from January 1, 2008 to December 31, 2014. Their records were reviewed to include follow-up until December 31, 2017. Patients diagnosed with endometrial adenocarcinoma and those who did not undergo definitive surgery were excluded from the study.

After obtaining approval from the Institution's Ethics Review Board, patients diagnosed with uterine sarcoma from January 1, 2008 to December 31, 2014 were identified from the outpatient clinic census. Using the medical charts of the identified cases, data on patient demographics, tumor histology, intraoperative findings, extent of surgical procedure, adjuvant chemotherapy and/or radiation therapy, recurrence/ progression, and survival were collected using a case registry form.

Patient demographics included age at diagnosis, body mass index, gravidity and parity, personal history of hypertension, diabetes, or other cancers and family history of associated cancers (breast, colon, etc.), and size of tumor (largest tumor diameter). Information on histologic sub-types were subdivided into: leiomyosarcoma, carcinosarcoma/MMMT, ESS, undifferentiated sarcoma and adenosarcoma. Data on the intraoperative findings regarding deep myometrial invasion, extra-uterine spread, pelvic and paraaortic lymph node involvement, LVSI and distant metastasis were also collected. Data on the surgical procedures performed were obtained and subdivided into either a complete surgical staging with bilateral pelvic lymph node dissection, paraaortic lymph node sampling or incomplete surgical staging or a fertility sparing surgery. Finally, information on the administration of adjuvant chemotherapy and/or radiotherapy was also obtained.

Data obtained were analyzed using the statistical software Stata 13. Prevalence rates of uterine sarcoma and recurrence rates by histologic subtypes were computed. Descriptive statistics such as the median, frequency and percentage were used for the socio-demographic variables of the study participants. The PFS and OS of the patients were determined. Records of all eligible patients within 7 years from initial diagnosis were reviewed to determine the overall and progression-free survival.

The primary outcome measures were the differences in the survival (OS and PFS) across patients with different histologic subtypes, demographic factors and treatment. Kaplan Meier survival curves were used to estimate OS and PFS and to further determine differences in the survival time among patients with different histologic subtypes. Log rank test was also conducted to compare median survival time across said groups.

Multivariate analysis was performed using Cox regression analysis to determine the association of progression and overall mortality with clinically important prognostic factors such as surgical procedure and histology, administration of adjuvant therapy, and age. The adjusted estimates were provided to evaluate the clinical importance of noted hazard ratios. Proportional hazards assumption was tested using goodness-of-fit. Multivariate analysis using logistic regression analysis was also done to determine the association of LVSI with clinically important prognostic factors. The level of significance for all sets of analysis was set at a p-value of less than 0.05 using two-tailed comparisons.

RESULTS

A total of 87 patients diagnosed with uterine sarcoma were included in this study. The median follow-up time was 9 months (Range=1 to 94 months). The median progression free survival of 75 patients was 4 months (Range= 1 to 93 months) while their median overall survival for 17 patients was 36 months (Range=2 to 84 months). The demographic characteristics and medical history of the study population disaggregated by histologic subtype of uterine sarcoma can be seen in Table 1. The distribution of histologic subtype of uterine sarcoma was as follows: 23 patients with Leiomyosarcoma, 15 with ESS, 10 with undifferentiated, 4 with adenosarcoma, and 31 with carcinosarcoma. The median age of the patients was 55 years old, and those diagnosed with Carcinosarcoma had the highest median age (60.4±1.1 years old). Majority had normal BMI=18.5-24.9 (34.5%). Majority had their menarche between ages 11 to 14 years old (65.5%). Most of the patients were also multiparous (81.6%) and had their menopause at age 45 years old and above (85.7%). Almost 98% of patients had no hormone replacement therapy and about 74% did not use oral contraceptives. Also, 83.0% of the patients were non-smokers. With regards to presence of medical co-morbidities, 17.2% had diabetes mellitus, 44.8% had hypertension, and 3.4% had cardiac disease. None of the patients had renal disease or polycystic ovaries. Almost 59% had no medical co-morbidity. Only 8 patients (9.2%) had a family history of cancer (3 breast, 2 colon and 3 endometrial cancer). In terms of preoperative diagnosis, almost half (41.4%) were diagnosed through endometrial biopsy while the rest were diagnosed through dilatation and curettage, fractional curettage, or during hysteroscopy. Twenty-nine patients (33.3 %) were diagnosed post-operatively.

The clinical characteristics of the patients diagnosed with uterine sarcoma disaggregated by histologic subtype can be seen in Table 2. In terms of symptoms experienced, 93.1% had vaginal bleeding, 28.7% had pelvic pain, 26.4% had pelvic mass, and 18.4% had other masses. Almost fifty- two percent (51.9%) had stage 1 disease while 31.2% had stage 3-4 disease. Majority had ECOG 0 scores (94.3%). Almost half (49.4%) had tumor size ranging between 5 to 10 cm. Thirty five percent had less than 50% depth of myometrial invasion and 40.2% had more than 50% to full depth invasion. The site with the highest reported incidence of metastasis was the cervix (36.8%). Seventy percent of patients had no lymphovascular space invasion and about 88.5% had no lymph node metastasis. Almost 90% had no recurrence.

The treatment characteristics of the patients diagnosed with uterine sarcoma disaggregated by histologic subtype can be seen in Table 3. Forty eight percent underwent EHBSO with BLND, PALS; 9.2% had TH+/-BSO with BLND, PALS; 35.6% underwent EHBSO/THBSO; 3.4% had RHBSO with BLND, PALS and 1.2% had subtotal hysterectomy, BSO. Fifteen percent had radiotherapy, 36.1% had chemotherapy, and 12.6% had both adjuvant therapies.

Data for Progression-free Survival (PFS) was available for 75 patients and can be seen in Table 4 and Figure 1. The PFS rates for this group were 45.7% for 1 year, and 41.5% for 2 and 3 years. The 1-year PFS rates for each histologic subtype were as follows: 34.5% for Leiomyosarcoma, 53.6% for ESS, 66.7% for undifferentiated, 33.3% for adenosarcoma, and 47.4% for carcinosarcoma (Table 4 and Figure 2). The 2-years PFS rates for each histologic subtype were as follows: 34.5% for Leiomyosarcoma, 53.6% for ESS, and 66.7% for the

Table 1. Demographic Characteristics and Medical History of the Study Population

Characteristics	Total N=87	Leiomyo-sarcoma N= 23 (26.4%)	ESS N=15 (17.2%)	Undifferen-tiated N=10 (11.5%)	Adenosarcoma N=4 (4.6%)	Carcino-sarcoma N=31 (35.6%)	Others N=4 (4.6%
Age (years, median)	55	51	48	50	51	60	55
BMI							
Underweight	5 (5.7%)	4 (17.4%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Normal	30 (34.5%)	9 (39.1%)	7 (46.7%)	5 (50.0%)	3 (75.0%)	5 (16.1%)	1 (25.0%)
Overweight	22 (25.3%)	1 (4.4%)	3 (20.0%)	3 (30.0%)	0 (0.0%)	13 (41.9%)	2 (50.0%)
Obese	22 (25.3%)	9 (39.1%)	1 (6.7%)	2 (20.0%)	0 (0.0%)	9 (29.0%)	1 (25.0%)
Obese II	8 (9.2%)	0 (0.0%)	3 (20.0%)	0 (0.0%)	1 (25.0%)	4 (12.9%)	0 (0.0%)
Age at menarche							
<15	57 (65.5%)	13 (56.5%)	11 (73.3%)	9 (90.0%)	1 (25.0%)	21 (67.7%)	2 (50.0%)
≥15	30 (34.5%)	10 (43.5%)	4 (26.7%)	1 (10.0%)	3 (75.0%)	10 (32.3%)	2 (50.0%)
Parity							
Nulliparous	16 (18.4%)	4 (17.4%)	3 (20.0%)	3 (30.0%)	2 (50.0%)	3 (9.7%)	1 (25.0%)
Multiparous	71 (81.6%)	19 (82.6%)	12 (80.0%)	7 (70.0%)	2 (50.0%)	28 (90.3%)	3 (75.0%)
Menopausal status							
<45	12 (14.3%)	6 (26.1%)	4 (30.8%)	1 (11.1%)	1 (25.0%)	0 (0.0%)	0 (0.0%)
≥45	72 (85.7%)	17 (73.9%)	9 (69.2%)	8 (88.9%)	3 (75.0%)	31 (100.0%)	4 (100.0%)
HRT							
Yes	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (33.3%)
No	83 (97.7%)	23 (100.0%)	15 (100.0%)	10 (100.0%)	4 (100.0%)	29 (96.7%)	2 (66.7%)
OCP							
Yes	23 (26.4%)	7 (30.4%)	5 (33.3%)	0 (0.0%)	0 (0.0%)	10 (32.3%)	1 (25.0%)
No	64 (73.6%)	16 (69.6%)	10 (66.7%)	10 (100.0%)	4 (100.0%)	21 (67.7%)	3 (75.0%)
Smoking status							
Yes	6 (7.0%)	1 (4.4%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	3 (10.0%)	0 (0.0%)
No	80 (93.0%)	22 (95.6%)	13 (86.7%)	10 (100.0%)	4 (100.0%)	27 (90.0%)	4 (100.0%)
Medical co-morbidity*							
DM	15 (17.2%)	4 (17.4%)	2 (13.3%)	1 (10.0%)	1 (25.0%)	5 (16.1%)	2 (50.0%)
Hypertension	39 (44.8%)	11 (47.8%)	4 (26.7%)	3 (30.0%)	3 (75.0%)	17 (54.8%)	1 (25.0%)
Cardiac	3 (3.4%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	2 (6.4%)	0 (0.0%)
Renal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Polycystic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
None	51 (58.6%)	12 (52.2%)	6 (40.0%)	4 (40.0%)	4 (40.0%)	21)67.7%)	4 (100.0%)
Familial history cancer*							
Breast	3 (3.4%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	2 (6.4%)	0 (0.0%)
Colon	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	1 (3.2%)	0 (0.0%)
Ovarian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Endometrial	3 (3.4%)	1 (4.3%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)
Mode of preoperative diagnosis							
Endometrial biopsy	36 (41.4%)	2 (8.7%)	7 (46.7%)	4 (40.0%)	4 (100.0%)	17 (54.8%)	2 (50.0%)
Dilatation and curettage	10 (11.5%)	1 (4.3%)	2 (13.3%)	2 (20.0%)	0 (0.0%)	5 (16.1%)	0 (0.0%)
Fractional curettage	9 (10.3%)	1 (4.3%)	1 (6.7%)	1 (10.0%)	0 (0.0%)	5 (16.1%)	1 (25.0%)
Hysteroscopic	3 (3.5%)	1 (4.3%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)
Others	29 (33.3%)	18 (78.3%)	5 (33.3%)	2 (20.0%)	0 (0.0%)	3 (9.7%)	1 (25.0%)

Table 2. Clinical Characteristics of the Study Population

Characteristics	Total N=87	Leiomyo-sarcoma N= 23 (26.4%)	ESS N=15 (17.2%)	Undifferen-tiated N=10 (11.5%)	Adenosarcoma N=4 (4.6%)	Carcino-sarcoma N=31 (35.6%)	Others N=4 (4.6%
Symptoms							
Vaginal bleeding	81 (93.1%)	19 (82.6%)	14 (93.3%)	10 (100.0%)	4 (100.0%)	30 (96.8%)	4 (100.0%)
Pelvic pain	25 (28.7%)	10 (43.5%)	4 (26.7%)	2 (20.0%)	1 (25.0%)	7 (22.6%)	1 (25.0%)
Pelvic mass	23 (26.4%)	5 (21.7%)	2 (13.3%)	3 (30.0%)	2 (50.0%)	8 (25.8%)	3 (75.0%)
Other mass	16 (18.4%)	4 (17.4%)	4 (26.7%)	2 (20.0%)	0 (0.0%)	5 (16.1%)	1 (25.0%)
Stage							
I	40 (51.9%)	16 (72.7%)	5 (62.5%)	7 (77.8%)	1 (33.3%)	9 (29.0%)	2 (50.0%)
II	13 (16.9%)	2 (9.1%)	1 (12.5%)	2 (22.2%)	0 (0.0%)	8 (25.8%)	0 (0.0%)
III	16 (20.8%)	2 (9.1%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	11 (35.5%)	2 (50.0%)
IV	8 (10.4%)	2 (9.1%)	1 (12.5%)	0 (0.0%)	2 (66.75)	3 (9.7%)	0 (0.0%)
ECOG status							
0	82(94.3%)	21(91.3%)	14(93.30%)	10(100.0%)	4 (100.0%)	30(96.8%)	3 (75.0%)
1-3	5 (5.7%)	2 (8.7%)	1(6.7%)	0(0.0%)	0 (0.0%)	1 (3.2%)	1 (25.0%)
Tumor size							
<2 cm	4 (4.6%)	0 (0.0%)	2 (13.3%)	1 (10.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)
2-<5 cm	17 (19.5%)	4 (17.4%)	3 (20.0%)	1 (10.0%)	1 (25.0%)	8 (25.8%)	0 (0.0%)
5-10 cm	43 (49.4%)	13 (56.5%)	8 (53.3%)	6 (60.0%)	1 (25.0%)	14 (45.2%)	1 (25.0%)
>10 cm	23 (26.4%)	6 (26.1%)	2 (13.3%)	2 (20.0%)	2 (50.0%)	8 (25.8%)	3 (75.0%)
Depth of myometrial invasion							
No invasion	8 (9.2%)	1 (4.4%)	4 (26.7%)	2 (20.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)
<50 % invasion	23 (26.4%)	4 (17.4%)	2 (13.3%)	4 (40.0%)	3 (75.0%)	8 (25.8%)	2 (50.0%)
>50 % invasion	25 (28.7%)	2 (8.7%)	3 (20.0%)	4 (40.0%)	0 (0.0%)	16 (51.6%)	0 (0.0%)
Full invasion	10 (11.5%)	1 (4.3%)	3 (20.0%)	0 (0.0%)	1 (25.0%)	3 (9.7%)	2 (50.0%)
unknown	21 (24.1%)	15 (65.2%)	3 (20.0%)	0 (0.0%)	0 (0.0%)	3 (9.7%)	0 (0.0%)
Metastasis*							
Cervix	32 (36.8%)	2 (8.7%)	1 (6.7%)	6 (60.0%)	2 (50.0%)	17 (54.8%)	4 (100.0%)
Adnexa	15 (17.2%)	2 (8.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	11 (35.5%)	1 (25.0%)
Parametria	7 (8.1%)	1 (4.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (16.1%)	1 (25.0%)
Vagina	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)
Extra-pelvic	16 (18.4%)	4 (17.4%)	3 (20.0%)	2 (20.0%)	2 (50.05)	4 (12.95)	1 (25.0%)
None	1 (4.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Presence of LVSI							
Negative	61 (70.1%)	20 (87.0%)	10 (66.7%)	7 (70.0%)	3 (75.0%)	17 (54.8%)	4 (100.0%)
Positive	26 (29.9%)	3 (13.0%)	5 (33.3%)	3 (30.0%)	1 (25.0%)	14 (45.2%)	0 (0.0%)
Lymph node involvement*							
None	77 (88.5%)	23 (100.0%)	14 (93.3%)	10 (100.0%)	4 (100.0%)	23 (74.2%)	3 (75.0%)
Pelvic node	10 (11.5%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	8 (25.8%)	1 (25.0%)
Paraaortic node	2 (2.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)
Recurrence							
No	78 (89.7%)	22 (95.6%)	14 (93.3%)	8 (80.0%)	4 (100.0%)	26 (83.9%)	4 (100.0%)
Yes	9 (10.3%)	1 (4.4%)	1 (6.7%)	2 (20.0%)	0 (0.0%)	5 (16.1%)	0 (0.0%)

