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ORIGINAL STUDIES

CASE REPORTS

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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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Knowledge, Attitude and Practices regarding Cervical cancer, its screening and prevention, among Filipino women at the Outpatient Clinic in a tertiary hospital in the Philippines

Karen Therese S. Abalos, MD and Jericho Thaddeus P. Luna, MD, FPOGS, FSGOP

ABSTRACT

Background: Cervical cancer is one of the leading causes of mortality and morbidity among the gynecologic cancers worldwide. In the Philippines, it is the second most common malignancy with a high incidence due to the lack or inefficiency of screening programs. Studies show that the reasons for underutilization of screening include lack of knowledge, cultural factors, and inaccessibility of screening facilities.

Objective: This study aims to determine the level of knowledge, attitude, and practices on cervical cancer screening and prevention among Filipino women.

Materials and Methods: A prospective cross-sectional study was conducted among women 21-65 years old, consulting at the outpatient department of a tertiary hospital. Data was collected using a pre-tested questionnaire consisting of 6 sections.

Results: Of the 383 respondents, 214 (55.57%) had heard about cervical cancer, 169 (78.79%) of whom had heard about its screening. 303 (83.70%) knew at least one preventive measure, while 325 (84.86%) knew at least one sign or symptom.

Conclusion: The study showed that Filipino women had poor knowledge, attitude and practices on cervical cancer screening and prevention. Health information campaigns are needed to increase awareness of cervical cancer. Utilizing the media for this purpose may be beneficial. An organized nationwide screening program is necessary to provide better access to screening facilities and increase the uptake of cervical cancer screening.

Keywords: *cervical cancer, screening, HPV, knowledge, attitudes and practices*

INTRODUCTION

Cervical cancer remains to be a burden of disease globally, especially in developing countries, with 266,000 reported deaths worldwide in 2012.[1] Due to limited access to screening and vaccination, cervical cancer has been a major cause of morbidity and mortality in resource-poor settings, such as the Philippines.[2] An estimated age-standardized national incidence rate for cervical cancer in the Philippines was 16 cases per 100,000, while the estimated national standardized mortality rate was 7.5 per 100,000 in 2012.[3,4] Because screening and treatment are costly and inaccessible, about 75% of women were identified and diagnosed at an advanced stage, accounting for high mortality and low survival rates. [2,5]

Cervical cancer is a highly preventable disease with the advent of HPV vaccination and presence of a well-organized cervical cancer screening program.[3,4] The incidence and prevalence of cervical cancer has dramatically decreased in countries where there is high coverage of Pap smear screening.[6] Progression to advanced stages could be deterred with screening and treatment of premalignant lesions.[7] In 2006, the Department of Health (DOH) has ordered the establishment of a Cervical Cancer Screening Program, including sustainable capability building, training, educating, and hiring of health workers on proper Visual Inspection of the cervix by Acetic acid (VIA), Pap smear cytology, colposcopy, and pathology.[3,5] However, this has yet to be implemented effectively in the Philippines.[3] Screening and treatment of cervical cancer remains to be a challenge in low-resource settings because of financial limitations and lack of health infrastructures.[8]

The positive effect of Pap testing depends on the proper utilization by the population.[6] However, in developing countries, only 5% of women are screened with Pap smear compared to 40 – 50% in developed countries.[9] Screening has been underutilized due to factors such as poor educational background, lack of knowledge on and affordability of screening, cultural barriers and unavailability of facilities.[9] Proper knowledge and the positive attitude will greatly influence a woman's health-seeking behavior and practice. Currently, there is still limited published data in the Philippines regarding cervical cancer knowledge, attitude and practices. This study aims to investigate women's knowledge, attitudes and practices regarding cervical cancer among patients at the outpatient clinic in a tertiary hospital in the Philippines. The data gathered may provide the basis for health interventions or strategies that can increase utilization of screening and vaccination by Filipino women.

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The authors did not report any potential conflicts of interest.

OBJECTIVES

The general objective is to determine the level of knowledge of, attitude towards, and practices related to cervical cancer, its screening and prevention among women at the outpatient clinic of a tertiary hospital.

The specific objectives are as follows:

1. To validate a translated questionnaire on cervical cancer among Filipino women at the outpatient clinic.
2. To describe the sociodemographic characteristics of the female patients seen at the outpatient clinic of Philippine General Hospital
3. To determine the association between socio-demographic characteristics and knowledge, attitude, and practices related to cervical cancer.

MATERIALS AND METHODS

Study design, population and sample size

A prospective cross-sectional study was conducted among women aged 21 to 65 years old at the outpatient clinic of the Philippine General Hospital from October to November 2018. The study excluded women with a history of cervical cancer or who underwent hysterectomy; women working as health care workers; women at the Obstetrics and Gynecology Outpatient Clinic; women who are cognitively or communicatively impaired or unable to consent

A minimum of 382 subjects were recruited for this study based on a level of significance of 5%, 45.7% of women who knew at least 1 type of test to screen for cervical cancer, and a desired width of the 95% confidence interval of +5%. A non-probability sampling, consecutive enrollment of women, who met the inclusion and exclusion criteria, was employed.

Ethical considerations

The study was reviewed and approved by the University of the Philippines – Manila Research Ethics Board to ensure the protection of the rights and welfare of the study participants. A written informed consent was obtained from all the respondents.

Data collection

A structured questionnaire was used to collect information from the participants. It was patterned from the questionnaire used in a similar study by Ukama et al entitled Women's knowledge and attitudes towards cervical cancer prevention: A cross sectional study in Eastern Uganda.[2] It was translated into Filipino – the main language used in the country – and back-translated into English with any inconsistencies addressed. Content and face validity testing were done with any suggestions or comments incorporated into the questionnaire. The questionnaire was pretested among a group similar to the study respondents for validation.

The questionnaire had 6 sections including questions on: basic sociodemographic profile and characteristics; sources of information on cervical cancer; knowledge on cervical cancer prevention, measures, symptoms and screening; knowledge on its risk factors; attitudes and practices towards cervical cancer screening and prevention. The questions on attitudes required respondents to state their level of agreement with the statements about cervical cancer on a 5-point Likert scale. Practice was evaluated by determining if the woman had been screened for or vaccinated against cervical cancer.

Statistical analysis

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion was used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. To obtain a binary outcome of knowledge and attitude, the median knowledge and attitude scores were determined and women who had scores above the median were considered to be more knowledgeable and have a positive attitude. Those who had scored below or equal the median were considered to have less knowledge and to have a negative attitude. Those who had been screened for cervical cancer or vaccinated against cervical cancer were regarded as having good practice.

Crude/Adjusted odds ratio and the corresponding 95% confidence interval from binary logistic regression was computed to determine the association between socio-demographic characteristics with knowledge, attitude, and practices to cervical cancer. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. STATA 15.0 was used for data analysis.

RESULTS

The study was conducted from October to November 2018 with a total of 383 Filipino women recruited. Their median age was 32 years old. Most of the study participants attained secondary education (37.6%). Nearly half of the respondents (47.78%) were married and were at least primiparous. The median reported household income of the respondents was PhP15,000 per month and 69% live in urban settings. Almost half of the respondents were practicing birth control (168, 43.86%), commonly with oral contraceptive pills (Table 1).

Knowledge about cervical cancer

Of the 383 respondents, 214 (55.87%) has ever heard of cervical cancer, and 169 of the 214 (78.97%) women have heard of cervical cancer screening. The most common sources of information are: the internet (130; 60.75%), television (108; 50.47%), and the health facility or medical practitioner (107; 50%).

The proportion of respondents with correct response to knowledge items on cervical cancer and screening is enumerated in Table 2. Among the respondents, 298 or 77.81% stated that cervical cancer could be prevented. There were still 21 (5.48%) women who thought that cervical cancer is not preventable while 30 (8.29%) were not aware of any preventive measure. Among the respondents, 162 (42.3%) thought that women can be vaccinated against cervical cancer but no one accurately gave the recommended age of vaccination. Moreover, only a limited number of women knew the recommended age to start screening (6; 1.57%) and the recommended frequency of cervical cancer screening per year (135; 25.26%). Interestingly,

Table 1. Demographic characteristics of patients (n = 383)

	Median (Range); Frequency (%)
Age	32 (21 – 61)
Education	
None	1 (0.26)
Primary	42 (10.97)
Secondary	144 (37.60)
Vocational	91 (23.76)
Tertiary	91 (23.76)
Postgraduate	14 (3.66)
Civil status	
Single	100 (26.11)
Married	183 (47.78)
Widowed	6 (1.57)
Divorced	7 (1.83)
Common-law partner	87 (22.72)
Parity	2 (0 – 9)
P0	114 (29.77)
P1-P3	202 (52.74)
≥P4	67 (17.49)
Average household monthly income [n=361]	15000 (1500 – 30000)
Address	
Rural	11 (2.87)
Semi-urban	104 (27.15)
Urban	268 (69.97)
Used any method to delay/ avoid getting pregnant	168 (43.86)
Pill	92 (54.76)
Condom	65 (38.69)
Rhythm/ calendar	16 (9.52)
IUD	11 (6.55)
Injectables	10 (5.95)
Implants	6 (3.57)
Female sterilization	4 (2.38)
Lactation amenorrhea	2 (1.19)
Diaphragm	0
Foam/jelly	0
Others	1 (0.01)

Table 2. Knowledge about cervical cancer and screening (n = 383)