**Multiple responses allowed*

Table 3. Treatment Characteristics of the Study Population

Characteristics	Total N=87	Leiomyo-sarcoma N= 23 (26.4%)	ESS N=15 (17.2%)	Undifferen-tiated N=10 (11.5%)	Adenosarcoma N=4 (4.6%)	Carcino-sarcoma N=31 (35.6%)	Others N=4 (4.6%
Surgical Procedure							
1. Inadequately staged/ EHBSO/ THBSO	31 (35.6%)	15 (65.2%)	9 (61.0%)	1 (10.0%)	2 (50.0%)	3 (9.7%)	1 (25.0%)
2. THBSO with BLND, PALS	8 (9.2%)	4 (17.4%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	3 (9.7%)	0 (0.0%)
3. EHBSO with BLND, PALS	42 (48.3%)	4 (17.4%)	4 (26.7%)	8 (80.0%)	1 (25.0%)	22 (71.0%)	3 (75.0%)
4. RHBSO with BLND, PALS	3 (3.4%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	2 (6.4%)	0 (0.0%)
5. Subtotal hysterectomy, BSO	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)
6. No surgery	2 (2.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)
Radiotherapy*							
None	74 (85.1%)	22 (95.6%)	12 (80.0%)	6 (60.0%)	4 (100.0%)	26 (83.9%)	4 (100.0%)
Pelvic EBRT	8 (9.2%)	0 (0.0%)	2 (13.3%)	3 (30.0%)	0 (0.0%)	3 (9.7%)	0 (0.0%)
Vaginal brachytherapy	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)
	4 (4.6%)	1 (4.4%)	1 (6.7%)	1 (10.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)
Chemotherapy							
None	55 (63.9%)	11 (50.0%)	14 (93.3%)	5 (50.0%)	4 (100.0%)	19 (61.3%)	2 (20.0%)
Monodrug	12 (14.0%)	6 (27.3%)	0 (0.0%)	3 (30.0%)	0 (0.0%)	2 (6.5%)	1 (25.0%)
Multidrug	15 (17.4%)	2 (9.1%)	1 (6.7%)	2 (20.0%)	0 (0.0%)	9 (29.0%)	1 (25.0%)
Incomplete treatment	4 (4.7%)	3 (13.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)

**Multiple responses allowed*

Table 4. Treatment follow-up per Histologic Subtype

	Progression-free Survival Rate					Overall Survival Rate				
Characteristics	**1 year (%)**	**2 years (%)**	**3 years (%)**	**X2**	**p value**	**1 year (%)**	**2 years (%)**	**3 years (%)**	**X2**	**p-value**
Leiomyosarcoma	34.5%	34.5%	-	3.33	0.5038	100.0%	60.0%	60.0%	2.99	0.3934
ESS	53.6%	53.6%	53.6%			100.0%	100.0%	100.0%		
Undifferentiated	66.7%	66.7%	66.7%			50.0%	50.0%	50.0%		
Adenosarcoma	33.3%	-	-			-	-	-		
Carcinosarcoma	47.4%	-	-			60.0%	30.0%	30.0%		
Total	45.7%	41.5%	41.5%			81.9%	61.4%	61.4%		

(-) survival function cannot be estimated due to lack of cases reaching this period

undifferentiated type. None of the patients with adenosarcoma and carcinosarcoma reached the 2-year and 3-year follow-up period due to poor or no follow-up. The 3-years PFS rates for ESS and undifferentiated sarcoma were 53.6% and 66.7%, respectively. None of the patients with Leiomyosarcoma reached the 3-year follow-up period. Log rank test showed no significant differences in PFS rates across the different histologic subtypes of uterine sarcoma (p-value=0.5038).

Data for Overall Survival (OS) were available for 17 patients (See Table 4 and Figure 3). The OS rates for this group were 8.9% for 1 year, and 61.4% for 2 and 3 years. The 1- year OS rates for each histologic sub type were as follows: 100.0% for Leiomyosarcoma, 100.0% for ESS, 50.0% for undifferentiated sarcoma, and 60.0% for carcinosarcoma (Table 4 and Figure 4). The 2- and 3-year OS rates for each histologic subtype were as follows: 60.0% for Leiomyosarcoma, 100.0% for ESS, 50.0% for undifferentiated, and 30.0% for carcinosarcoma. Log rank test showed no significant differences in OS rates across the different histologic subtypes of uterine sarcoma (p-value=0.3934).

Table 5 shows the results of Cox proportional hazards regression analysis to determine significant predictors of progression (n=75 patients) and overall mortality (n=17 patients). Proportional-hazards assumption was tested using goodness-of-fit and showed that this was not violated. There was

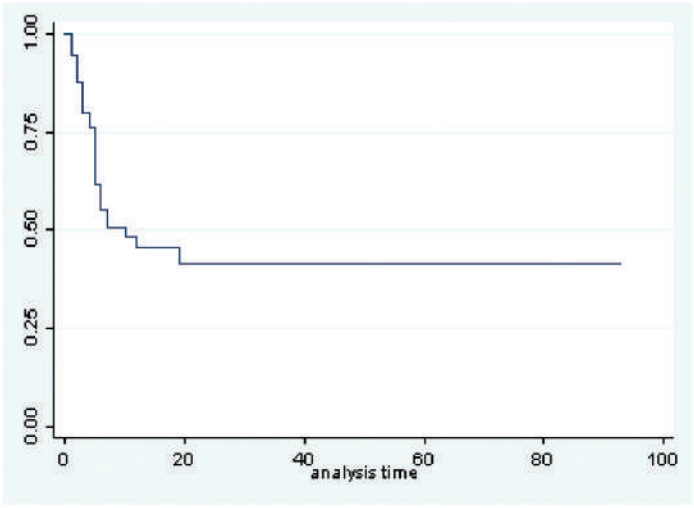

Figure 1. Kaplan-Meier Estimate for Progression Free Survival (months)

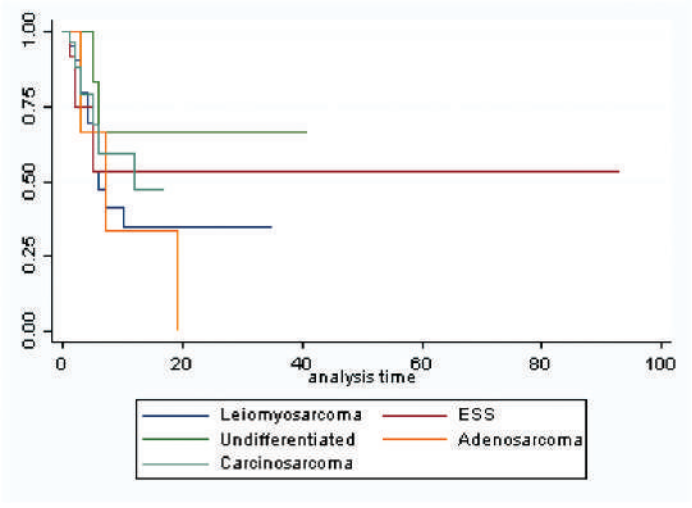

Figure 2. Kaplan-Meier Estimate for Progression Free Survival by Histologic Subtype (months)

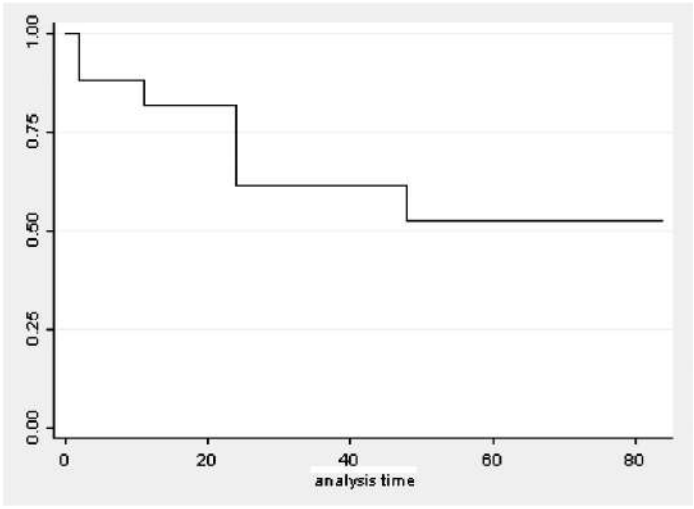

Figure 3. Kaplan-Meier Estimate for Overall Survival (months)

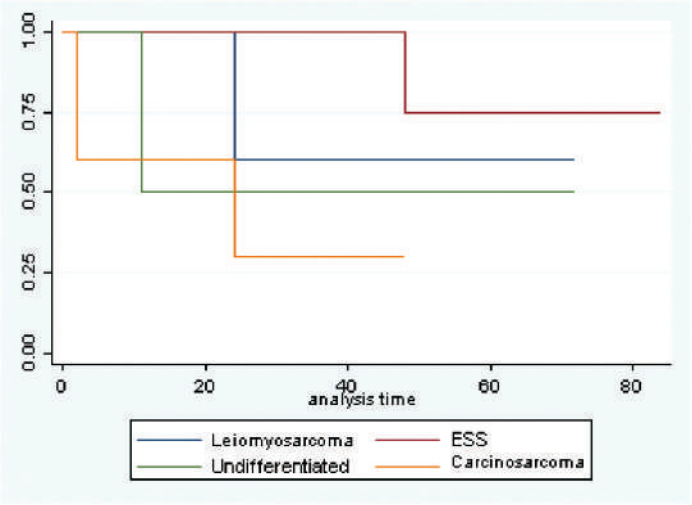

Figure 4. Kaplan-Meier Estimate for Overall Survival by Histologic Subtype (months)

no sufficient association between progression and histologic subtype, age, tumor size, and adjuvant therapy. It was, however, observed that surgical approach and staging were significantly associated with disease progression. Patients who underwent surgery but did not have staging were at higher risk for progression compared to those who underwent staging (HR=8.11, 95%CI=1.871-35.184, p-value= 0.005). Patients with more advanced stages of the disease (Stages 3-4) were at higher risk for progression compared to those with Stage 1 disease (HR=4.10, 95%CI=1.011-16.620, p-value= 0.048). Due to lack of cases with information on OS, only histologic subtype and age can be included in the multivariate analysis for overall mortality. Both of these variables showed no significant association with OS (p-values > 0.05).

In terms of lymphovascular space involvement, regression analysis involving 87 patients showed that ESS histologic subtype is associated with higher risk (OR=21.11, 95%CI=1.360-327.76, p-value = 0.029) (see Table 6). Also, tumor size of >10 cm is associated with higher risk of LVSI (OR=6.59, 95%CI=1.012-42.864). No significant associations were observed for the other clinical variables (p-values > 0.05).

DISCUSSION

In spite of advances in cancer screening and therapies over the past few decades, less progress has been made in improving survival of patients with uterine sarcoma. The ideal treatment protocol for uterine sarcoma is still lacking and the prognostic factors are not well understood. The current single-center retrospective study was done to determine the clinical and demographic characteristics, and outcomes of Filipino patients diagnosed with uterine sarcoma.

Uterine sarcoma is reported to be rare and it was estimated to occur in 1:8300 to 1:352 women undergoing uterine surgery.[3] Out of 110 patients, 87 cases of uterine sarcoma who consulted the institution in a span of 10 years showed that indeed, this disease has a very small incidence. The mean age of the participants was 54.0 years old. In another study from Thailand, the mean age of patients with uterine sarcoma was also 54.0 years old.[2,7] This is almost comparable to the study of Chen et al (2018) which showed a mean age of 62.1 years old among patients with uterine sarcoma.[3] Eighty-six percent were already menopause at the time of diagnosis. Post-menopausal status

Table 5. Cox proportional hazards regression analysis of progression and overall mortality

	Progression			Overall Mortality		
Variables	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Histologic subtype						
Leiomyosarcoma	Ref	-	-	Ref	-	-
ESS	1.55	0.197-12.237	0.675	0.98	0.054-17.819	0.989
Undifferentiated	1.09	0.098-12.131	0.943	1.75	0.150-20.503	0.654
Adenosarcoma	1.35	0.46-12.453	0.792	-	-	-
Carcinosarcoma	1.40	0.313-6.241	0.661	1.71	0.235-12.455	0.596
Age	1.03	0.966-1.091	0.394	1.07	0.919-1.247	0.379
Tumor size						
<5 cm	Ref	-	-	-	-	-
5-10 cm	1.10	0.268-4.499	0.895			
>10 cm	0.43	0.092-2.059	0.294		-	-
Radiotherapy						
None	Ref	0.00	1.000	-	-	-
Yes	0.00					
Chemotherapy						
None	Ref	-	-	-	-	-
Yes	0.57	0.161-2.010	0.380			
Surgical Approach						
EHBSO/ THBSO with BLND, PALS	Ref	-	-	-		
EHBSO/ THBSO without BLND, PALS	8.11	1.872-35.184	0.005			
Stage						
1	Ref	-	-			
2	2.90	0.609-13.829	0.181			
3-4	4.10	1.012-16.620	0.048			
LVSI						
No	Ref	-	-			
yes	1.13	0.313-4.063	0.854			

among patients with uterine sarcoma was common. In fact, in the study of Chen et al (2018), as much 81.8% were already post-menopausal (p-value<0.0001).[3] There is direct correlation between age and the incidence of cancer. Older women may have more potential exposure to toxins and unhealthy habits which leads to mutations in the cells and eventual development of cancer.

Majority of patients in the present study were either overweight or obese (59.8%). The strength of association between obesity and endometrial cancer risk increases with increasing BMI: RR for overweight is 1.32 (95% CI 1.16-1.50) and for obesity is 2.54 (95% CI 2.11-3.06).[4] There was, however, no direct association between obesity and uterine sarcoma.

The most common medical co-morbidity was found to be hypertension (44.8%). It was also noted that patients with family history of cancers was found among 2.3-3.4% of patients with uterine sarcoma. Currently, no studies were found showing that these factors were significantly associated with increased risk for having uterine sarcoma.

In this group of patients, the most common symptom experienced was vaginal bleeding (93.1%). This is higher compared to the findings of Chen et al (2018) wherein vaginal bleeding was experienced by 68.4% of patients.[3] In the study of Potikul et al (2016), 63.0% also experienced abnormal vaginal bleeding.[5] Three-fourths of the patients in the present study had tumor size greater than 5cm (75.8%). In the study of Chen et al (2018), the mean size of the largest tumors were reported to be as much as 9.6cm.[3]

Presence of LVSI was found in only 29.9% of patients and lymph node involvement was found among 11.5% of patients. These rates were smaller compared to the findings observed by Potikul et al (2016) wherein 59.5% of uterine sarcoma patients had LVSI and 22.4% had lymph node involvement.[5]

Table 6. Association of clinical characteristics with lymphovascular space invasion

Variables	OR	95% CI	p-value
Histologic subtype			
Leiomyosarcoma	Ref	-	-
ESS	21.11	1.360-327.76	0.029
Undifferentiated	1.66	0.138-19.978	0.688
Adenosarcoma	7.78	0.222-272.77	0.258
Carcinosarcoma	3.33	0.500-22.154	0.214
Age	1.04	0.958-1.121	0.373
Tumor size	Ref	-	-
<5 cm	2.30	0.434-12.204	0.327
5-10 cm	6.59	1.012-42.864	0.049
>10 cm			
Radiotherapy			
None	Ref	-	-
Yes	0.82	0.149-4.521	0.822
Chemotherapy			
None	Ref	-	-
Yes	3.05	0.692-13.453	0.140
Surgical Approach			
EHBSO/ THBSO with BLND, PALS	Ref	-	-
EHBSO/ THBSO without BLND, PALS	0.61	0.105-3.631	0.591
Stage			
1	Ref	-	-
2	1.88	0.370-9.539	0.447
3-4	1.92	0.384-9.647	0.426

About 15% of the patients in this study had radiotherapy and 36% had chemotherapy. These observed rates of adjuvant therapies were very similar with those reported by Potikul et al (2016) wherein 15.2% of uterine sarcoma patients underwent radiation therapy and 26.1% had chemotherapy.[5]

This study demonstrated that uterine sarcomas are rare malignant gynecological tumors with poor prognosis. In a span of 10 years, there were only 87 cases of uterine sarcoma diagnosed in a tertiary government hospital. The observed 3-year PFS was 41.5% and OS was 61.4%. The median progression free survival was 4 months while the median overall survival was 36 months. These estimates are almost similar to previous studies on uterine sarcoma from other populations. In the study of Akman et al (2016), 57 cases of uterine sarcoma had 36.7% 80-month OS.[6] The study of Sharma et al (2011) had 50 cases with 42.0% OS while the study of Livi et al (2003) had 141 cases with OS of 41.8%.[6,7]

The results of the current study showed that PFS after 3 years was highest in undifferentiated histologic sub-type while OS after 3 years was highest in ESS sub-type. There were, however, no significant differences in both PFS and OS across the different histologic sub-types of uterine sarcoma. There is conflicting evidence whether histologic sub-types are associated with survival or not.[5,8,9,10] In the study of Sharma et al (2011), LMS patients had significantly poorer 3-year OS (21%, p-value=0.01) but the difference in survival between CS and ESS was not significant (65% versus 50%, respectively, p-value=0.8).[11] In the study of Livi et al (2003), LMS also predicted the worst prognosis, followed by MMT and ESS with a 5-year survival rate of 18.8%, 22%, and 62%, respectively (p-value=0.05).[7] In contrast, the study of Akman et al (2016) did not show any difference in the OS across the different histologic subtypes.[6]

Carcinosarcoma is an abnormal growth of tissue characterized by two cellular elements, which are epithelial and mesenchymal elements. This neoplasm is common among women in the postmenopausal age group. They usually present with uterine enlargement and abnormal vaginal bleeding. Carcinosarcomas are large polypoid masses that fill the uterine cavity, and has high tendency to prolapse. Spread of tumor outside the uterus was seen in approximately one-third of cases. On microscopic examination, carcinomas are serous in nature in two-third of the cases and endometrioid in one-third of the cases. According to Akman et al (2016), the over-all 5-year survival for carcinoma patients was approximately 30%, and those diagnosed in stage I had better survival at 50%.[6] In the current study, the most common histological sub-type was CS (35.6%, 31/87 cases). The 1-year PFS and OS were 47.4% and 60.0%, respectively. This has recently been removed from the sarcoma group and categorized under the poor histologic type of endometrial carcinoma but its behavior, spread and prognosis are similar to uterine sarcoma. Most of the literatures still include carcinosarcoma in the sarcoma group.

Endometrial stromal tumors are unusual types of uterine mesenchymal neoplasms which are composed of cells resembling endometrial stromal cells of the proliferative endometrium. In the present study, the prevalence of ESS was 17.2% (15/87 cases). The 1-year PFS and OS were 53.6% and 100.0%, respectively. Only 10 patients had undifferentiated sub-type, and the 1-year PFS and OS were 66.7% and 50.0%, respectively.

Leiomyosarcoma is a infrequent type of neoplasm that affects the smooth muscle tissues of the uterus.[10] LMS occurs commonly in women over the age of 40 years old. Its usual manifestations include abnormal vaginal bleeding, palpable pelvic mass and pelvic pain. Leiomyosarcoma is difficult to treat even when still confined within the uterus or even diagnosed early. In the current study, most patients were preoperatively diagnosed with myoma and were only diagnosed correctly on the final histopathology report. Tumor size and mitotic index are said to be major predictive factors for LMS. Radiotherapy may be used in the management of local recurrences while chemotherapy with doxorubicin or docetaxel gemcitabine can be used for advanced stages and/ or recurrent ones. The use of adjuvant radiotherapy, however, still remains uncertain. Recurrence rate of LMS is reported to be from 53% to 71%.[6] In the study done by Akman et al (2016), overall survival for LMS was 37.5% at the end of 46 months.[6] In the current study, the prevalence of LMS was 26.4% (23/87 cases). The 1-year PFS and OS were 34.5% and 100.0%, respectively.

Adenosarcoma is a neoplasm of the female genital tract, accounting for only about 5% of the uterine sarcomas.[12] It has low malignant potential, and has better prognosis compared to other uterine sarcomas. Adenosarcomas have late local recurrence in about 20% of cases. The standard treatment for this type of neoplasm is TAH with BSO.[6] In the present study, only 4 patients had adenosarcoma and the 1-year PFS was 33.3%.

This study demonstrated that the extent of surgery and staging were significantly associated with PFS. Patients who underwent surgery without staging were 7.76 times at higher risk for progression or poor outcomes compared with those who underwent staging. Also, patients with more advanced stages of the disease (Stages 3-4) were 4.23 times at higher risk for progression or poor outcomes compared to those with Stage 1 disease.

Several studies report on the association of demographic factors and survival among patients with uterine sarcoma.[6,5,7] Aside from histological sub-type, the most frequently assessed prognostic factors were tumor stage, grade, lymphovascular invasion, menopausal status, and adjuvant radiotherapy.

In the study of Livi et al (2003), the only significant prognostic factors for survival were the stage (p-value=0.02) and histology (p-value=0.05). Age, grade, and adjuvant treatment were not significant predictors based on their study.

The findings on factors associated with lymphovascular space involvement were consistent with previous studies. The study by Zhang et al (2019) showed that patients with Low-Grade Endometrial Stromal Sarcoma were more likely to have LVSI (21.15%) compared to uterine adenosarcoma (10.71%)[13]. On the other hand, the study by Watanabe et al (2019) showed that higher tumor grade was significantly associated with LVSI (p-value <0.001)[14].

CONCLUSION

In a span of 10 years, there were only 87 cases of uterine sarcoma diagnosed in this institution. The observed 3-year PFS was 41.5% and OS was 61.4%. The prevalence of each histologic subtype among patients with uterine sarcoma was as follows: 26.4% for Leiomyosarcoma, 17.2% for ESS, 11.5% for undifferentiated, 4.6% for adenosarcoma, and 35.6% for carcinosarcoma. The median progression free survival was 4 months while the median overall survival was 36 months. No significant differences in both PFS and OS among different histologic sub-types of uterine sarcoma were observed across different follow-up periods. Multivariate analysis showed that lack of staging during surgery and more advanced stages of the disease were significant predictors of disease progression. Findings, should be interpreted with caution due to limited number of uterine sarcoma cases included in the study.

LIMITATION OF STUDY

Since this was a retrospective study, all data were based on medical and histopathologic records. Some patients were lost to follow-up after their initial consults. No further assessment and management was done. Data on the final histopathologic reports were lacking on a number of patients since no surgical intervention was performed on them. Some data were not reported and there were no other means by which they could be verified. One limitation of this study is the small number of cases falling in some histologic sub-types of sarcoma. Also, only 17 patients had information on OS. This finding is consistent with other studies and a commonly cited reason for this is the rarity of the disease. The small sample size in some sub-types could have affected the ability of the statistical tests to detect significant associations between the other variables and survival. Another limitation is the retrospective nature of this study wherein temporal relationship is difficult to assess. There is also no means to validate outcomes reported in patient records especially among those lost to follow-up. Despite these limitations, this is the first study to determine the clinical and demographic characteristics, and outcomes of Filipino patients diagnosed with uterine sarcoma.

RECOMMENDATIONS

It is recommended that prospective studies involving multiple institutions and large number of cases be done to determine other significant predictors of OS and PFS among Filipino women with uterine sarcoma.

A detailed checklist should be provided in the charts for further future investigation. There should be proper documentation of the family pedigree of cancer and other associated medical co-morbidities and risk factors. The patient or the next of kin should be contacted to verify information written in the chart and to know the present status of the patient. Also, it will be beneficial for hospitals to have a database for uterine sarcoma patients which includes socio-demographic characteristics and survival outcomes. This will facilitate better estimation of prognostic factors that may impact management guidelines for uterine sarcoma.

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Cutaneous metastases: A rare primary presentation of cervical cancer recurrence

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ABSTRACT

Carcinoma of the cervix rarely metastasizes to the skin. Their presence may be the first sign of recurrence and heralds a poor prognosis.

We report a case of a 48-year-old woman with previous history of cervical cancer who developed skin metastasis forty months after treatment. Histopathology result of the skin biopsy revealed poorly differentiated carcinoma, consistent with metastases most probably from a cervical primary. The patient expired five months after the appearance of cutaneous disease before any definitive treatment could be initiated.

The proposed mechanism of cutaneous metastasis in the index patient is most probably radiation-induced endothelial cell damage culminating in tumor cell trapping.

At present, there is no effective treatment for skin metastases. It is vital to establish the primary source and extent of metastatic spread when a patient presents with skin metastases in order to devise appropriate treatment programs. It is advisable to include examination of the skin during the course of follow-up, and prompt skin biopsy should be done when there are suspicious cutaneous lesions.

INTRODUCTION

Cervical cancer is the second most common cancer among women in the Philippines. The frequent sites of distant metastases are the lungs, bone and liver. Carcinoma of the cervix rarely metastasizes to the skin even in the late stages of disease with a reported incidence of 0.1 to 2%.[1-4] Their presence may be the first sign of recurrence and heralds a poor prognosis.

We report a case of a 48-year-old woman with a previous history of cervical cancer who developed skin metastasis forty months after concurrent chemotherapy and pelvic radiation.

CASE

The patient was a 48 year-old, gravida 4 para 4 (4004), diagnosed with squamous cell carcinoma, non-keratinizing, of the cervix, FIGO stage IIIB in 2011 after presenting with profuse vaginal bleeding and foul-smelling vaginal discharge. She received concurrent chemotherapy with weekly Cisplatin and radiation with external beam radiation therapy of 5040 cGy in 28 fractions followed by intracavitary brachytherapy. After completion of treatment, the patient was followed up regularly with no evidence of disease for 40 months.

Four months prior to admission, the patient noted bilateral lower extremity edema and multiple erythematous, hyperpigmented, tender papules and nodules on the bilateral thighs predominantly on the medial aspect. Within two months, there was progressive bilateral lower extremity edema and an increase in the number of hyperpigmented papules and nodules, which had spread to the right lower anterior abdominal wall. She consulted at a regional hospital where she was managed as a case of deep vein thrombosis. She was given anticoagulation in the form of enoxaparin, which was subsequently overlapped with warfarin.

After one month of treatment, there was no resolution of symptoms. The patient then consulted at our institution. On physical examination, there were note of multiple hyperpigmented papules coalescing into plaques with excoriation and ulceration on the bilateral proximal thighs with most lesions concentrated on the medial aspect, and hypogastric area of the abdomen (Figures 1 and 2). There was no palpable supraclavicular or groin lymph node. The patient had difficulty tolerating pelvic examination due to the tender nature of the lesions. Pelvic and internal examination revealed normal external genitalia, smooth cervix measuring 1.5 x 1.0 centimeters, small corpus, and absence of adnexal mass and tenderness. Bilateral parametria were shortened but smooth on rectovaginal examination.