	Correct Response
	Frequency (%)
Early detection of cervical cancer is helpful	309 (80.68)
Cervical cancer is curable if detected early	300 (78.33)
Someone can be vaccinated against cervical cancer	162 (42.30)
Recommended age for someone to go under vaccination	0
Age where a woman should start screening for cervical cancer	6 (1.57)
Frequency of cervical cancer screening per year	135 (25.26)
Cervical cancer can be prevented	
No	21 (5.48)
Yes	298 (77.81)
Don't know	64 (16.71)
Cervical cancer preventive measures known	
Early screening	229 (63.26)
Avoiding smoking	40 (11.05)
Vaccination	163 (45.03)
Safe sex	67 (18.51)
Limit sexual partners	113 (31.22)
Others (Check-up, healthy eating habit, proper hygiene)	3 (0.01)
Knew at least one preventive measure for cervical cancer	303 (83.70)
Don't know any preventive measures	30 (8.29)
Symptoms of cervical cancer	
Is symptomatic	363 (94.78)
Foul-smelling vaginal discharge	217 (56.66)
Vaginal bleeding	209 (54.57)
Abdominal pain	92 (24.02)
Bleeding after sexual activity	69 (18.02)
Pain after sexual activity	56 (14.62)
Weight loss	34 (8.88)
Knew at least one symptom of cervical cancer	325 (84.86)
Tests that can be carried out to detect cervical cancer	
VIA test	43 (11.23)
Pap smear test	265 (69.19)
HPV test	42 (10.97)
Knew at least one test used to screen for cervical cancer	284 (74.15)

69.19% of the respondents have heard of Pap smear. The more commonly known risk factors among the respondents were: multiple sexual partners (80.16%), early onset of sexual activity (53.26%), HPV (48.56%), HIV (45.69%), and sexually transmitted diseases (43.34%).

Attitudes toward cervical cancer

Table 3 shows the attitudes of the respondents towards various statements on cervical cancer. When individual statements are examined, more than half of the respondents believed that cervical cancer screening is important and that the chances of curing cervical cancer are better when discovered at an early stage. Majority of the respondents had also agreed to being vaccinated themselves and allowing their children to be vaccinated against cervical cancer. Overall, the majority (201 or 52.48%) of the respondents had a negative attitude towards cervical cancer.

Practices on cervical cancer screening and prevention

Out of 383 respondents, only 53 (13.84%) has ever been screened for cervical cancer, and only 13 (3.39%) had been vaccinated against cervical cancer. There were 309 respondents who were willing to undergo pap smear.

Association between sociodemographic characteristics and knowledge, attitude and practices

Binary logistic regression analysis was performed to determine factors associated with good knowledge scores, positive attitudes and good practices on cervical cancer. On simple binary logistic regression analysis, those who had secondary to tertiary education compared to primary (cOR

Table 3. Attitudes towards cervical cancer and screening (n = 383)

	Strongly Disagree (1)	Disagree (2)	Neutral (3)	Agree (4)	Strongly Agree (5)
	Frequency (%)				
Cervical cancer is a very severe disease.	13 (3.39)	10 (2.61)	44 (11.49)	201 (52.48)	115 (30.03)
I am at risk of getting cervical cancer.	46 (12.01)	65 (16.97)	64 (16.71)	145 (37.86)	63 (16.45)
Cervical cancer screening is important.	8 (2.09)	5 (1.31)	42 (10.97)	184 (48.04)	144 (37.6)
Only women who are sexually active need to be screened for cervical cancer.	64 (16.71)	97 (25.33)	63 (16.45)	122 (31.85)	37 (9.66)
Women who have had sexually transmitted diseases are more likely to get cervical cancer.	56 (14.62)	47 (12.27)	76 (19.84)	155 (40.47)	49 (12.79)
Once cervical cancer has been found, there is not much that can be done about it.	86 (22.45)	84 (21.93)	95 (24.8)	90 (23.5)	28 (7.31)
Chances of curing cervical cancer are better when the disease is discovered at an early stage.	14 (3.66)	14 (3.66)	87 (22.72)	189 (49.35)	79 (20.63)
Cervical cancer is a death sentence for most people.	27 (7.05)	62 (16.19)	133 (34.73)	134 (34.99)	27 (7.05)
There is little a woman can do to reduce her chances of getting cervical cancer.	50 (13.05)	117 (30.55)	109 (28.46)	85 (22.19)	22 (5.74)
Women who have cervical cancer will have some kind of symptoms showing it.	15 (3.92)	83 (21.67)	91 (23.76)	170 (44.39)	24 (6.27)
Cervical cancer runs in families.	26 (6.79)	111 (28.98)	132 (34.46)	92 (24.02)	22 (5.74)
Women only need cervical cancer screening tests during child-bearing years.	49 (12.79)	124 (32.38)	82 (21.41)	102 (26.63)	26 (6.79)
I would vaccinate myself against cervical cancer.	5 (1.31)	15 (3.92)	62 (16.19)	203 (53)	98 (25.59)
I would allow my children to be vaccinated against cervical cancer.	7 (1.83)	15 (3.92)	90 (23.5)	171 (44.65)	100 (26.11)
My family would approve of children being vaccinated against cervical cancer.	3 (0.78)	19 (4.96)	98 (25.59)	159 (41.51)	104 (27.15)

3.036 and cOR 5.800, p = 0.005), married (cOR 1.692, 95% CI 1.03 – 2.77, p = 0.037), those with income > PhP15,000 monthly (cOR 2.734, 95% CI 1.80 – 4.15, p < 0.001) and those who were using any form of birth control methods (cOR 1.824, 95% CI 1.21 – 2.74, p = 0.004), were more likely to get good knowledge scores. Those who were multiparous (P4 and up) were less likely to get good knowledge scores (cOR 0.526, 95% CI 0.28 – 1.00, p = 0.049) (Table 4).

As for attitudes, on simple binary logistic regression analysis, those who had postgraduate education compared to primary (cOR 4.217 p = 0.046), married (cOR 2.189, 95% CI 1.32 – 3.62, p = 0.002), those with income > PhP15,000 monthly (cOR 1.827, 95% CI 1.22 – 2.748, p = 0.004) and those who were using any form of birth control methods (cOR 1.543, 95% CI 1.03 – 2.32, p = 0.036), were more likely to get good attitudes (Table 5).

For practices, on simple binary logistic regression analysis, those who had tertiary and postgraduate education compared to primary (cOR 9.649 and cOR 23.33), those with income > PhP15,000 monthly (cOR 4.427, 95% CI 2.16 – 9.09, p < 0.001) were more likely to have good practices. Those with common-law partners, compared to single women, were less likely to have good practices (cOR 0.346, 95% CI 0.12 – 0.99, p = 0.049) (Table 6).

After adjusting for all other factors, secondary to tertiary education, married civil status, income > PhP15,000, and use of any birth control method were associated with increased odds of having good knowledge, while parity >P4 was associated with decreased odds of having good knowledge scores. A married civil status and income > PhP15,000 per month were associated with increased odds of having positive attitude, while only income was associated with increased odds of having good practice for screening and vaccination (Table 7).

DISCUSSION

Although early screening and HPV vaccination have been shown to reduce the incidence of cervical cancer, it still ranks as the second most common cause of cancer-related mortality among Filipino women. In the Philippines, an organized cervical cancer screening program has yet to be properly implemented since a nationwide organized screening program may be costly to establish and sustain.[3] The success and positive effect of any screening test depends as well on the proper utilization by the target population.[6,9] A better understanding of the factors associated with underutilization of screening tools is essential in order to establish ways to increase cervical cancer screening rates.[10] In this study, the knowledge, attitudes and practices among Filipino women regarding cervical cancer were determined.

The present investigation has shown that 214 (55.87%) Filipino women has heard about cervical cancer. This is similar with the studies conducted in Nepal[9] and India[11] but lower compared to the findings reported in the studies in Uganda,[2] Kuwait[6] and Cambodia.[7] The differences in these studies could be due to the different populations involved. Also, various screening programs or campaigns may exist in other countries that may account for better coverage of cervical cancer. Of the 214 women who have heard of cervical cancer, only 169 were aware of its screening, accounting for less than half (44.1%) of

Table 4. Binary logistic regression analysis, association of knowledge about cervical cancer screening and prevention (n = 383)

	Good knowledge (n = 180)	Poor knowledge (n = 203)	Crude Odds Ratio (95% CI)	P-value
	Frequency (%) Median (Range)			
Age (years)	32 (21 – 61)	32 (21 – 60)	1.004 (0.98 – 1.03)	0.706
Education				
None/Primary	10 (5.56)	33 (16.26)	Reference	-
Secondary	69 (38.33)	75 (36.95)	3.036 (1.39 – 6.62)	0.005
Vocational	37 (20.56)	54 (26.50)	2.261 (0.99 – 5.14)	0.052
Tertiary	58 (32.22)	33 (16.26)	5.800 (2.54 – 13.26)	<0.001
Postgraduate	6 (3.33)	8 (3.94)	2.475 (0.69 – 8.84)	-
Civil status				
Single	40 (22.22)	60 (29.56)	Reference	-
Married	97 (53.89)	86 (42.36)	1.692 (1.03 – 2.77)	0.037
Widowed	1 (0.56)	5 (2.46)	0.3 (0.03 – 2.66)	0.280
Separated	5 (2.78)	2 (0.99)	3.75 (0.69 – 20.28)	0.125
Common-law partner	37 (20.56)	50 (24.63)	1.11 (0.62 – 1.99)	0.726
Parity				
P0	51 (28.33)	63 (31.03)	Reference	-
P1-P3	109 (60.56)	93 (45.81)	1.448 (0.91 – 2.30)	0.116
≥P4	20 (11.11)	47 (23.15)	0.526 (0.28 – 1.00)	0.049
Average household monthly income				
<15000	59 (32.78)	116 (57.14)	Reference	-
≥15000	121 (67.22)	87 (42.86)	2.734 (1.80 – 4.15)	<0.001
Address				
Rural	7 (3.89)	4 (1.97)	Reference	-
Semi-urban	47 (26.11)	57 (28.08)	0.471 (0.13 – 1.71)	0.252
Urban	126 (70)	142 (69.95)	0.507 (0.15 – 1.77)	0.288
Used any method to delay/avoid getting pregnant				
No	87 (48.33)	128 (63.05)	Reference	-
Yes	93 (51.67)	75 (36.95)	1.824 (1.21 – 2.74)	0.004

all the respondents. This reveals that the majority of Filipino women still lack awareness on its screening. Inadequate knowledge on the various screening tests is the greatest barrier to an effective cervical cancer screening.[6]