There were multiple enlarged bilateral pelvic lymph nodes on abdominopelvic computed tomography (CT) scan. There was no metastatic disease identified in the liver on CT scan.

Initial impression on the skin lesions was herpes zoster, rule out cutaneous metastasis. A sample of the skin lesion on the left anterolateral thigh was obtained. Histopathology result revealed poorly differentiated carcinoma, consistent with metastases most probably from a cervical primary given the background of the patient. The microscopic picture depicted an encapsulated dermal nodule with non-keratinizing squamous cells that appear like clear cells with numerous mitotic figures arranged in nests with intervening fibrocollagenous stroma. (Figures 3 and 4). The tumor cells were round to ovoid in shape with clear to pale eosinophilic cytoplasm. There were note of irregularities in the nuclear contour and prominence of the nucleoli. Immunohistochemistry was recommended to ascertain the diagnosis. The results were positive for Cytokeratin 5/6

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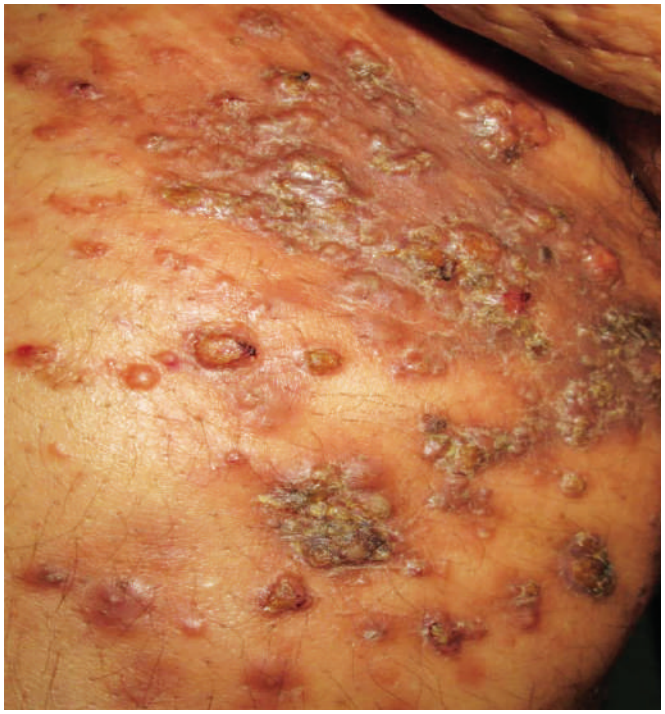

Figure 1. Erythematous, hyperpigmented papules, plaques and nodules on the patient's right upper thigh

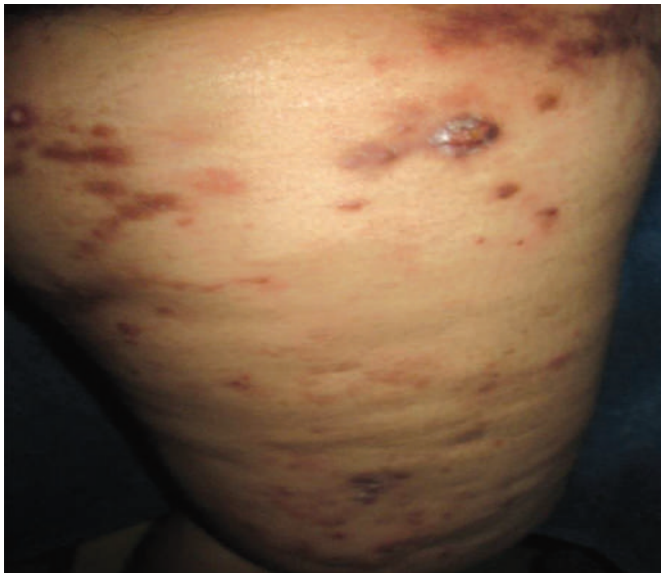

Figure 2. Erythematous, hyperpigmented papules and nodules on the patient's left thigh

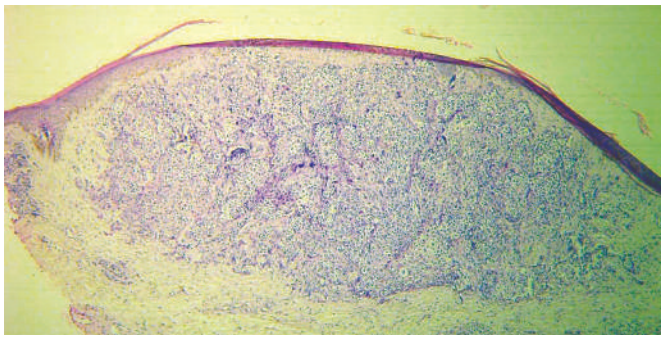

Figure 3. Metastatic poorly differentiated carcinoma (H&E stain, Scanning view). An encapsulated dermal nodule with tumor cells arranged in nests with intervening fibrocollagenous stroma

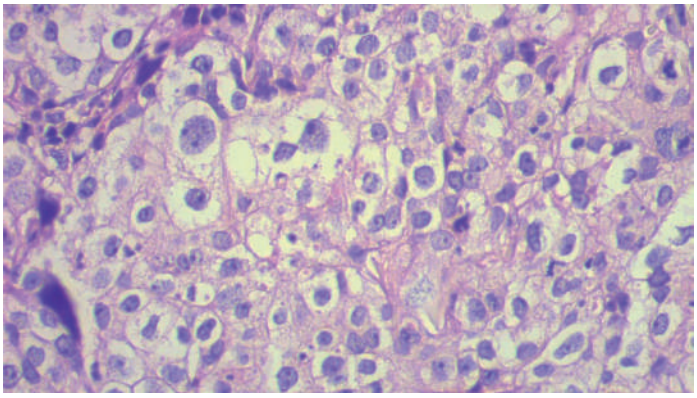

Figure 4. Metastatic poorly differentiated carcinoma (H&E stain, High power view). Non-keratinizing squamous cells that appear like clear cells with numerous mitotic figures

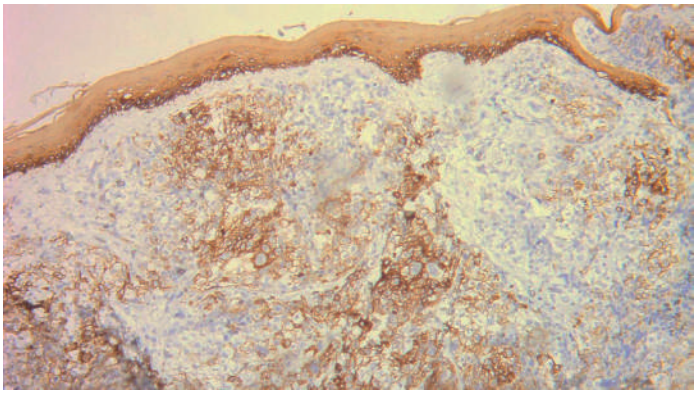

Figure 5. Positive for cytokeratin 5/6

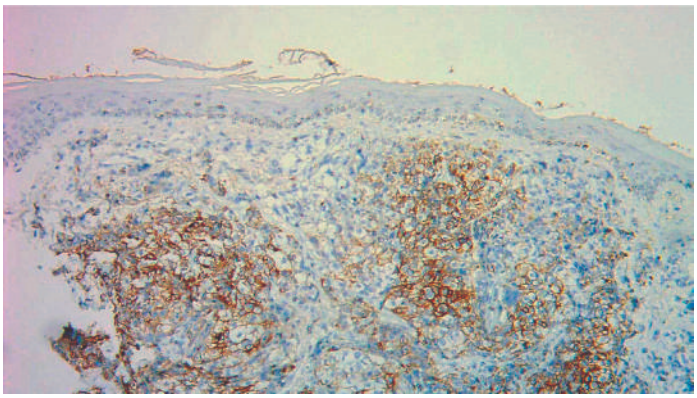

Figure 6. Positive for cytokeratin 7

(Figure 5) and Cytokeratin 7 (Figure 6).

The plan of treatment was combination chemotherapy with paclitaxel and carboplatin. Before any intervention could be instituted, the patient expired five months after the appearance of cutaneous metastatic disease.

DISCUSSION

The most common solid tumors presenting with cutaneous involvement originate from the breast, lungs, large intestines, kidneys and ovary. Rarely reported are cutaneous metastases from cervical cancer with an incidence of 0.1 to 2%.[1-4] Cervical carcinoma usually spreads locally through direct extension into adjacent structures. Distal spread can occur through the

hematogenous and lymphatic routes, and the lungs, bone and liver are the main sites.

There are two proposed mechanisms of cutaneous metastasis. First is alteration of the lymphatic flow by tumor wherein the tumor obstructs the deep lymphatic pathways leading to retrograde shunting to the cutaneous vasculature.[5-6] The tumor cells are disseminated into circulation and proliferate at a secondary center. The second mechanism is endothelial cell damage as a consequence of radiation culminating in tumor cell trapping.[7-8] The sites are commonly limited to the irradiation fields such as the lower abdominal wall and vulva, but can also be found at a substantial distance from the primary site. The lesions may appear months to years after completion of treatment.

Cutaneous nodules are the most common morphological pattern followed by plaques and maculopapular rashes.[9] More than one anatomical site may be involved in the majority of patients while others may present with an inflammatory rash at a single site such as the scalp or face. These metastases tend to be close to the primary tumor site, appearing most commonly on the abdominal wall and vulva followed by the lower extremities and chest. The lesions occur predominantly in cases of tumor recurrence developing up to ten years after initial diagnosis. In the largest series on cervical cancer patients, the mean interval between diagnosis of the primary tumor and development of cutaneous metastases was 16.9 months.[10]

The index patient presented with tumor recurrence diffusely located on the skin of the bilateral proximal thighs and lower abdominal wall in the absence of a cervical pathology. The location of the lesions is similar to the reported cases wherein the lesions commonly appear proximal to the primary tumor site. Forty months elapsed between the initial diagnosis of cervical carcinoma and treatment with concurrent chemotherapy and radiation, and presentation with cutaneous disease. The patient had no evidence of disease during that period. The development of recurrence for this patient is most likely secondary to cell damage and tumor cell trapping from the radiation treatment.

Histopathology result of the skin biopsy showed poorly differentiated carcinoma probably metastatic, most probably from the cervix. However, the question still arose whether the cutaneous carcinoma was another primary malignancy or metastases from the known primary. Immunohistochemistry with cytokeratin 5/6 and 7 were employed to establish the site of origin. The specimen stained strongly positive for both cytokeratin 5/6 and 7. Cytokeratin 5/6 has strong, diffuse presence in cells of mesothelial origin. It has excellent sensitivity and specificity for the detection of squamous differentiation in poorly differentiated carcinomas. Furthermore, positivity of cytokeratin 7 points to squamous dysplasias and squamous cell carcinoma of the cervix.[11]

At present, there is no effective treatment for skin metastases. The intent of therapy is palliation, whether using chemotherapy, radiation and surgery either alone or sequential.[5,10] Majority of patients received palliative chemotherapy either with carboplatin or bleomycin as a single agent or with paclitaxel and carboplatin as combination chemotherapy.[9,10,12] The planned therapy for the patient was chemotherapy with paclitaxel and carboplatin due to the widespread area of skin metastases which would not be suitable for surgery and presence of enlarged lymph nodes which further signifies disseminated disease. Skin metastasis has come to signal a poor prognosis with a mean reported survival of 8.5 months from time of initial presentation of cutaneous lesions.[9] Cutaneous lesions signify widespread disease and rarely present as the initial manifestation whether in the primary diagnosis of the disease or during recurrence. The earlier the metastasis becomes apparent, the poorer prognosis of the patient. This late manifestation is widely regarded as a sign of terminal disease as in the case of the index patient who expired within 5 months of initial presentation with cutaneous lesions.

It is vital to establish the primary source and extent of metastatic spread when a patient presents with metastases to the skin in order to devise appropriate treatment programs. Patients with known cervical carcinoma who develop nodules, papules or diffuse inflammatory rash should undergo systematic skin inspection and prompt skin biopsy to rule out metastatic disease. It is advisable to include examination of the skin during the course of follow-up of these patients. A timely diagnosis and institution of therapy may improve survival.

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Malignant mixed mullerian tumor of the cervix synchronous with ovarian clear cell carcinoma: First case reported

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ABSTRACT

Malignant mixed mullerian tumors comprised 0.005% of all malignancies of the cervix. It has better prognosis than its uterine counterpart. To date, there is still no published case of cervical MMMT in the Philippines.

Our index case is a 58-year-old, nulligravid who presented with vaginal spotting due to a polypoid mass on the posterior cervical lip. Ovarian new growth was also noted on transvaginal ultrasound. She underwent exploratory laparotomy, peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingooophorectomy, bilateral pelvic lymph node dissection, para-aortic lymph node sampling, infracolic omentectomy, random peritoneal biopsy. Histologic examination of the cervical polyp showed malignant mixed mullerian tumor (MMMT) while that of the right ovary showed clear cell carcinoma. The synchronous occurrence of cervical MMMT and ovarian clear cell carcinoma makes this case even rarer.

Ovarian clear cell carcinoma accounts for 5-25% of all epithelial ovarian cancers. It usually presents at an earlier stage but carries a poor prognosis when diagnosed late.

Although, there are still no guidelines regarding the management, prognosis, and outcome of cervical MMMT, few reports have suggested the use of platinum-based chemotherapy. With the synchronous occurrence of the cervical and ovarian malignancies, chemotherapy with Carboplatin-Paclitaxel and radiotherapy were advised.

Keywords: cervical malignant mixed mullerian tumor, clear cell carcinoma

CASE

The patient is a 58-year-old, nulligravid from Cavite, a diabetic maintained on Metformin and Gliclazide. Her sister underwent mastectomy and chemotherapy for breast cancer. Her paternal aunt died of endometrial cancer. She had one sexual partner, with coitarche at age 29. She had no history of OCP nor IUD use. Her menarche was at age 15 and menopause was at 51.

Patient had a 3-month history of vaginal spotting followed by profuse vaginal bleeding. Review of systems showed occasional hypogastric pain but no anorexia, weight loss, fever, abdominal enlargement, diarrhea, constipation, hematuria and edema. On consult, physical examination was unremarkable except for the pelvic exam findings of a 2.5 x 2.5 cm, smooth cervix, with a 3.0 x 3.0 cm fleshy polypoid mass at the posterior lip. The corpus was small, and no adnexal mass nor tenderness was noted. On rectovaginal examination, both parametria were smooth and pliable.