Furthermore, majority of the respondents still have poor knowledge (203; 53%) on cervical cancer screening, prevention and its risk factors. This is consistent with reports showing that women still had inadequate understanding of causes, risks and prevention of cervical cancer in many developing countries.[12] Several studies have shown that the lack of awareness and unfavorable attitude towards cervical cancer has hindered early screening. In 2001, the Cervical Cancer Screening Study Group by the University of the Philippines, together with the Department of Health, had identified several causes why cervical cancer screening fails.[5] These include lack of knowledge about symptoms associated with cervical cancer, fatalistic attitude towards cancer and lack of awareness that cervical cancer is curable; lack of cytologic screening facilities and expertise and of treatment facilities in rural areas, and lastly, lack of patient compliance with follow–up and treatment.[5] The lack of knowledge of most women in this study could explain why only 13.84% of the respondents have ever been screened for cervical cancer. According to Mukama et al, when women are aware of symptoms of the disease and at the same time perceive themselves to be at risk, they are more likely to take up measures to prevent acquiring the disease and in turn, intend to have themselves screened for cervical cancer.[2]

The media, particularly the television and internet, plays a major role in disseminating health information as shown in this study. Advocacies on cervical cancer should emphasize on the signs and symptoms of the disease and the risk perception in order to motivate early screening and detection.[2] Additionally, since the health facility or medical practitioner is also a major source of information of cervical cancer, health care systems delivery should be improved in the country. The Department of Health has advocated screening, yet less than half of the 389 Philippine hospitals surveyed offer screening and early detection services for cervical cancer, while only 8% have screening clinics.[5] There is a need for better communication between health professionals and their patients to convey the importance of early screening. The study of Sairafi et al have underscored the importance of providing proper information on the value of Pap smear through leaflets and giving a clear explanation on the test procedure to reduce stress and embarrassment of the patient.[6]

Apart from poor knowledge on cervical cancer, a negative attitude was also demonstrated by the majority (201 or 52.48%). This is in contrast to the findings of most studies by

Table 5. Binary logistic regression analysis, association of attitude about cervical cancer screening and prevention (n = 383)

	Positive Attitude (n = 182)	Negative Attitude (n = 201)	Crude Odds Ratio (95% CI)	P-value
	Frequency (%) Median (Range)			
Age (years)	33 (21 – 61)	31 (21 - 60)	1.011 (0.99 – 1.03)	0.293
Education				
None/Primary	20 (10.99)	23 (11.44)	Reference	-
Secondary	68 (37.36)	76 (37.81)	1.029 (0.52 – 2.04)	0.935
Vocational	37 (20.33)	54 (26.87)	0.788 (0.38 – 1.64)	0.523
Tertiary	46 (25.27)	45 (22.39)	1.176 (0.57 – 2.43)	0.663
Postgraduate	11 (6.04)	3 (1.49)	4.217 (1.03 – 17.28)	0.046
Civil status				
Single	35 (19.23)	65 (32.34)	Reference	-
Married	99 (54.40)	84 (41.79)	2.189 (1.32 – 3.62)	0.002
Widowed	3 (1.65)	3 (1.49)	1.857 (0.36 – 9.69)	0.463
Separated	3 (1.65)	4 (1.99)	1.393 (0.29 – 6.58)	0.676
Common-law partner	42 (23.08)	45 (22.39)	1.733 (0.96 – 3.12)	0.067
Parity				
P0	49 (26.92)	65 (32.34)	Reference	-
P1-P3	100 (54.95)	102 (50.75)	1.301 (0.82 – 2.06)	0.265
≥P4	33 (18.13)	34 (16.92)	1.288 (0.70 – 2.36)	0.414
Average household monthly income				
<15000	69 (37.91)	106 (52.74)	Reference	-
≥15000	113 (62.09)	95 (47.26)	1.827 (1.22 – 2.748)	0.004
Address				
Rural	6 (3.30)	5 (2.49)	Reference	-
Semi-urban	48 (26.37)	56 (27.86)	0.714 (0.21 – 2.49)	0.597
Urban	128 (70.33)	140 (69.65)	0.762 (0.23 – 2.56)	0.660
Used any method to delay/avoid getting pregnant				
No	92 (50.55)	123 (61.19)	Reference	-
Yes	90 (49.45)	78 (38.81)	1.543 (1.03 – 2.32)	0.036

Mukama et al in Uganda[2], Sairafi et al in Kuwaiti,[6] Touch et al in Cambodia[7] and Bansal et al in India.[11] The overall negative attitude translated in their poor practice of screening as only 13.84% or 53 of the respondents have ever been screened for cervical cancer. This number is a little higher than that reported in the 2001/2002 WHO Health survey which reported Pap smear coverage of Filipino women aged 18 – 69 years to be at 7.7%.[5] The findings in the present study were slightly higher probably because this investigation was conducted in a tertiary hospital and those seeking medical attention at the outpatient clinic may have better health-seeking behavior. This is similar to a study reported by Shrestha et al in Nepal but a little higher as well compared to the studies by Bansal et al in India[11] and Touch et al in Cambodia.[7] Some knowledge gaps among these women may account for the poor practice of screening and vaccination. Most women were not aware of the existence of a vaccine against cervical cancer and no one knew the recommended age to start vaccination. In turn, only 3.39% of the respondents were vaccinated against cervical cancer. Although majority showed a negative attitude, more than 80% of the women were willing to undergo Pap smear free at cost.

The association between their sociodemographic characteristics and knowledge, attitude and practices was also established in this study. These results were similar to the findings in the study reported by Sairafi et al in Kuwaiti.[6] It is expected that women with a higher level of education are more likely to acquire knowledge on the disease and in turn, know about the benefits of screening leading to better screening practices. A study by Chinwe et al showed that health education brought about significant impact on the knowledge, attitude and practices of cervical screening among the teachers in Enugu state, Nigeria.[13] Their findings were consistent with the Knowledge Attitude and Practices (KAP) model of health education, that is, if knowledge of cervical cancer screening is increased among participants, this will positively influence their attitude and thereby change their practice of screening.[13] Also, women with higher level of income would have higher knowledge scores because they are able to gain more information with better access to health services and screening facilities. Moreover, the high cost of HPV vaccines results in poor vaccination coverage in those with low monthly incomes.

CONCLUSION

The study demonstrated that most women had poor knowledge, negative attitude and practices on cervical cancer

Table 6. Binary logistic regression analysis, association of practice on cervical cervical cancer screening and prevention (n = 383)

	Good Practice (n = 54)	Poor Practice (n = 329)	Crude Odds Ratio (95% CI)	P-value
	Frequency (%) Median (Range)			
Age (years)	34.5 (21 – 60)	32 (21 – 61)	1.016 (0.99 – 1.05)	0.287
Education				
None/Primary	1 (1.85)	42 (12.77)	Reference	-
Secondary	22 (40.74)	122 (37.08)	7.574 (0.99 – 57.93)	0.051
Vocational	9 (16.67)	82 (24.92)	4.610 (0.56 – 37.61)	0154
Tertiary	17 (31.48)	74 (22.49)	9.649 (1.24 – 75.10)	0.030
Postgraduate	5 (9.26)	9 (2.74)	23.333 (2.42 – 224.62)	0.006
Civil status				
Single	15 (27.78)	85 (25.84)	Reference	-
Married	32 (59.26)	151 (45.90)	1.201 (0.62 – 2.34)	0.591
Widowed	1 (1.85)	5 (1.52)	1.133 (0.12 – 10.39)	0.912
Separated	1 (1.85)	6 (1.82)	0.944 (0.11 – 8.41)	0.959
Common-law partner	5 (9.26)	82 (24.92)	0.346 (0.12 – 0.99)	0.049
Parity				
P0	15 (27.78)	99 (30.09)	Reference	-
P1-P3	33 (61.11)	169 (51.37)	1.289 (0.67 – 2.49)	0.450
≥P4	6 (11.11)	61 (18.54)	0.649 (0.24 – 1.76)	0.397
Average household monthly income				
<15000	10 (18.52)	165 (50.15)	Reference	-
≥15000	44 (81.48)	164 (49.85)	4.427 (2.16 – 9.09)	<0.001
Address				
Rural	2 (3.70)	9 (2.74)	Reference	-
Semi-urban	16 (29.63)	88 (26.75)	0.818 (0.16 – 4.14)	0.808
Urban	36 (66.67)	232 (70.52)	0.698 (0.14 – 3.36)	0.654
Used any method to delay/avoid getting pregnant				
No	24 (44.44)	191 (58.05)	Reference	-
Yes	30 (55.56)	138 (41.95)	1.730 (0.97 – 3.09)	0.064

screening and prevention. This shows that a health education program on cervical cancer which focuses on the risk factors, its screening and prevention, is needed to increase awareness among Filipino women. Utilizing the media, particularly the television and internet, in the campaign for cervical cancer awareness may prove beneficial. Moreover, the implementation of an organized nationwide screening program in the country is crucial to improve access of women to screening facilities and in turn, increase the uptake of cervical cancer screening.

LIMITATIONS AND RECOMMENDATIONS

The present study was limited in a hospital setting and did not include Filipino women in the community. There could also be response bias because it is a study which made use of a questionnaire. Since the Filipino language was used in the questionnaire, the tone might vary by interviewer. For future studies on KAP on cervical cancer, the barriers or reasons for not undergoing a Pap smear and vaccination may be explored.

Table 7. Final model, predictors of knowledge, attitudes, and practices about cervical cancer and its risk factors (n=383)

	Good knowledge		Good attitude		Good practice	
	Adjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value	Adjusted Odds Ratio (95% CI)	P-value
Education						
None/Primary	Reference					
Secondary	1.705 (1.03 – 2.83)	0.039				
Tertiary	2.463 (1.37 – 4.41)	0.002				
Civil status						
Single	Reference	-	Reference	-	Reference	-
Married	1.951 (1.21 – 3.16)	0.006	1.674 (1.11 – 2.52)	0.014		
Common-law partner					0.307 (0.12 – 0.81)	0.017
Parity						
P0	Reference	-				
≥P4	0.379 (0.20 – 0.72)	0.003				
Average household monthly income						
<15000	Reference	-	Reference	-	Reference	-
≥15000	2.117 (1.35 – 3.31)	0.001	1.839 (1.22 – 2.78)	0.004	4.429 (0.12 – 0.81)	0.017
Used any method to delay/avoid getting pregnant	1.626 (1.37 – 4.41)	0.034				

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Survival Outcome and Disease-Free Survival of Locally Advanced Cervical Cancer with CT-Detected Para-Aortic Lymph Nodes

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ABSTRACT

Background: In the Philippines, cervical cancer is the 2nd most common cancer among women and is the country's second leading cause of female cancer deaths. Majority of the patients seek consult at advanced stage of the disease with distant metastasis. In the absence of histologically proven lymph node (LN) metastasis, imaging may be requested to determine spread to the para-aortic lymph nodes (PALN) which should be treated with Extended Field Radiation Therapy (EFRT).

Objective: The aim of this study is to compute the over-all survival (OS) and disease-free survival (DFS) of advanced cervical cancer with Computed Tomography (CT) Scan detected PALN metastasis after concurrent chemoradiotherapy using EFRT with weekly platinum-based chemotherapy followed by High Dose Brachytherapy.

Methodology: This is a retrospective study which included patients diagnosed with locally advanced cervical carcinoma according to the 2009 International Federation of Obstetrics & Gynecology (FIGO) staging (stage IB2 – stage IIIB) who had CT-detected PALN metastasis and underwent EFRT with weekly chemotherapy followed by brachytherapy at a single institution from January 2002 – December 2015. The 3-year OS and DFS of the patients were computed and analyzed.

Results: There were 51 patients who satisfied the inclusion criteria and were included in the study. The 3-year OS and DFS rates were 81.3% and 58.6%, respectively. The median survival time was 35.5 months and the median disease free time was 25.04 months.

Conclusion: The current recommendation of EFRT with concurrent chemotherapy followed by brachytherapy is an effective treatment for cervical cancer patients with CT-detected PALN metastasis with a satisfactory 3-year survival outcome. Patients with Non-Squamous Cell Carcinoma have lower survival outcome and higher risk for recurrence, with central tumor recurrence being the most common site.

Keywords: Cervical carcinoma, CT-detected para-aortic lymph nodes

INTRODUCTION

With an estimated 527,624 new cases and 265,672 fatalities reported in 2012, cervical cancer ranks 4th among the most prevalent cancer in females globally. In the Philippines, it is the 2nd most common cancer among females with about 6,670 new cases diagnosed annually. It is also the country's 2nd leading cause of female cancer deaths with 2,832 cervical cancer deaths per annum. [1]

Several cancer screening programs have been made available in the Philippines including Pap smears, single visit approach using visual inspection with acetic acid followed by cryotherapy, as well as colposcopy [2]. However, only 9.3% of women aged 25-64 years was being screened every 3 years as reported in 2017 [3]. Little knowledge about the disease, lack of patient's compliance or late consultations are the reasons why majority of the cases are diagnosed at advanced stage, most of them already having distant metastasis and poorer outcome.

Cervical cancer spreads in a progressive but predictable pattern. Metastasis to lymph node (LN), though not included in the 2009 FIGO staging, is an important, and independent prognostic factor for cervical cancer patients. Obturator nodes will typically be the first location of LN metastasis with gradual spread to the ipsilateral common iliac LN and para-aortic lymph node (PALN) [4].

In cervical cancer, PALN metastasis occurs midway between locoregional and systemic disease. Berman et al. revealed that for cervical cancer stage IB, the prevalence of PALN metastasis was 5%, for stage II 16% and for stage III 25% [5]. These patients in general, have lower survival rates and need Extended Field Radiation Therapy (EFRT). [4,6] The distant metastasis rate beyond the PALNs ranges from 18.2–54.9% following EFRT. The 5-year survival rate is from 24–57.1% [6]. In a study by Yoon et al. [8], patients with stage IB – stage IVA disease with PALN metastasis, diagnosed by either imaging studies or histopathology, who underwent EFRT with or without concurrent chemotherapy were found to have a higher 5-year OS of 62.6% and PFS of 43.9%.

In the 1970s and 1980s, the use of high-dose EFRT for treatment of patients with PALN metastasis showed relatively

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low 5-year overall survival rates (10% to 15%), with unacceptable treatment-related adverse effects [4]. In 1999, with the advances in the treatment of cervical cancer supported by the findings from multiple randomized controlled trials, the National Cancer Institute recommended synchronous chemoradiation for the treatment of these patients. Although these trials included only patients with pelvis-confined disease, the improved survival rates that were observed with administration of concurrent chemotherapy suggested a theoretical advantage of concurrent chemotherapy for patients with PALN metastasis. Retrospective analyses indicated that weekly Cisplatin can be safely administered concurrently with EFRT. Hence, clinicians have adopted concurrent chemoradiation as standard treatment for women with PALN metastasis from cervical cancer [4].

Most patients examined in different studies had PALN metastasis confirmed by histopathology. The Clinical Practice Guidelines of the Society of Gynecologic Oncologists of the Philippines (SGOP) also recommend EFRT plus brachytherapy plus concurrent platinum-based chemotherapy in para-aortic lymphadenopathy (size > 1.0 cm) by CT, magnetic resonance imaging (MRI), or 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan confirmed by fine needle aspiration or extraperitoneal or laparoscopic lymphadenectomy [7].

Since surgical staging has some risks of complications that may have negative impact on treatment outcomes, many patients may not have histologically proven PALN metastasis. In these cases, imaging such as CT, MRI or PET Scan are widely used as non-invasive staging tool for patients with cervical cancer [6].

There are few researches on the treatment outcomes for patients with CT-detected PALN metastasis. Also, no comprehensive report had discussed the prognostic factors for PALN metastasis. Although PET is more sensitive than CT, PET is not routinely used because of its relatively high cost and limited availability [9]. Therefore, CT remains a very important tool for clinical staging of cervical cancer, especially in hospitals without PET scan. The aim of this study is to compute the over-all survival (OS) and disease-free survival (DFS) of advanced cervical cancer with CT Scan detected PALN metastasis after concurrent chemoradiotherapy using EFRT with weekly platinum-based chemotherapy followed by High Dose Brachytherapy.

MATERIALS AND METHODS

This is a retrospective study that included patients diagnosed with locally advanced cervical carcinoma according to the 2009 FIGO Staging Classification (stage IB2 – stage IIIB) who had CT-detected PALN metastasis and underwent EFRT with weekly chemotherapy followed by brachytherapy at a single institution from January 2002 – December 2015.

Data collected were patient's demographic data, such as age, parity, histologic type and stage of cancer, and number of chemotherapy cycles. The 3-year over-all survival outcome (OS) and disease-free survival (DFS) of the patients were documented and analyzed.

STUDY SUBJECTS

A. Inclusion Criteria:

This study included patients diagnosed with locally advanced cervical carcinoma who had CT-detected PALN metastasis measuring > 1 cm in size or confluent lymph nodes in CT planning prior to treatment and underwent EFRT with weekly platinum-based chemotherapy followed by brachytherapy at a single institution from January 2002 – December 2015.

Treatment of the patients consisted of radiotherapy with concurrent chemotherapy. Protocol for the EFRT included giving a total dose of 45 Gy to the PALN and 50 Gy to the whole pelvis with daily fraction of 1.8 – 2 Gy per fraction. Midline shield was started after 40 Gy. Parametrial boost of 10 Gy was given as needed. The common field borders were: superior border – Th12-L1 interspaces; inferior border – inferior border of obturator foramen or 3 cm below the lowest tumor; lateral border of pelvis – 1.0 - 1.5 cm lateral to the true pelvis; lateral border of PALN – 1.5-2.0 cm lateral to the vertebral body. This was followed by high dose rate intracavitary brachytherapy. The usual dose was 39.6 Gy at point A, at 7 Gy per fraction, at a frequency of one fraction per week for 4 weeks. Concurrent chemotherapy with Cisplatin 40 mg/m2 or Carboplatin 150 mg was given once a week during the course of EFRT.