Punch biopsy of the fleshy polypoid mass was done. Histopathologic examination revealed a combination of poorly differentiated epithelial malignancy admixed with a sarcomatous element suggestive of a Malignant mixed mullerian tumor, hetorologous type.

Transvaginal ultrasound revealed a heterogenous mass, 2.9 x 3.9 x 2.9 cm, prolapsing out of the endocervical canal and attached to the anterior cervical stroma with moderate central vascularity. The corpus, which measured 4.1 x 3.9 x 3.3 cm, had a smooth contour and homogenous echopattern. The endometrium was thin (0.3 cm) and hyperechoic with intact subendometrial halo. There was a predominantly solid mass, 5.4 x 3.5 x 3.6 cm, at the right adnexal area with scant peripheral vascularity. The left ovary was not visualized. Sonologic impression was prolapsed cervical mass, consistent with malignancy; thin endometrium; ovarian new growth, right, probably malignant. Admitting impression was Malignant mixed mullerian tumor, heterologous type, cervix, stage IB1; Ovarian new growth probably metastatic, rule out double primary tumor.

She underwent exploratory laparotomy, peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingo-oophorectomy, bilateral lymph node dissection, para-aortic lymph node sampling, infracolic omentectomy, random peritoneal biopsy under epidural anesthesia. Intraoperatively, the uterus had smooth serosal surface. The right ovary was converted to a 5.0 x 4.0 x 3.0 cm cystic mass with a 3.0 x 4.5 x 2.0 cm solid necrotic area (Figure 1). The cervix measured 2.5 x 2.5 x 1.5 cm, with smooth ectocervix. Attached to the posterior cervical lip, just beneath the internal os, was a polypoid mass, 2.0 x 1.5 x 1.2 cm, with a 0.5 cm stalk, which was 1.5 cm from the external os (Figure 2). There was only superficial stromal invasion. Patient was discharged on the 4th hospital day, with unremarkable stay in the ward.

Histopathology of the cervix showed endocervical epithelium lining proximal and distal to the polyp. The polyp

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itself had an atypical proliferation of cells arranged in solid and glandular patterns (Figure 3). The more well-differentiated glandular areas showed atypical columnar to cuboidal cells with increased nuclear-cytoplasmic ratio lining the glandular spaces. The cytoplasm was granular, and eosinophilic to amphophilic, with occasional clearing of the cytoplasm. Nuclei were vesicular with prominent nucleoli. Some areas exhibited a more solid proliferation. The stromal portion was cellular and fibrous, with areas of significant atypia. Some areas showed malignant-appearing heterologous elements, most notably a chondrosarcoma-like area (Figure 4). Both malignant epithelial and stromal elements invaded only minimally into the cervical stroma.

Histologic sections from the right ovary showed a neoplastic proliferation of cells in varied architectures. Solid, tubular, and papillary-like areas were all seen (Figure 5). Neoplastic cells had moderately abundant, clear cytoplasm or lightly eosinophilic, finely granular cytoplasm. Nuclei were vesicular with prominent nucleoli and moderate atypia. Occasional hob-nailing of the cells were seen in the lining of the papillary portions (Figure 6). Prominent, deeply eosinophilic hyaline globules were also present. A fine fibrovasculature was seen in the tubular and solid areas. Combinations of all these features pointed to a clear cell carcinoma of the ovary. The left ovary, omentum and peritoneal fluid were positive for metastases from the clear cell carcinoma.

Immunohistochemistry studies for pancytokeratin (panCK) and monoclonal carcinoembryonic antigen (CEA) were done on the cervical and ovarian tumor. PanCK showed a diffuse cytoplasmic and membranous staining in almost all the neoplastic epithelial cells, as well as few of the sarcomatous elements (Figure 7). CEA showed extremely focal, but strong cytoplasmic and membranous staining, in few epithelial tumor cells (Figure 8). Normal staining of the surrounding endocervical epithelium was seen in both specimens. This immunohistomorphologic pattern is supportive of a primary endocervical neoplasm, especially in the background of normal-staining endocervical epithelium. The possibility of metastasis to the ovary is likely. In the ovary, PanCK showed diffuse and strong membranous and cytoplasmic staining, whereas CEA was negative in all tumor cells. This implied a carcinoma that is not of cervical origin, but without a specific stain, immunomorphologic finding is not pathognomonic of neoplasm of ovarian origin. However, in the absence of other clinically detectable masses, the staining pattern is compatible with a primary ovarian carcinoma.

Final diagnosis was malignant mixed mullerian tumor, heterologous type, cervix stage 1B1; Clear cell adenocarcinoma, ovary, stage IIIA2. The post-operative plan was for chemotherapy using Carboplatin-Paclitaxel every 21 days for 6 cycles. CA 125 taken after the surgery was 10.52 U/mL.

DISCUSSION

Squamous cell carcinomas comprise 80-90% of cervical malignancies while the remaining 10–20% are adenocarcinomas. Only 0.005% of cervical malignancies are malignant mixed mullerian tumors. Ferriera and colleagues first described it in 1951.[1] Around 50 cases were noted in literature[2] but only a smaller part was thoroughly described. In the Philippine General Hospital, there were 3 cases noted from 2008 to 2014. The first two were seen only on initial consult and were lost to follow-up.[3] Presently, there are no consensus guidelines regarding its treatment, and very little information is available on its prognosis and outcome.[1]

MMMT's or carcinosarcoma are rare biphasic malignant tumors. It includes both malignant epithelial and mesencyhmal components of mullerian origin.[4] Squamous cell carcinoma with homologous sarcoma are the most common components as shown in Table 1.[1]

The uterine body, fallopian tubes, cervix, and upper part of the vagina are from the mullerian ducts, which are derived from the mesenchyme of the urogenital ridge and the celomic lining epithelium.[4] Cervical MMMTs may contain non-glandular carcinomatous elements.[2,4,5,6,7] In such cases, the overlying squamous epithelium may show intraepithelial neoplasia.[4] The sarcomatous component may be homologous (fibroblasts and smooth muscle) or heterologous (cartilage, striated muscle, and bone). Their ability to form heterologous mesenchymal elements reflects the totipotentiality of the mullerian duct.[8]

There are four main theories that seek to explain the origin of carcinosarcoma. The first is the collision theory, which states that two independent malignancies, namely, carcinoma and sarcoma, collide distinctly rather than admixed. Second is the combination theory, which emphasized mutual pluripotential cells contributing to both the epithelial and mesenchymal components. Third is the composition theory that acknowledged the malignant transformation of both the glandular epithelial cells and mesenchymal stromal cells in a single tissue or organ. Fourth is the conversion theory that proposed that the sarcomatous components develop from the carcinomatous elements by a metaplastic process of dedifferentiation. This theory supports the dominant role of the epithelial elements and suggests that the sarcoma evolves from the carcinoma as a secondary phenomenon. The sarcomatous component is a manifestation of increased aggressiveness.[4]

The epithelial and stromal elements show identical patterns of X chromosome inactivation, signifying a single stem cell clone origin. Malignant epithelial cells transdifferentiate to malignant mesenchymal cells by loss of E-cadherin expression, appearance of non-epithelial cadherins (N-cadherin and cadherin-11) and acquisition of mesenchymal markers (vimentin, fibronectin, and others). This is known as the epithelial-mesenchymal transition (EMT). This promotes the communication of tumor cells with the stroma and enabling invasion and metastasis.

The key regulator of EMT is the miR-200 family of miRNAs and these are down-regulated in the mesenchymal cells of MMMT. Inhibition of this miR-200 allows an increase in the transcriptional repressors (ZEB1 and ZEB2), which diminishes E-cadherin expression.[4,9,10]

Etiologic factors of cervical MMMT are obesity, nulliparity, and exogenous estrogen use, radiation exposure to the pelvic area, previous chemotherapy and HPV infection. The most common types are HPV 16 and 18. Grayson et al.

Table 1. Clinical profile and spectrum of neoplastic differentiation of cases of cervical carcinoma published from 1973 to date

CASE NUMBER	AGE (years)	RACE	SPECIMEN	Surface epithelium	Epithelial Component	Sarcomatous component
1 (Grayson, 2001)	68	Asian	Biopsy + hysterectomy	CIN III (focal)	Adenoid basal carcinoma Keratinizing squamous cell carcinoma Adenoid cystic carcinoma	Homologous (spindled and focally myxoid)
2 (Grayson, 2001)	55	African	Biopsy	CIN III	Basaloid squamous cell carcinoma Adenoid basal carcinoma Adenoid cystic carcinoma	Homologous (spindled and giant cell, with osteoclastic giant cells)
3 (Abell, 1973)	61	African	Biopsy	CIN III (focal)	Non-keratinizing squamous cell carcinoma	Homologous (spindled and focally myxoid)
4 (Clement, 1998)	74	African	Polypectomy	CIN II-III Condylomatous atypia	Well-differentiated keratinizing squamous cell carcinoma	Homologous (high-grade spindled and giant cell)
5	67	African	Biopsy	CIN III	Undifferentiated carcinoma Non-keratinizing squamous cell carcinoma Keratinizing squamous cell carcinoma	Homologous (spindled)
6 (Clement, 1998)	36	African	Biopsy	Ulcerated	Basaloid squamous cell carcinoma Adenoid cystic carcinoma Moderately-differentiated keratinizing squamous cell carcinoma	Homologous (spindled and focally myxoid)
7	32	African	Hysterectomy	CIN III	Moderately-differentiated keratinizing squamous cell carcinoma	Homologous (spindled and focally giant cell)
8 (Clement, 1998)	93	African	Polypectomy	CIN III	Basaloid squamous cell carcinoma Moderately-differentiated keratinizing squamous cell carcinoma	Homologous (spindled and giant cell)
9 (Maheshwari, 2006)	60	Indian	Hysterectomy		Basaloid squamous carcinoma	Homologous
10 (Kudela, 2013)	65	Slovakian	Biopsy + hysterectomy + chemoradiation		Basaloid squamocellular carcinoma	Homologous (high-grade stromal sarcoma)

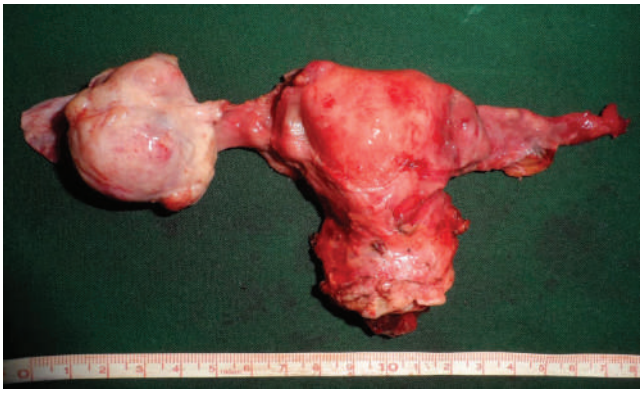

Figure 1. The Uterus and the Ovary (Uncut Section)

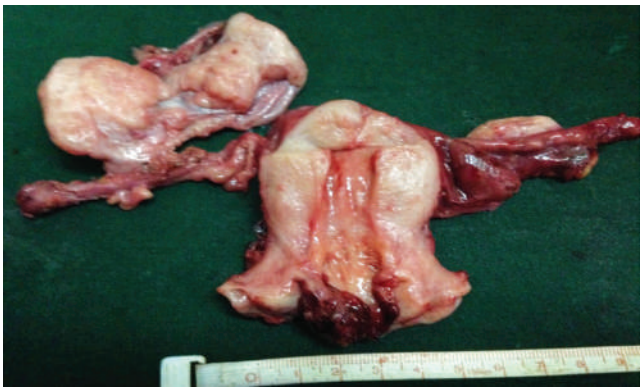

Figure 2. Cut Section of the Uterus and Right Ovary

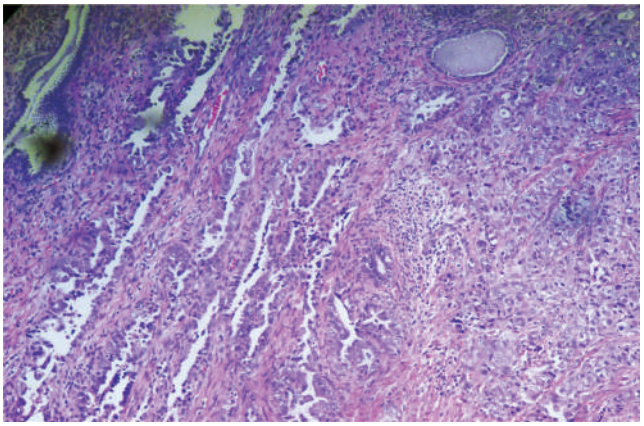

Figure 3. Endocervical polyp with atypical proliferation of cells arranged as solid and glandular components (scanning view)

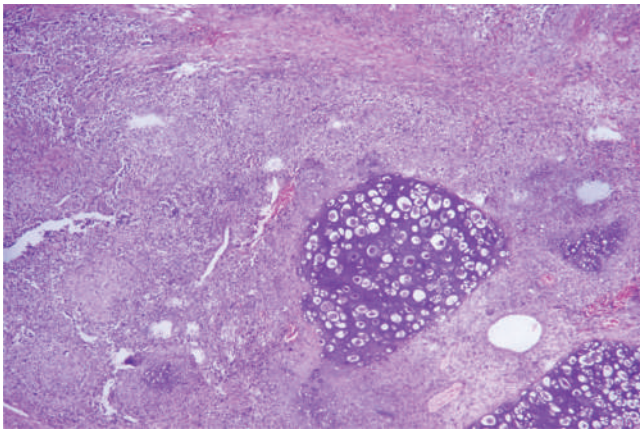

Figure 4. Epithelial and Stromal Components with chondrosarcoma-like heterologous sarcomatous component invading into the Cervical Stroma (scanning view)