B. Exclusion Criteria:

Exclusion criteria were the following: 1.) patients who were not able to complete the concurrent chemoradiotherapy treatment; 2.) patients with missing data or medical records; 3.) patients with primary malignancies other than cervical cancer; 4.) patients who underwent different treatment other than concurrent chemoradiotherapy.

DATA COLLECTION AND STATISTICAL ANALYSIS

Retrieval and review of records in the Out Patient Department of the patients who satisfied the Inclusion Criteria was done.

The primary outcomes of the study will be OS and DFS at 3 years. OS is defined as the time from the date of diagnosis until the date of death from any cause. Survivors will be censored from the date of last contact. DFS will be defined as the time from last fraction of brachytherapy to disease recurrence or progression. OS and DFS will be assessed using Kaplan-Meier method and will be compared using Cox proportional hazard models. Logistic regression analysis will be used to determine the association of different patient's characteristics such as number of chemotherapy cycles, type and stage of cancer to the overall survival and disease-free survival. All p values < 0.05 will be considered significant.

LIMITATIONS OF THE STUDY

This was a retrospective study and was limited by the availability and accuracy of the records retrieved at the Medical Records. The population was derived from a single tertiary hospital and data may not be generalizable to other populations due to a minimal number of patients who underwent the treatment being studied during the whole study period. Also, adverse effects experienced by the patients during treatment were not taken into account in this study.

RESULTS

From January 2002 – December 2015, there were 110 patients with locally advanced cervical carcinoma who had

CT detected PALN metastasis. Only 51 patients satisfied the inclusion criteria. The remaining 59 patients did not undergo brachytherapy and were excluded from the study. Nineteen of these patients were lost to follow-up or opted to have their brachytherapy in another institution. 40 patients had persistent or progressive disease and were treated with active chemotherapy instead of brachytherapy.

Table 1 shows the clinicopathologic profile of the 51 patients included in the study. The mean age group was 54 years old. Majority of the patients had SCCA (72.5%), were stage IIIB (88.2%) and were able to complete the 6 cycles of weekly chemotherapy (80.4%).

Variables	Number (%)
Age	54 yo (mean)
Stage IIB-IIIA IIIB	 6 (11.8%) 45 (88.2%)
Histology SCCA Non-SCCA	 37 (72.5%) 14 (27.5%)
Cycles of chemotherapy 6 <6	 41 (80.4%) 10 (19.6%)

Table 1. Baseline demographics and clinical characteristics of all patients

3-year OS and DFS rates were 81.3% and 58.6%, respectively (Figures 1 and 2). The median survival time was 35.5 months and the median disease-free time was 25.04 months.

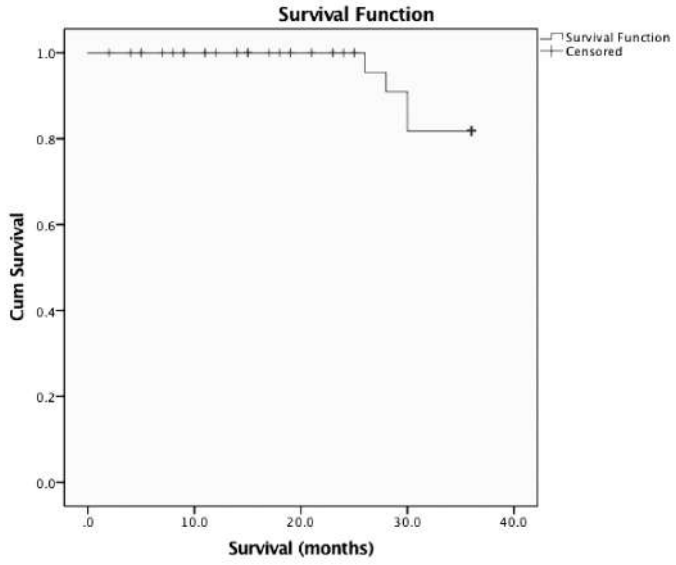

Figure 1. Kaplan-Meier Curve of the 3-year over-all survival

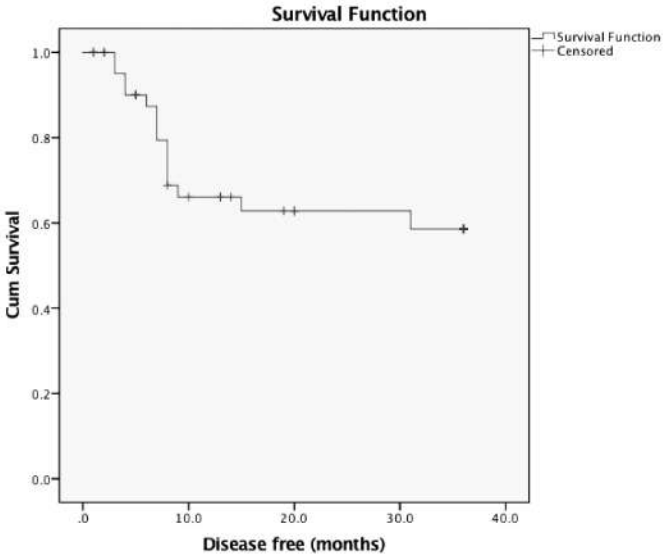

Figure 2. Kaplan-Meier Curve of the 3-year disease-free survival

Central tumor recurrence was the most common site of recurrence (58.8%). This was followed by supraclavicular lymph node and lungs (11.8%) and bladder, brain and scalp (5.8%) (Table 2).

Sites	Number (%)
Central tumor recurrence	10 (58.8%)
Bladder	1 (5.8%)
Brain	1 (5.8%)
Supraclavicular lymph node	2 (11.8%)
Scalp	1 (5.8%)
Pulmonary	2 (11.8%)

Table 2. Different sites of recurrences

Logistic regression analysis found that only histopathologic type was found to have significant effect in terms of recurrence after treatment. Those who have Non-SCCA were associated with lower survival rate and higher risk for recurrence (Table 3, Figures 3 and 4).

Category	OR (95% CI)	p Value
Stage	1.14 (0.01 – 174.66)	0.959
Histopathology	18.01 (1.14 – 285.08)	0.040
Tumor size	1.32 (0.07 – 24.08)	0.851
Number of chemotherapy	4036225.40 (0.00 – -)	0.993

Table 3. Logistic analysis on factors affecting survival rate

Category	OR (95% CI)	p Value
Stage	1.142 (0.293 – 4.443)	0.849
Histopathology	3.090 (1.109 – 8.608)	0.031
Tumor size	1.266 (.950 – 1.687)	0.108
Number of chemotherapy	1.323 (0.342 – 5.122)	0.685

Table 4. Logistic analysis on factors affecting recurrence

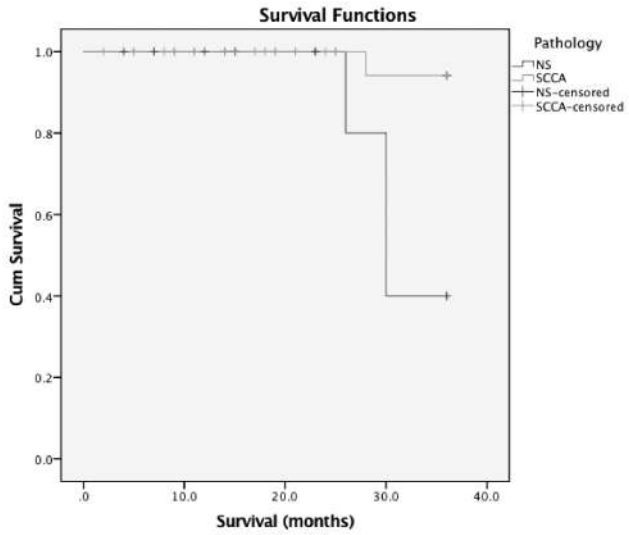

Figure 3. Kaplan-Meier Curve. 3-year over-all survival of SCCA vs. Non-SCCA type

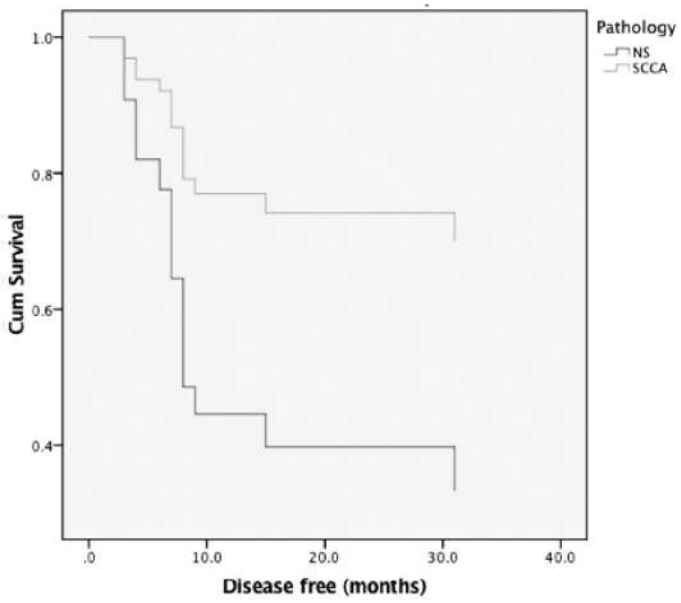

Figure 4. Kaplan-Meier Curve. 3-year disease-free survival of SCCA vs. Non-SCCA type

DISCUSSION

Surgical staging remains to be the most accurate method to detect PALN metastasis. However, there are situations where PALN biopsy is not yet routinely done, for reasons like prevention of some surgical complications, delayed radiotherapy due to long list of surgical patients or unavailability of surgeons or resources for the said procedure. Wu et al. [9] suggested that though routine pre-treatment with surgical staging is not recommended, non-invasive detection of PALN may be done through imaging techniques. CT scan, though it may have a lower specificity and sensitivity in detecting PALN, because of its availability and cost-effectiveness, may be used to determine patients who will be needing EFRT as compared to Pelvic External Beam Radiation which is the standard treatment.