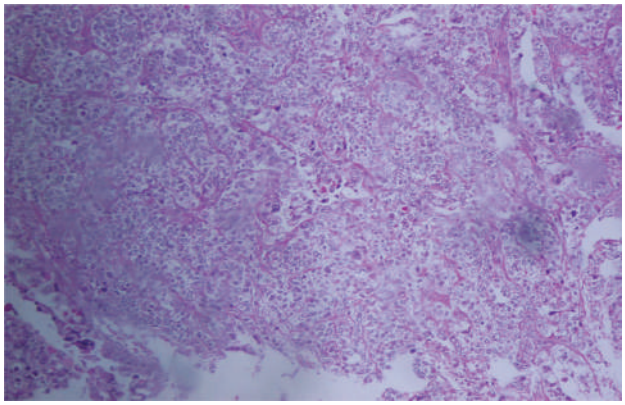

Figure 5. Microscopic View of the Ovarian clear cell carcinoma (Low Power View)

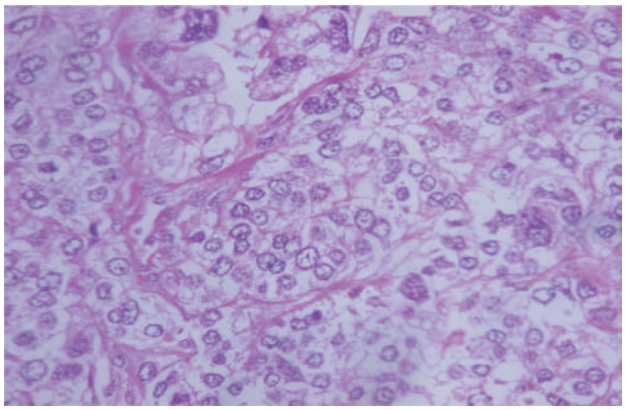

Figure 6. Microscopic View of the Ovarian tumor with Hob-Nail Appearance (High Power View)

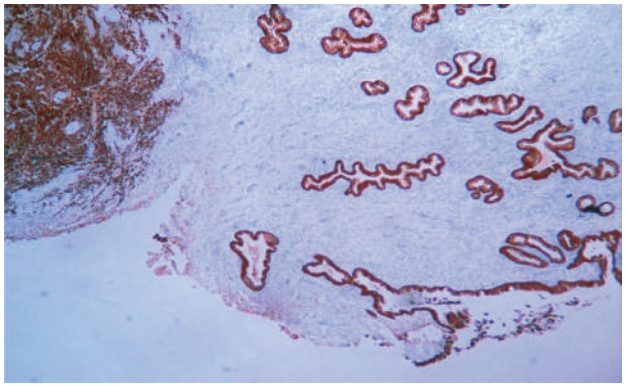

Figure 7. Cervical Mass Immunohistochemistry (pancytokeratin)

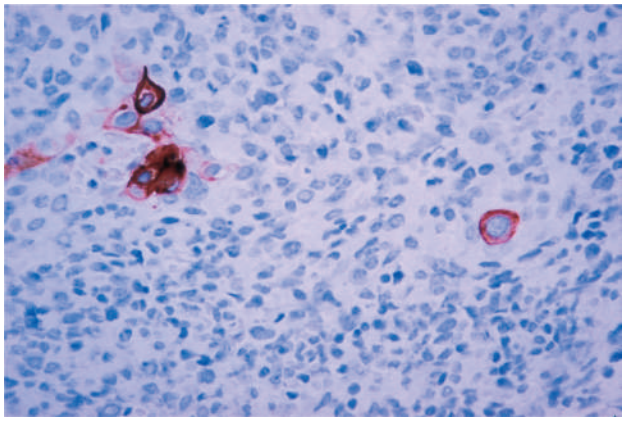

Figure 8. Cervical Mass Immunohistochemistry (CEA)

detected HPV DNA by PCR in eight patients with cervical MMMT. Among these patients, three had HPV-16 DNA in the nuclei of both epithelial and sarcomatous components. This study supports the conversion or metaplastic theory mentioned above.[4,5]

Cervical MMMT usually occurs in postmenopausal women,[1] with 90 % of them presenting with postmenopausal bleeding. In approximately 50% of cases, a polypoid mass (around 1.1-10 cm)[1] is seen within or protruding from the endocervical canal.[11] Our case presented with post-menopausal bleeding and a fleshy polypoid mass (around 3.0 x 3.0 cm) attached to the posterior cervical lip.

Both elements of MMMT may stain positive for cytokeratins and epithelial membrane antigen. The sarcomatous components may be positive for vimentin, desmin and smooth muscle-specific actin (SMA).[2]

Spread of carcinosarcomas is primarily via the lymphatics, local extension and regional lymph node metastasis. Most frequent areas of extension are the pelvis, lymph nodes, lungs and liver. Bulky tumors, vaginal and parametrial metastases have been detected in carcinosarcomas of the cervix more frequently than in other epithelial cancer.[11]

There is no consensus regarding the treatment, prognosis, and outcome of cervical MMMT. Aggressive surgical cytoreduction (i.e., radical hysterectomy, removal of pelvic and aortic lymph nodes, omentectomy and peritoneal cytology in cases of abdominal extension)[4] combined with adjuvant platinum-based chemotherapy and/or radiotherapy is recommended as the treatment of choice.[12] The role of adjuvant radiotherapy and chemotherapy is uncertain. Advantage of radiotherapy for disease-specific survival in early stage tumors has been shown. Aggressive primary therapy may cure early-stage tumors but not those with extracervical tumors which have a very poor prognosis. Taxanes and cisplatin-based chemotherapy, ifosfamide, along with pelvic irradiation, may increase survival of those with metastatic carcinosarcomas.[4] Other chemotherapeutic agents that have been used include doxorubicin and cyclophosphamide.[2]

Clement et al reported nine cases of cervical MMMT. Compared to its uterine counterpart, cervical MMMT is more often confined to the uterus at presentation, with non-glandular epithelial element and with better prognosis. Their clinical behavior is dominated by the carcinomatous component.[4,7] Abell and Ramirez reported a median length of survival of 11 months.[4,6]

In our case, radical hysterectomy was not performed because of the incidental sonologic finding of a right adnexal mass, which turned out to be clear cell carcinoma.

When presented with a cervical MMMT, one should rule out an endometrial primary. One case report documented a 50-year old patient who was diagnosed with cervical MMMT which turned out to have arisen from the endometrium.[11] A biphasic endometrial tumor mimicking a cacinosarcoma is the endometrioid carcinoma with spindle cell elements, but this is composed of low-grade glandular elements. Furthermore, the endometrioid glands frequently show squamous metaplasia and merge imperceptibly with spindle cell elements that are never histologically high-grade. These tumors are less aggressive than MMMT. Carcinosarcoma, on the other hand, shows easily distinguishable high-grade epithelial and mesencyhmal element Our case presented with an endocervical polyp with atrophic endometrium.

Another differential diagnosis is "dedifferentiated' endometrial adenocarcinoma. This refers to a well- or moderately differentiated endometrioid adenocarcinoma juxtaposed with an undifferentiated carcinoma. In contrast to carcinosarcoma, the endometrioid component is usually well-differentiated; the undifferentiated component is made of sheets of small rounded cells of uniform size instead of spindle shaped or obviously pleomorphic cells. Glandular, nested or trabecular cell arrangements are not encountered in the undifferentiated component. The undifferentiated component shows only focal keratin expression and the intervening stroma is of myxoid type. These tumors are more aggressive than MMMT and are usually encountered in Lynch syndrome II.[4] Histopathology of our patient revealed well-differentiated glandular areas with cellular and fibrous stroma, and some areas with a chondrosarcoma-like area.

To date, there is no reported case on the synchronous occurrence of malignant mixed mullerian tumor and ovarian clear cell carcinoma.

Ovarian clear cell carcinomas (OCCC) show clear cells growing in a solid, tubular or papillary pattern, with hobnail cells lining tubules and cysts.[13] Our index patient exhibited this pattern (Figures 5 & 6). About 5-25% of all epithelial ovarian cancers (EOC) are clear cell.[14] In the Philippines, the incidence was 3.2% and 6.3% in 2013 and 2014, respectively.[2] It is often misdiagnosed as serous epithelial ovarian tumors but OCCC will stain positive for HNF1B and stain negative for WT1, ER, PR and p53. High-grade serous EOC, on the other hand, will show the opposite staining results.[15]

Chan et al. reported that women with clear cell carcinoma were younger than those with serous histology (median age of 55 vs. 64 years). Atypical endometriosis is believed be a malignant precursor of OCCC resulting in nine-fold increased risk of developing this malignancy.[14]

Ovarian CCC presents at earlier stages, which might be due to its association with endometriosis, and its low proliferation rate. Patients usually have a pelvic mass, up to 20 cm. Clinical examination or imaging detects it pre-operatively.[15]

For patients with locally advanced or metastatic disease, surgery plays an important role. Ovarian CCC clinically confined to the ovary has high risk of lymph node involvement. Retroperitoneal node involvement arises in 50–60% of patients with advanced disease. Ovarian tumors often extend intraperitoneally.[8] The median over-all survival of patients was 21.3 months. OCCC has 85.3% survival rate compared to 86.4% for serous EOC.[15]

Combination chemotherapy (platinum-based plus paclitaxel) has been adopted as the standard regimen for front line treatment of EOC. Studies have shown that paclitaxel was more efficacious in CCC.[16] There is still paucity on the treatment guidelines on cervical MMMT. However, data on the use of taxanes and cisplatin-based chemotherapy on carcinosarcomas have been reported. With these in mind, patient was advised to undergo chemotherapy with carboplatin-paclitaxel to be followed by pelvic radiotherapy.

CONCLUSION

Malignant mixed mullerian tumor of the cervix is a very rare tumor. Because of its rarity, there is still no consensus on its management and outcome. The role of adjuvant radiotherapy and chemotherapy is uncertain. The finding of coexisting ovarian clear cell carcinoma in this case makes it even rarer. Based on literature search, no case on cervical MMMT synchronous with ovarian clear cell carcinoma has ever been reported. Treatment was based on few reports on cervical MMMT recommending surgery with adjuvant platinum-based chemotherapy and/or radiotherapy and on the fact that the co-existent ovarian clear cell carcinoma was also historically treated with platinum-paclitaxel combination chemotherapy.

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Proximal epitheliod sarcoma of the vulva: A case report and Review of related literature

Mark Q. Antonio, MD, FPOGS, FSGOP and Jean Anne B. Toral, MD, MSc

ABSTRACT

Vulvar cancer is a rare gynecological malignancy, which occurs most commonly among elderly women. Majority are carcinomas with squamous histopathology, followed by melanoma and sarcoma. Epithelioid sarcoma (ES) is a distinct sarcoma of unknown lineage showing predominantly epithelioid cytomorphology. Two sub-types have been described, the classic "distal' type and the proximal type. It is important to distinguish the two because the latter connotes a poorer prognosis. We present a case of a 51-year-old, female, with a gradually enlarging vulvar mass with an initial histopathologic diagnosis of malignant mixed mullerian tumor. However, on further investigation with the aid of immunohistochemical studies, a diagnosis of proximal type ES was clinched. This case proves that histopathologic diagnosis of ES can be a challenge and that immunohistochemical studies are essential in coming up with a definite diagnosis. The patient underwent wide local excision with groin node dissection and is currently undergoing chemotherapy. There is still no clear guideline with regard to the appropriate treatment of this tumor. However, excision of the tumor with a 2 cm tumor-free margin is the most effective treatment. The role of radiotherapy and chemotherapy is still unclear.

Keywords: epithelioid sarcoma, soft tissue sarcoma, vulvar malignancy

INTRODUCTION

Vulvar cancers are rare gynecological malignancies, accounting for 4% of all gynecologic malignancies worldwide[1]. It is ranked as the 31st most common cancer site world-wide and in the Philippines, with a 0.16% crude mortality rate.[2] Majority of vulvar cancers have squamous histopathology, which accounts for 86.2%, followed by melanoma at 4.8% and sarcoma at 2.2%. Sarcomas of the vulva include leiomyosarcoma, malignant fibrous histiocytoma, malignant rhabdoid tumor, angiosarcoma, rhabdomyosarcoma and epithelioid sarcoma[1].

The term epithelioid sarcoma has been applied to a morphologically distinct neoplasm that is often misdiagnosed[3]. These are further subdivided into two types, the distal type and the proximal type[4]. The World Health Organization (WHO) classifies epithelioid sarcoma (ES) within the category of tumors of unknown origin[5,6]. Optimal treatment for proximal type epithelioid sarcoma (PES) of the vulva is not yet established due to its rarity. At present, treatment is patterned after the management of distal type and extra-genital sarcomas[7]. The role of chemotherapy and radiotherapy remains to be proven.

THE CASE

This is the case of E.L. a 51-year old, female, gravida 1 para 1 (1001) who consulted at the outpatient clinic with a chief complaint of a vulvar mass. Her past medical and family medical histories were non-contributory. She had her first coitus at 32 years old with one non-promiscuous sexual partner. There was no use of oral contraceptive pills and no history of sexually transmitted diseases. She had her menarche at 15 years of age with regular monthly intervals thereafter, soaking 2-3 pads per day with no associated dysmenorrhea. She delivered by spontaneous vaginal delivery with unremarkable course.

She presented with a 3-year history of a gradually enlarging vulvar mass, which started as a pimple-like lesion with no associated signs and symptoms. The patient did not seek any consultation. Three months prior to her admission, she noted a significant increase in the size of the vulvar mass, described as a furuncle-like lesion; still, there were no associated signs and symptoms. A biopsy of the vulvar mass showed malignancy; hence, the patient was referred to the Section of Gynecologic Oncology.

On physical examination, she had normal vital signs and essentially normal physical examination findings except for the pelvic examination. There was a 4.0 x 3.0 x 3.0 cm necrotic solid mass at the 3-6 o'clock position of the left labium majus. There was no involvement of the urethra, vagina and rectum (Figure 1). On speculum examination, the vaginal wall and the cervix were smooth. On internal examination, the cervix was 2.0 x 2.0 cm, and the corpus was small with no adnexal mass nor tenderness. On rectovaginal examination, both parametria were smooth and pliable. There was no inguinal lymphadenopathy palpated.

On transvaginal ultrasound, there was a well-circumscribed, heterogeneous, predominantly solid mass measuring 3.5 x 3.7 x 3.6 cm at the left labium. Color flow mapping of the mass showed moderate central branching vascularity, which on Doppler interrogation revealed low resistance indices. There was no inguinal mass seen. However, there were multiple

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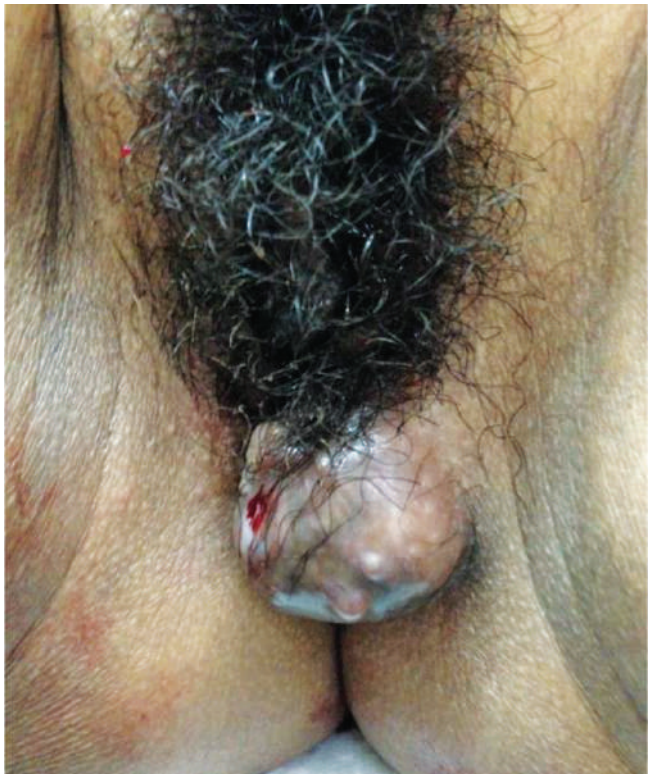

Figure 1. This is the gross picture of the 3.0 x 4.0 x 3.0 cm vulvar mass of the patient

hypoechoic ovoid masses along the right iliac vessel measuring 1.8 x 1.2 cm, 2.0 x 1.0 cm and 2.3 x 1.2 cm with absent flow on Color flow mapping. Sonologic impression was: Left labial mass, consistent with malignancy; Atrophic uterus with thin endometrium with right pelvic lymphadenopathies.

Histopathologic diagnosis of the vulvar biopsy during that time was poorly differentiated round to spindle cell neoplasm with the following considerations: 1. poorly differentiated squamous cell carcinoma; 2. amelanotic melanoma; 3. malignant mixed mullerian tumor (MMMT). Immunohistochemical studies were done which showed that the round and spindle cell components of the tumor are positive for pancytokeratin (CK) (Figure 2), epithelial membrane antigen (EMA) (Figure 3) and smooth muscle actin (SMA) (Figure 4). The tumor was negative for human melanoma black 45 (HMB 45) and S-100 thus excluding melanocytic differentiation of a tumor. Due to the positivity for both epithelial (EMA and CK) and sarcomatoid (SMA) component of the tumor, the results were interpreted as a staining pattern that is consistent with MMMT, homologous type.

Review of related literature on MMMT of the vulva showed no difference in the overall survival rate of patients who underwent a more radical surgery but resulted to a more morbid post-operative course. Based on these, the patient underwent wide local excision with bilateral groin node dissection under regional anesthesia. Intraoperatively, there was a 4.5 x 4.0 x 3.0 cm nodular friable mass attached to the left labia majora with extension up to 1.0 cm medial to the left genitocrural fold, with no involvement of the labia minora, vagina, clitoris and urethra. The excised specimen had a 2.0 cm margin circumferentially, which was grossly free of tumor (Figure 5). The harvested

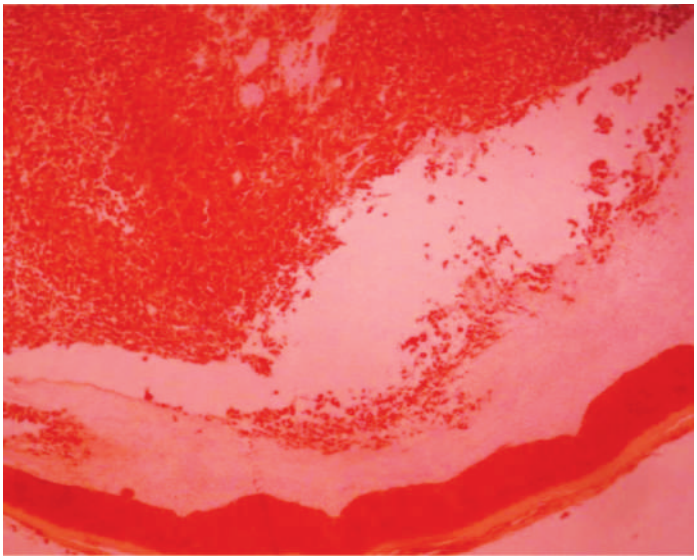

Figure 2. Scanning view of tumor showing cytokeratin AE1/AE3 positivity

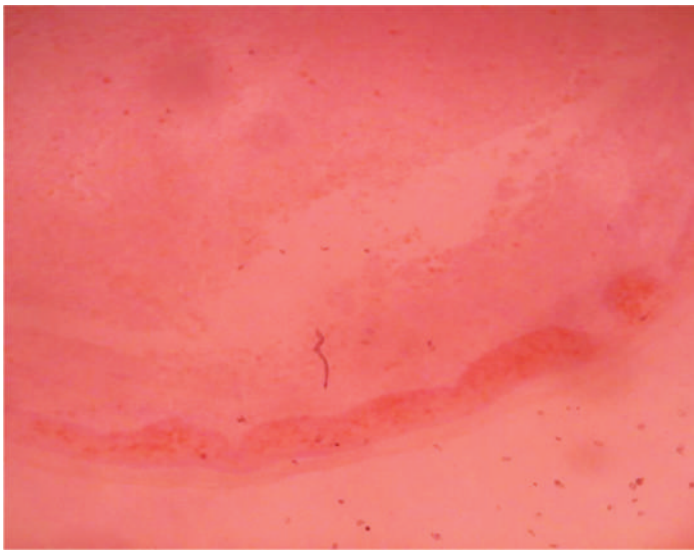

Figure 3. Scanning view of tumor showing epithelial membrane (EMA) positivity

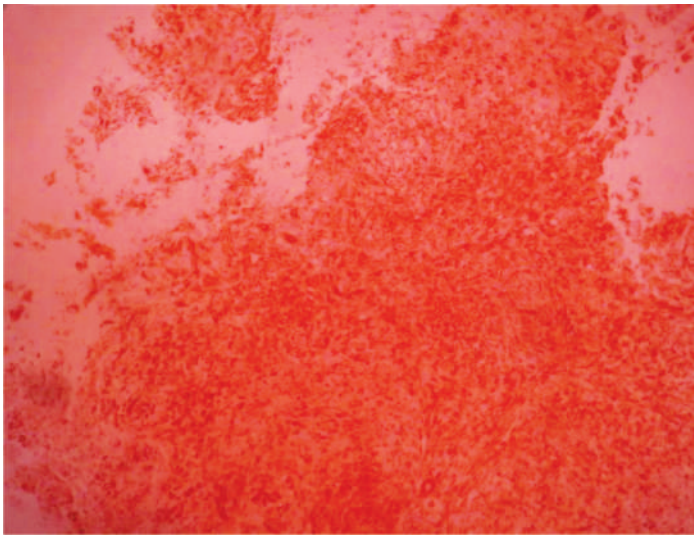

Figure 4. Scanning view of tumor showing smooth muscle actin (SMA) positivity

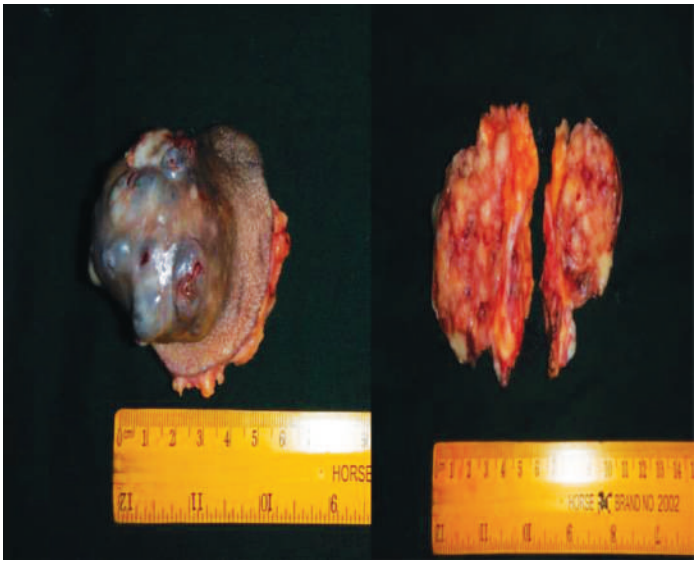

Figure 5. Gross picture of the tumor after wide local excision

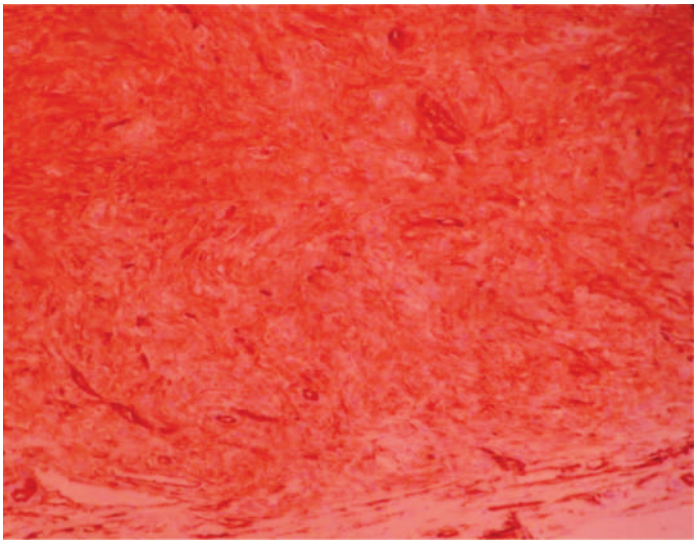

Figure 6. Scanning view of tumor showing CD34 positivity

Figure 7. Scanning view of tumor showing cytokeratin 5/6 negativity

bilateral superficial and deep inguinal nodes were not suspicious for malignancy. The intraoperative diagnosis was stage IB. Final histopathologic diagnosis then was Malignant mixed mullerian tumor, homologous type. There was no lymphovascular space invasion seen and all surgical margins and all inguinal lymph nodes were negative for tumor. The final diagnosis was Malignant mixed, mullerian tumor, homologous type, vulva, stage IB. She was given adjuvant chemotherapy in the form of Cisplatin 20 mg/m2 and Ifosfamide 1.5 g/m2 x 5 days every 21 days.

During the course of writing this paper, consultation with other pathologists raised an issue of a conflicting diagnosis. Slide review and further staining for CD34 (Figure 6) and cytokeratin 5 and 6 (CK 5/6) were done (Figure 7), which revealed positive and negative results, respectively. CK 5/6 has been found to be an excellent marker of squamous cell carcinoma, including spindled variants[22]. CD34 on the other hand was requested to rule in PES because in most reports it is positive in 50% of cases[14]. In summary, the tumor has an epithelioid and spindled morphology. IHC showed positivity for CK, SMA and CD34; it was negative for S-100, HMB-45 and CK 5/6. Because of this immunohistomorphology, the final diagnosis is Epithelioid sarcoma, proximal type, involving the vulva.

DISCUSSION

In a major tertiary hospital, there were 14 combined new cases of malignancies arising from the vulva and the vagina, accounting for 1.56% of all gynecological malignancy cases seen in the year 2019. Most of the patients were in their 6th decade of life and the most common histology was squamous cell carcinoma[23].

Vulvar malignancy is usually a disease of the elderly women with a peak incidence between 65-75 years old. Majority of vulvar cancers have squamous histopathology, which accounts for 86.2%. Melanoma is the next most common accounting for 4.8% and sarcoma is the third most common, accounting for 2.2%[1]. Sarcomas of the vulva include leiomyosarcoma, malignant fibrous histiocytoma, malignant rhabdoid tumor, angiosarcoma, rhabdomyosarcoma and epithelioid sarcoma[1].

Laskowski first described epithelioid sarcoma in 1961 as a distinct sarcoma of unknown lineage showing predominantly epithelioid cytomorphology[5,7]. However, it was only in 1970 when Enzinger established it as a morphologically distinct neoplasm that is often misdiagnosed[3]. It is common for biopsies of these lesions to be misinterpreted, as in the case of our index patient[6]. The World Health Organization (WHO) classifies these tumors under the category of tumors of unknown origin[5].

Epithelioid sarcomas are further subdivided into the distal type and the proximal type[4]. The classic (distal type) is more common and it grows mainly on the distal extremities such as the hands and wrist. The proximal type was described in 1997 by Guillou and colleagues and tends to arise in axial locations, such as the pelvis, perineum and genital tract[7]. It is important to distinguish between the two variants because the latter connotes a poorer prognosis, more aggressive behavior, higher risk of multiple recurrences and distant metastasis, resistance to chemotherapy and higher mortality[9,10]. Most of the reported cases in Asia are from Singapore and Japan and there have been no reported cases from the Philippines[11]. To our knowledge,

this is the first report of proximal epithelioid sarcoma of the vulva from the Philippines.

CLINICAL PRESENTATION

Classic or distal ES occurs in adolescents and young adults with a peak incidence during the second decade of life with a median age of 26[12]. It has a male predilection with a 2:1 ratio but no racial predilection[13]. The tumor commonly arises on the flexor surfaces of the fingers, hands and forearm, followed by the knee and the lower leg. On the other hand, proximal type epithelioid sarcoma (PES), are found in patients between the third and fifth decades of life and has a predilection to the pelvis, perineum and genital tract[10]. In the review by Hasegawa and colleagues, patient age ranged from 13 to 80 years old, with a mean of 40 years old. Twelve patients were male (60%) while eight were females (40%), all of whom had PES at the vulvar and inguinal region[14]. In the review of Lavazzo and colleagues[11], the mean age was 31 years old, with average of 17-84 years old.