Cervical cancer patients with PALN metastasis may benefit from the delivery of 45 Gy to PALN in EFRT but they may also experience some treatment adverse effects. Yoon et al [8] stated that acute adverse effects in cervical cancer patients treated with EFRT include acute leukopenia, acute anemia, and acute thrombocytopenia while late toxicities consist of gastrointestinal and urogenital effects. Unfortunately, documentation of treatment toxicities was not included in this study.

Other studies reported age, size and number of PALNs detected and number of chemotherapy as predictive factors which affect survival outcome and recurrence rate after EFRT. For this study, only the type of histopathology appeared to be significant in terms of OS and DFS.

Non-SCCA patients with CT-detected PALN should still be encouraged to undergo treatment because of its relatively good survival outcome. However, compared to those who have SCCA, they should be counselled more regarding the tumor's aggressiveness and the possibility of recurrence that may necessitate other treatments such as high dose chemotherapy. Other treatment modalities may also be explored for these patients. In one study by Chauhan [10], wherein the survival outcome of patients with PALN metastasis was as low as 46.66%, it was suggested that debulking of enlarged nodes and adjuvant chemotherapy to reduce distant metastasis may be done to improve the prognosis of such patients.

In terms of recurrence, supraclavicular lymph nodes appeared to be the most common site of distant metastasis after EFRT [6]. This is expected considering the pattern of spread of the disease, and the anatomy of lymphatic drainage. Bilateral lumbar trunks formed by the union of the efferent vessels from the lateral aortic lymph glands receive the lymph from the common iliac chains, ovaries, uterine tubes, and body of the uterus. Ultimately, the lumbar trunks drain into the cisterna chyli, a dilated sac at the beginning of the thoracic duct that empties into the left subclavian vein. In the present study, distant metastasis appeared to be low as compared to local recurrences. More importantly, the high number of central tumor recurrence should be considered in planning for the patient.

Currently, the availability of image guided brachytherapy and interstitial brachytherapy may lead to lesser central tumor recurrence. The first uses cross-sectional image data to create 3D models, as compared to 2D models, to precisely plan and deliver radiation to the target organ while minimizing exposure to the surrounding healthy tissue. The second is reserved for patients

with extensive pelvic or vaginal lesions to improve local control of the disease. In this technique, the aim of tailoring the dose of radiation based on the anatomy of the patient will provide a better target volume coverage.

Given that the common sites of recurrences are the pelvis and supraclavicular lymph nodes, thorough physical examination including speculum and pelvic examination on regular follow-up, as recommended by the SGOP guidelines, should be stressed for early detection of recurrences, especially in the pelvic area. The need for additional imaging procedures should be entertained if recurrence to other sites is suspected.

CONCLUSION AND RECOMMENDATION

The current recommendation of EFRT with concurrent chemotherapy followed by brachytherapy shows a good outcome for cervical cancer patients with CT-detected PALN metastasis, particularly with SCCA type, with a relatively higher 3-year survival outcome as compared to other foreign studies reported. Thus, EFRT should be continuously done to patients with CT-detected PALN metastasis until techniques on how to have histopathologic diagnosis, such as laparoscopy, will be more available and accessible for patients.

The 2018 FIGO staging for cervical cancer states that Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent, is classified as Stage IIIC, with r and p notations for radiologic and pathologic findings respectively [11]. Using this new staging denotes use of EFRT for cervical cancer patients with Stage IIIC2r.

Future prospective studies including response to treatment based on number and size of PALN and amount of radiation received may be done to further investigate the role of EFRT in these locally advanced stage of cervical cancer patients. The different toxicities and tolerability of patients may also be incorporated to substantiate the OS and DFS of patients.

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Clinical characteristics and prognosis of young Filipino women ages 30 and below with endometrial cancer: A ten-year retrospective cohort study

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ABSTRACT

Endometrial cancer is more common in the postmenopausal age group. In recent years, there have been more cases seen in younger women. Few studies have been published regarding endometrial cancer in young patients. In the Philippines, no study has yet focused on the occurrence of endometrial cancer in women 30 years old or younger. This study aimed to determine the clinico-pathologic characteristics and prognosis of women diagnosed with endometrial cancer aged 30 years old and below managed in Philippine General Hospital from January 2004 to December 2013. This was a ten-year retrospective cohort study that reviewed medical records and histopathology database of women aged 30 and below with endometrial cancer and treated conservatively and/or surgically including adjuvant treatment in Philippine General Hospital.

A total of 47 patients were included during the study period. Among the 47 subjects, 61% were single and 76% were nulligravid. The median age was 26 years, and the median BMI was 27 kg/m2. The median age of menarche was 12 years. Sixty-one percent (61.7%) of these patients had irregular menstrual interval while eighty-two percent (82.98%) of the subjects had no family history of cancer. Dyslipidemia, polycystic ovarian syndrome, and primary infertility were noted but most of the subjects (87.23%) had no risk factors. There was no Lynch syndrome documented. No patient with hypertension nor diabetes mellitus was recorded.

Seventy-two percent (72.34%) of the subjects had endometrial adenocarcinoma, endometrioid type. There was a note of poorly differentiated adenocarcinoma with neuroendocrine differentiation in one case. Thirty eight percent (38.30%) of cases were stage 1A. Lymphovascular space invasion was noted in 10.64%, lymph node involvement in 8.51% and adnexal involvement in 8.51% of the subjects.

Sixty-five percent (65.96%) of the patients underwent surgical intervention while 6.38% of the subjects initially had conservative or medical management. However, these same patients eventually underwent surgery.

Survival analysis was performed using the Kaplan-Meier estimates of survival probabilities across defined age groups and log-rank test which showed no statistical difference across age groups, 30 years old and below.

Keywords: *endometrial cancer, young*

INTRODUCTION

When discussing endometrial cancers, "young" is defined as either premenopausal or 45 years or younger.[1] Age range of patients is usually between 50 to 59 with mean age of 63 years. Only 5% of adenocarcinoma cases are younger than 40 years old, while 20-25% are pre-menopausal.[2] 47 to 48 is the menopausal age of Filipino women.[3] A two-fold increase in the incidence of this cancer among Filipino women less than 40 years old was noted from 2010 to 2012. The youngest patient was a 21-year-old.[4]

Cases of endometrial cancer among women ≤ 30 years old have been published. Galina reported three 20-year-old patients and one 19-year-old who all complained of menorrhagia; diabetes mellitus, hypertension, irritable bowel syndrome were the risk factors.[5] Sunanda reported a 30-year-old woman who underwent myomectomy for a fibroid which turned out to be a well-differentiated endometrial adenocarcinoma.[6] Fadhlaoui reported a 27-year-old with abnormal uterine bleeding and endometrial polyp who underwent curettage which showed a well-differentiated adenocarcinoma.[7] An endometrial polyp in a 20-year-old who underwent hysteroscopy for menorrhagia showed moderately differentiated adenocarcinoma.[8] Guruvare reported a 22-year-old with endometrial carcinoma.[9]

In the Philippines, no study has yet been done on endometrial cancer among women ≤ 30 years old. This study aimed to determine the clinico-pathologic characteristics and prognosis of women with endometrial cancer ≤ 30 years old managed in the Philippine General Hospital (PGH) from January 2004 to December 2013.

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METHODOLOGY

This was a ten-year retrospective cohort study. The study population were endometrial cancer patients ≤ 30 years old who were either treated conservatively and/or surgically in PGH or diagnosed and managed from other institutions and subsequently referred to PGH. For those referred from other institutions, slide reviews of the histopathologic result were conducted by one of the faculty of the Department of Pathology of PGH.

The study underwent technical review by the Research Technical Review Board of the Department of Obstetrics & Gynecology. It was then reviewed and approved by the University of the Philippines Manila Research Ethics Board.

All endometrial cancers cases from January 2004 to December 2013 were obtained through review of medical records and histopathologic results at the Surgical Pathology database. Data collected were anonymized and kept confidential; patients' names did not appear in the analysis or in the reporting of the results.

Clinical data included age upon diagnosis, presenting symptoms, BMI, gravidity, parity, menstrual history, oral contraceptive use, personal history of diabetes, hypertension, personal and family history of breast, colon, endometrial or ovarian cancer. Pathologic information consisted of histology, grade, depth of myometrial invasion, staging, lympho-vascular space invasion, lymph node and adnexal involvements. Survival and time to recurrence were noted.