The tumors can arise from superficial and deep soft tissues. A solitary or multiple firm nodules is the most common presentation if the tumor arises superficially and usually grows slowly and is usually painless. When the tumor invades the dermis, it usually becomes ulcerated. Tumors arising from deep tissue are usually firmly attached to tendons, tendon sheaths, or fascial structures. These tumors are larger, less defined and manifest as areas of induration, or multinodular masses, which move with the extremity[13]. In our index patient, the tumor was superficial, and the course of enlargement was slow and painless. The size of the tumor is variable ranging 2-6 cm with a mean diameter of 7.8 cm during excision[13]. Considerable treatment delay is due to the variability in the growth rate and symptomatology with a median time to diagnosis of 6 months[9]. Some benign lesions such as infectious granuloma, bartholin cyst, fibroma, lipoma and teratoma can be misdiagnosed as ES[14].

Due to the rarity of PES of the vulva, there are no established risk factors. A history of trauma is reported in 20% to 25% of cases[13].

HISTOPATHOLOGY

The World Health Organization (WHO) classifies epithelioid sarcoma within the category of tumors of unknown origin[5,6]. Epithelioid mesenchymal malignancies are a diagnostic challenge because epithelioid morphology is observed in a variety of soft tissue neoplasms and shows overlapping morphology. Accurate diagnosis of epithelioid mesenchymal tumors requires a complex integration of morphological, immunohistochemical, and in some cases, genetic findings[12]. The cut surface of the tumor shows a whitish lesion often with a yellow to brown center due to necrotic and hemorrhagic changes[5]. The distal type ES has a characteristic nodular arrangement while proximal type ES has multinodular pattern of growth (Figure 8). Nodules are formed by large, epithelioid, carcinoma-like cells with marked cytological atypia, vesicular nuclei and prominent nucleoli (Figure 9). Cells are mitotically active (as opposed to distal type ES, where mitotic activity is low) and often show a rhabdoid phenotype, characterized by the presence of eosinophilic cytoplasm and eccentric vesicular nuclei with large nucleoli (Figure 10).

Immunohistochemical profiles are similar in distal and proximal type ES10. Both express EMA, cytokeratin and vimentin and approximately 50% expresses CD34 positivity. All of these immunohistochemistry markers were positive in our index patient . A few tumors were positive for desmin and SMA[14].

DIFFERENTIAL DIAGNOSIS

The differential diagnoses include extrarenal rhabdoid tumors, atypical melanoma, epithelioid type malignant peripheral nerve sheath tumor (MPNST), rhabdomyosarcoma, angiosarcoma, leiomyosarcoma, and undifferentiated carcinoma. These entities may have similar clinical presentation, histopathology and immunohistochemical staining pattern.

The histology of melanomas is highly variable. They may present with epithelioid or sarcomatoid morphology and a significant number of cases lack melanin pigments. Epithelioid MPNST is another entity that can present with epithelioid and sarcomatoid morphology. However, epithelioid sarcoma is completely negative for S-100 and these two cases usually show diffuse and strong cytoplasmic staining for S-100[4]. Extrarenal rhabdoid tumors usually occur in the younger age group. They are composed of cells with deeply eosinophilic and granular cytoplasm and eccentrically-placed nuclei with prominent nucleoli. Although this case had areas with rhabdoid morphology, the predominant component is still the epithelioid phenotype. Also, the immunohistochemical staining pattern is more consistent with ES. Extrarenal rhabdoid tumors express EMA and vimentin, and they are usually negative for CD34[4].

Rhabdomyosarcoma, leiomyosarcoma and angiosarcoma may present with an epithelioid morphology. However, positivity for cytokeratins and epithelial markers makes a rhabdomyosarcoma and leiomyosarcoma unlikely as well. Also, rhabdoid tumors are negative for CD34, which was positive in the index patient. Epithelioid sarcomas are distinguished from leiomyosarcomas by the absence of the classic feature of fascicles of elongated tumor cells with blunt-ended “cigar-shaped” atypical nuclei. Immunohistochemically, leiomyosarcoma will stain positive for desmin and SMA4.

The distinction between proximal-type epithelioid sarcoma and undifferentiated carcinoma is the most difficult consideration[13]. In the index patient, the absence of histologic features of squamous or glandular differentiation, and presence of CD34 reactivity, and absence of reactivity to cytokeratin 5/6 favor the diagnosis of epithelioid sarcoma over undifferentiated carcinoma because the latter are negative for CD34 in most cases and are positive for cytokeratin 5/6[13].

MANAGEMENT

Optimal treatment for PES of the vulva is not yet established due to its rarity. At present, treatment is patterned after the management of distal and extra-genital sarcomas[7]. Surgical resection with a 2.0 cm tumor-free margin remains the primary treatment because the tumor has the tendency to

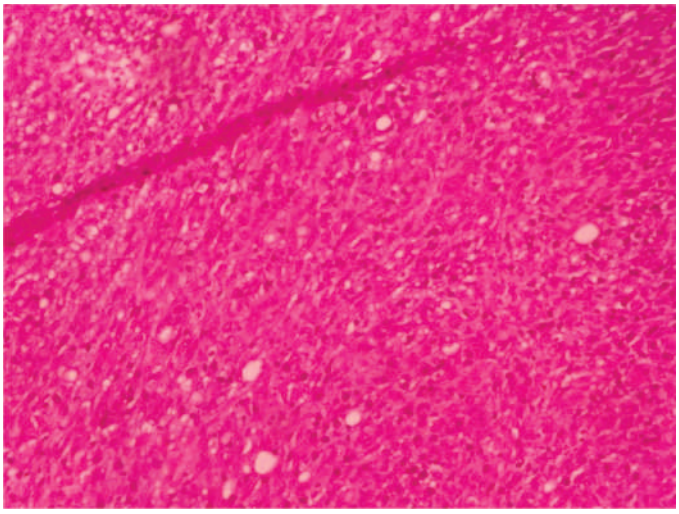

Figure 8. A scanning view of patient's tumor which shows the typical multinodular pattern typically seen in PES

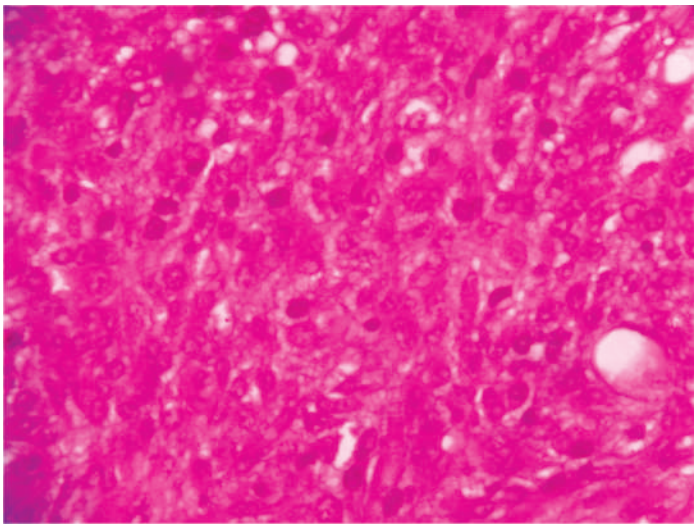

Figure 9. An HPO view of the patient's tumor nodule which is formed by large, epithelioid, carcinoma-like cells with marked cytological atypia, vesicular nuclei and prominent nucleol

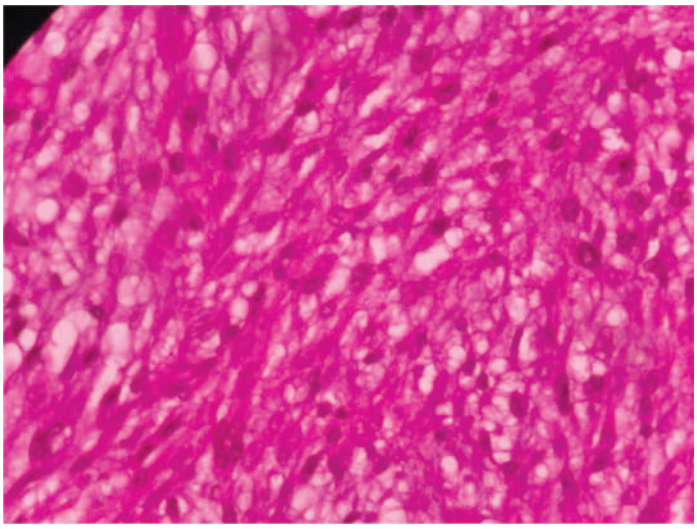

Figure 10. An HPO view of the patient's tumor which shows that the cells are mitotically active and often show a rhabdoid phenotype, characterized by the presence of eosinophilic cytoplasm and eccentric vesicular nuclei with large nucleoli

form satellite lesions[14]. It is important to note that prognosis is not changed despite a more radical surgery such as vulvectomy[11]. In our index patient, a wide local excision was performed with a 2 cm tumor free margin. Increased risk of local recurrences has been associated with inadequate margin[7]. Although the presence of lymphatic metastases worsens the prognosis, the role of routine bilateral groin node dissection is still controversial[7,8]. In the report of Lavazzo and colleagues, there was no statistically significant difference of survival was found in patients with or without groin node dissection (11.5 vs. 6 months)[11]. The removal of the locoregional lymph nodes should only be considered if they are suspicious or enlarged at physical or imaging examination. There is no evidence that the resection of metastatically invaded locoregional lymph nodes has any beneficial effect on the local or distant recurrence rate, but in some cases, it may have a palliative benefit[8,15].

Postoperative radiotherapy is commonly used in the classical type epithelioid sarcoma. The tumor is relatively insensitive to radiotherapy, although it reduces the incidence of amputation through the reduction of the local recurrence. However, its role in the treatment of vulvar epithelioid sarcoma is controversial[17, 18]. Standers and colleagues reviewed the role of external beam radiotherapy, low-dose-rate brachytherapy and radiosensitizers for high-grade soft tissue sarcoma and found that similar local control rates are achieved for inoperable soft tissue sarcomas, but no benefit was seen in the adjuvant setting[19]. In the report of Argenta and colleagues, patients who received adjuvant radiotherapy after surgical resection had a recurrence rate of 14% compared to 71% for those who did not. Death from the disease occurred in 29% of patients receiving adjuvant radiation after primary surgery and 50% in patients who did not[7]. However, adjuvant radiotherapy did not show statistically significant reduction in mortality from the disease but a statistically significant decrease in the recurrence rate was observed[7]. In the report of Hasegawa and colleagues, they advocate adjuvant radiotherapy in the presence of high-grade tumors or inadequate surgical margins[14]. When surgery and radiotherapy are combined, better local control can be achieved[19].

The role of adjuvant chemotherapy is also questionable. Soft tissue sarcomas per se have a poor response to chemotherapy. Chemotherapy has been used both in adjuvant situations and in locally advanced or metastatic disease[19]. Agents with the most documented cytotoxic effect are doxorubicin, dacarbazine, ifosfamide, cyclophosphamide, etoposide, vincristine, and methotrexate[21]. In the review of Argenta and colleagues, 7 patients were given adjuvant chemotherapy, three of the patients were disease free at 8, 11, and 21 months. The other 4 died of disseminated disease within 8 months of diagnosis[7]. Also, chemotherapy regimens for the treatment of recurrence were variable and of modest benefit, with only one patient surviving more than a year from initiation of chemotherapy (median of 3 months)[7]. The index patient completed systemic chemotherapy in the form of Cisplatin-Ifosfamide every 21 days.

Novel systemic and targeted therapies are currently being investigated. Cytogenetic studies identified the role of SMARCB1 in the tumorigenesis of epithelioid sarcomas. SMARCB1 is a tumor-suppressor gene which is the core subunit of the SWI/

SNF ATP-dependent chromatin remodeling complex[25]. The phosphatidylinositol 3-kinase/protein kinase-B/mammalian target of rapamycin (PI3K/AKT/mTOR) and human epidermal growth factor signaling pathway are also being investigated. These pathways regulates cell proliferation and differentiation, cellular metabolism, and cytoskeletal reorganization leading to apoptosis and cancer cell survival[26].

Although control of localized disease is possible, metastatic spread is seen in almost half of patients[24]. Treatment of local recurrences is still excision, however for distant metastases, no proven benefit of radiotherapy or chemotherapy exists in the literature[7].

PROGNOSIS

The five-year overall survival rates for "distal-type" epithelioid sarcoma range from 50% to 80%, but those for "proximal-type" appear worse[8]. Patients usually develop multiple local recurrences of long duration, with subsequent metastases in 30-50% of cases[13]. Local recurrences usually occur in the early post-operative period and presents as fleshy to solid nodules at or near the surgical bed[7]. Regional recurrences via the lymphatics or direct extension may occur, as well as distant recurrences, with either the typical hematogenous pattern in the lung or liver or the atypical pattern such as distant cutaneous lesions (scalp) as reported by Weismann and colleague[21]. In the study of Hasegawa and colleagues, 13 (65%) of the patients developed local recurrence. Fifteen patients (75%) developed metastases in the lymph node, lungs, bone and skin. In this review, tumor size of more than 7.8 cm seemed to be a significant predictor of survival[14]. In the review of Lavazzo and colleagues, recurrence was present in 42% (13 out of 31), with recurrences commonly appearing in local tissues (22.6%), lymph nodes (22.6%), lung (25.8%), abdominal wall (3.2%), scalp (3.2%), liver (3.2%) and kidney (3.2%)[11]. Reported indicators of a poor prognosis include vascular invasion, tumor size of more than 5 cm, more than 30% necrosis, presence of local recurrence, and advanced stage at presentation[8]. At present, the index patient has no evidence of disease four years after the initial surgery and completion of systemic chemotherapy.

CONCLUSION

Proximal epithelioid sarcoma is a rare gynecological malignancy which has a poorer prognosis compared to the distal type. It may be difficult to differentiate from other sarcomas but immunohistochemical staining may help in clinching the diagnosis. Due to the rarity of this tumor, there is still no definite guideline as to its treatment. Based on the review of available literature, excision with wide surgical margins is the most effective form of primary treatment. Surgical removal of local recurrences is also advocated. Adjuvant therapy in the form of radiotherapy can be used to decrease local recurrence rates, or in cases of close surgical margins or high-grade histology. The role of adjuvant chemotherapy has not been proven; also, chemotherapy appears to be only minimally effective when used to treat metastatic disease. The index patient remains to have no evidence of disease four years after the initial surgery and adjuvant chemotherapy.

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