All data were encoded in MS Excel and analyzed using SPSS software. Tables, figures, simple frequency counts, percentages, mean, distribution patterns in the cohort, and Kaplan-Meier analysis with Log-rank test for the 10-year disease-specific survival were done. Chi-square test was used for the demographic, clinical, histologic, and treatment characteristics. Survival analysis was performed using the Kaplan-Meier estimates of survival probabilities across defined age groups. P-value less than 0.05 was considered significant.

RESULTS

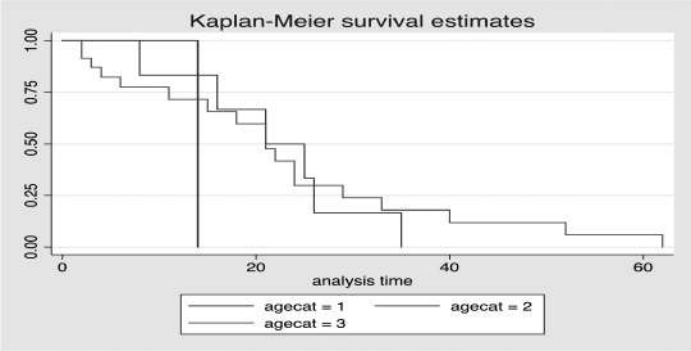
A total of 47 subjects were included in the study. The median age of the group was 26 yrs, with the youngest patient being 21 years old. Sixty-one percent of the patients were single. Median age of menarche was at 12 years and most experienced irregular menstruation. Seventy-six percent (76.06%) were nulligravid. Median BMI was 27 kg/m2.

Majority of the subjects (82.98%) had no family history of cancer. Two patients had family history of endometrial and breast cancer; none had a history of solely endometrial cancer in the family. Heredo-familial carcinomas noted were ovarian and colon cancer. While most patients had no risk factor, 6 patients had either dyslipidemia, PCOS, or primary infertility. Seventy present (70.21%) had no history of any OCP use. Most common presentation (55%) was meno- or metrorrhagia, (now replaced by "heavy menstrual bleeding"). Seventeen percent (17.02%) complained of vaginal bleeding with no note on its relation to menses. Among these patients, ten (21.3%) had an ultrasound finding of thickened endometrium, two with polycystic ovaries, one with sonologic impression of complete abortion and one with molar pregnancy on ultrasound. One patient was diagnosed with endometrial cancer during fertility work-up.

The majority of patients (72.34%) had endometrial adenocarcinoma, endometrioid type. One case had poorly differentiated endometrial carcinoma with neuroendocrine differentiation. Full thickness myometrial invasion was noted in 2.13% and serosal involvement in 2.13% of the subjects. Only 38.30% were stage 1A on final biopsy. Lymphovascular space invasion, lymph node involvement, and adnexal metastasis were present in 10.64%, 8.51%, and 8.51%, respectively. One patient with endometrial adenocarcinoma with only superficial myometrial invasion had synchronous ovarian carcinoma; there was no report of lymph node involvement, nor lymphovascular space.

Sixty five percent of these subjects underwent surgery while three (6.38%) had hormonal treatment. Two patients were directly given chemotherapy. Nine subjects (19%) were lost to follow-up before treatment was instituted.

Using Kaplan-Meier survival estimates, the longest overall survival time was 5 years and 2 months. Analysis using the log-rank test showed no significant difference among the three age categories.



agecat (age category) = 1 (< 20 years old)
agecat (age category) = 2 (20 – 25 years old)
agecat (age category) = 3 (26 – 30 years old)

Figure 1. Kaplan-Meier Survival Estimates among women with endometrial cancer <30 years old (January 2004 – December 2013)

DISCUSSION

Endometrial cancer in young patients is related to prolonged unopposed estrogen exposure from hormone-related disorders, such as obesity, nulliparity and polycystic ovarian syndrome (PCOS).[5,8,10] This is similar with our findings of obesity and nulliparity among our 47 subjects. A Danish cohort study of 12,131 PCOS patients showed increased risk of endometrial malignancy in those <50 years old.[11] The association of polycystic ovary (PCO) and endometrial cancer is consistent with the effect of unopposed estrogen on the endometrium, inducing endometrial carcinogenesis.[7] Medically documented PCO has a 5.3- fold increased risk.[12] Aside from elevated estrogen, other contributory causes are hyperinsulinemia and reduced apoptosis.[13] PCO-associated endometrial carcinomas do not have better prognosis than those with normal ovaries.[7] Our study noted only four patients (8.51%) with PCOS and two patients with primary infertility. Work-up and documentation

Table 1. Clinico-demographic profile of patients diagnosed with endometrial cancer ≤ 30 years old from January 2004 – December 2013

CIVIL STATUS	FREQUENCY	PERCENT
Married	17	36.17
Single	29	61.70
(no mention)	1	2.13
AGE	26.87 (± 3.18)	
WEIGHT	65.75 (± 18.64)	
HEIGHT	154.54 (± 6.65)	
BMI	27.00 (± 7.30)	
GRAVIDITY/PARITY	**FREQUENCY**	**PERCENT**
G0	36	76.60
G1P0 (0010)	2	4.26
G1P1 (1001)	5	10.64
G2P1 (1011)	1	2.13
G2P2 (2001)	1	2.13
G2P2 (2002)	2	4.26
MENSTRUAL HISTORY		
Menarche	12.55 (± 2.02)	
Duration	7.13 (±5.92)	
INTERVAL	**FREQUENCY**	**PERCENT**
Irregular interval	29	61.7
Regular	18	38.3

Table 2. Medical history of patients diagnosed with endometrial cancer ≤ 30 years old from January 2004 – December 2013

Family History	Frequency	Percent
• Breast cancer and endometrial cancer	2	4.26
• Breast cancer	3	6.38
• Kidney disease (not sure if cancer)	1	2.13
• Ovarian cancer	1	2.13
• Colon cancer	1	2.13
• None	39	82.98
Past Medical History	**Frequency**	**Percent**
• Dyslipidemia, PCOS	1	2.13
• PCOS	2	4.26
• Primary infertility	2	4.26
• Primary infertility for 12 years, PCOS	1	2.13
• None	41	87.23
Use of OCP	**Frequency**	**Percent**
Yes	14	29.79
None	33	70.21
Presentation at the time of Diagnosis	**Frequency**	**Percent**
Meno/metrorrhagia	26	55.32
Vaginal bleeding	8	17.02
Vaginal spotting	7	14.89
Amenorrhea	2	4.26
Abdominal mass and abdominal enlargement	1	2.13
Hypogastric pain	1	2.13
Post-coital spotting	1	2.13
Fertility work-up	1	2.13

of the cases might not be accurate since patients were lost to follow-up after their initial consult. Other risk factors identified by previous studies were hypertension, diabetes, sole use of estrogens, tamoxifen, chronic anovulation, and infertility.[7] Chronic anovulation has 3.1-fold increased risk of endometrial cancer.[12] No diabetes mellitus or hypertension was noted in our subjects since such conditions are usually identified among older women.

Lynch syndrome or HNPCC causes majority of inherited endometrial cancers in young patients.[7] Our study identified family history of endometrial, ovarian and colon cancer, but Lynch syndrome was not documented. In our setting, most cases were not diagnosed since most patients were not compliant with their follow-up and further evaluation of their family members with similar manifestations was not done.

Burleigh reported young women with endometrial cancer without excess estrogen or suspected hereditary risk factors. This populace exemplifies diverse population of women with alternate tumorigenesis.[20]

Young patients usually have favorable pathologic features (minimal myometrial invasion, low grade, organ-confined disease) and an excellent outcome.[14] Myometrial involvement and stage are significantly lower in younger women.[15] Vaccarello observed endometrioid type, well-differentiated (Grade 1) and superficial invasion (Stage I) in young women.[7] A study by Crissman et al and another by Kim et al showed young patients with well-differentiated and favorable histologic type, infrequent myometrial invasion, and lack of extrauterine spread.[1] A local study by Sy-Fernando et al showed earlier stage, less myometrial invasion and well-differentiated tumors in younger age group (≤40 years old) than older age group (> 40 years). However, she reported no statistical significance in the overall survival between the two groups.[16]

Some reports showed less favorable pathologic features in young patients. Tran et al showed equivalent outcome of young and older patients, with most pathologic features present in young women. Adverse features are not equally distributed among young women. Discordance exists between myometrial invasion, tumor grade, and lymph node involvement.[14]

Evans-Metcalf et al and Fahri et al showed 90% rate of Grade 1 tumors in young women. They noted similar incidence of extrauterine spread, unfavorable histologies and outcome for both younger and older women. Another study reported myometrial invasion rate of 24% in young women vs. 49% in older women.[7,14,17] Gitsch reported 35% incidence of lymph node involvement in younger women.[18] Most of our subjects had lower stage, with superficial myometrial invasion and no lymph node involvement. There were cases of clear cell

Table 3. Histopathologic profile of patients diagnosed with endometrial cancer ≤ 30 years old from January 2004 – December 2013

Histology	**Frequency**	**Percent**
Endometrial adenocarcinoma, endometrioid type	34	72.34
Adenocarcinoma	2	4.26
Adenosquamous carcinoma	1	2.13
Clear cell carcinoma	2	4.26
Endometrial adenocarcinoma, endocervical type	1	2.13
Endometrial adenocarcinoma, endometrioid type, with squamous differentiation	3	6.39
Endometrioid carcinoma with serous component	1	2.13
Focal adenocarcinoma, endometrioid type, background of complex hyperplasia with atypia	2	4.26
Poorly differentiated endometrial carcinoma with neuroendocrine differentiation	1	2.13
Depth (Myometrial Invasion)	**Frequency**	**Percent**
Superficial (<50%)	23	48.94
Deep (>50%)	7	14.89
Full thickness	1	2.13
Serosal involvement	1	2.13
(No mention)	15	31.91
Stage	**Frequency**	**Percent**
Clinical stage II	1	2.13
Stage 1A	18	38.30
Stage 1B	4	8.51
Stage II	4	8.51
Stage IIIA	1	2.13
Stage IIIC1	2	4.26
Stage IVB (Omentum)	3	6.38
(Not indicated)	14	29.79
Lymphovascular Space Invasion	**Frequency**	**Percent**
Negative	21	44.68
Positive	5	10.64
Not reported (with biopsy post-OR)	8	17.02
Not reported (biopsy only)	13	27.66
LYMPH NODE INVOLVEMENT	**Frequency**	**Percent**
Negative	28	59.57
Positive	4	8.51
Not reported (complex hyperplasia on final; only lymph node assessment done intraoperatively)	2	4.26
Not reported (biopsy only)	13	27.66
ADNEXAL METASTASIS	**Frequency**	**Percent**
Negative	28	59.57
Positive	4	8.51
Not reported (post-OR)	2	4.26
Not reported (biopsy only)	13	27.66

carcinoma and poorly differentiated endometrial cancer with neuroendocrine differentiation noted.

Young patients have increased risk of synchronous tumors of the ovary when compared with the general population (5-29%).[8] Two studies showed ovarian carcinoma associated with endometrial adenocarcinoma in 29% of young women and 4.6% in older women.[7] Soliman noted similar findings.[19] In our study, there was one with synchronous tumor.

In premenopausal women, endometrial carcinoma has a favorable prognosis. Myometrial invasion is one of the most important prognostic factor. Patients with superficially or non-invasive tumors have 80–90% 5-year survival rate, while those with deep invasion have 60–70% survival rate. Ingram found progesterone receptor level, and not estrogen receptor, as the

Table 4. Histopathologic profile of patients diagnosed with endometrial cancer ≤ 30 years old from January 2004 – December 2013

Management	Frequency	Percent
Medical	3	6.38
Surgical	31	65.96
Chemotherapy	2	4.26
Radiotherapy	2	4.26
Not treated	9	19.15

Table 5. Log-rank test for equality of survivor functions

Age category	Events observed	Events expected
1 (<20 years old)	1	0.33
2 (20 – 25 years old)	6	5.90
3 (26 – 30 years old)	18	18.77
TOTAL	25	25.00

chi2(2) = 1.46
Pr>chi2 = 0.4821

Interpretation: There is no significant different KM survival curves by age categories.

single most important prognostic indicator. Women, 26-30 years old, have increased survival beyond 28th month but further analysis revealed no significant difference among these young women.[22]

Our patients mostly presented with heavy menstrual bleeding and irregular menstruation and underwent ultrasound, which revealed thickened endometrium in 21.3% of the subjects. One patient in our study underwent polypectomy for a grossly benign polyp which on biopsy was endometrial carcinoma, endometrioid type. Thus, polyps in young patients are not always benign. Endometrial polyps may be present in those with persistent abnormal uterine bleeding. 5% were malignant in one study. 1.5% in hypertensive patients were malignant, 7.1% were atypical hyperplasia. 4.8% incidence of endometrial cancer in patients with abnormal bleeding referred for SIS was noted.[23,24] Kilcdag noted that polyp number and PCOS were associated with malignancy. PCOS had 9.6 times greater risk. Women with ≥2 polyps had 31.3 times risk of malignancy than those with 1 polyp.[25]

Endometrial sampling in young women with anovulatory cycles is needed for hyperplasia diagnosis and treatment. Endometrial cancer should be considered when evaluating young women with PCOS for abnormal uterine bleeding.[9] One patient in our study had both primary infertility and PCOS, stage II disease, >50% myometrial invasion, and positive lymphovascular space invasion. She only survived for 3 months after surgery.

Total Hysterectomy with Bilateral Salpingo-oophorectomy, with pelvic and aortic lymphadenectomy is the classic treatment for endometrial cancer. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database indicated the preservation of fertility in some cases. Ovarian preservation had no effect on cancer-specific or overall survival in younger women with early-stage.[27]

In Geneva, 3.2% of women with endometrial cancer were ≤45 years old, 18% of them had stage IA, grade 1 endometrial cancer. It is imperative to select good candidates for fertility-sparing methods. Conservative treatment criteria include well-differentiated histology, absence of myometrial invasion, absence of extrauterine or pelvic and para-aortic lymphatic spread, absence of synchronous ovarian tumour,[28] and higher chance of pregnancy.[29]

Young patients are anxious for fertility preservation. Since young patients with stage I and grade 1 carcinomas have a good prognosis, other therapeutic possibilities may be used instead of the standard radical treatment.[17] Progestin therapy alone may be used for fertility-sparing management. Medroxyprogesterone acetate is not always a consistent management for every patient. Progestogens may be associated with embolism, deep-vein thrombosis, lipid metabolism disturbance, atherogenesis, reduced libido and mood disorders.[7] Three of our cases initially had megestrol acetate and medroxyprogesterone before surgery. One had no evidence of disease for 5 years and 2 months.

Well-differentiated adenocarcinoma, endometrioid type express progesterone receptors (PR) and may be suppressed by progestins. Response rate to progestins in PR-positive carcinoma is 70% compared to 16% in PR-negative tumors. These tumors also express gonadotropin-releasing hormone (GnRH) receptors, implying the usefulness of GnRH agonists.[7] Tumor grade is better evaluated by dilatation and curettage. In one study, only 10% of cases diagnosed by curettage were upgraded at hysterectomy compared with 26% among those diagnosed by endometrial biopsy.[29]

Endometrial lesions disappeared in 57%-75% after conservative treatment, recurrence rate is 40% after 7-22 months and 67% after 30 months.[7] In our study, one patient initially managed conservatively died after 2 months from treatment.

CONCLUSION

Majority of our 47 subjects were nulligravid, pre-obese, irregularly menstruating with heavy menstrual bleeding. Some of our subjects showed thickened endometrium and polycystic ovaries on ultrasound and most of them had stage 1 disease. However, there were still cases reported in this study with poor prognostic histologies, which may suggest that young Filipino patients may still present with poor prognostic factors.

One case in this study showed a grossly benign polyp, which turned out to be malignant. Thus, a grossly benign polyp in a young patient may still warrant further investigation as in post-menopausal patients.

The commonly associated risk factors such as hypertension and diabetes mellitus were not noted in our study as opposed to most post-menopausal women. Most patients were pre-obese or overweight (BMI of 27 kg/m2). In this study, the median BMI was 27 kg/m2, which may suggest that non-obese young patients presenting with such features may have underlying malignancy.

Although, a number of subjects were lost to follow up, survival was similar among age groups (30 years old and below).

A young Filipino patient presenting with abnormal uterine bleeding, thickened endometrium and/or polycystic ovaries on ultrasound, or with grossly benign polyp, slightly overweight and without family history of cancer may still warrant further

investigation. An index of suspicion for endometrial malignancy in this young age group is still rational.

LIMITATIONS

Since this was a retrospective study, all data were just based on medical and histopathologic records. Some patients were lost to follow-up after their initial consults. No further assessment and management were done. Data on the final histopathologic reports were not done on a number of patients since no surgical intervention was performed. Thus, the actual survival per case was not accounted for. Some data were not reported and no other means by which these could be verified. Few patients were directly given chemotherapy and were not surgically staged, so that no final histopathologic results were reported. Other limitations were lack of specific data on hormonal history of the pattern of use of OCP, bleeding patterns or irregularities, and clinical signs of hyperandrogenism.

RECOMMENDATIONS

A detailed checklist for risk factors should be provided in the charts. With respect to the proper documentation of the family history of cancer, a detailed diagram of the family pedigree should be included. The patient or the kin if feasible should be contacted to document the actual death or year of recurrence and the survival.

When presented with a young patient, the clinician should not be complacent; endometrial biopsy is still warranted or recommended even in patients without noted risk factors.

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Synchronous Primary Cervical and Fallopian Tube Carcinoma: A Case Report

Cecilia S. Cabanag, MD and Jocelyn Z. Mariano, MD, FPOGS, FSGOP

ABSTRACT

Multiple primary malignant tumors (MPMT) are defined as two or more independent primary malignancies from different sites and are of different histology in the same individual[2]. Incidence of MPMTs ranges from 0.4-21%[7]. Though a primary fallopian tube carcinoma (PFTC) is a rare malignancy with only <1% of female genital malignancies, a synchronous cervical and fallopian tube carcinoma is a more uncommon clinical entity with only a few documented cases worldwide.

This is a case of a 64-year-old nulligravid, who presented with post-menopausal bleeding. She underwent fractional curettage. Histopathology of the endometrial scrapings and endocervical tissue showed Squamous Cell Carcinoma, Large Cell Non- Keratinizing. She subsequently underwent exploratory laparotomy for Stage IB2 cervical carcinoma vs a primary endometrial carcinoma with cervical extension. Contemplated radical hysterectomy was abandoned because of the dense adhesions to the bladder. The fallopian tubes were noted to be bulbous with multiple fleshy papillations, hence bilateral salpingo-oophorectomy, biopsy of the tumor implant, excision of left external iliac lymph node and infracolic omentectomy was done. Histopathology showed High-grade Papillary Serous carcinoma of the fallopian tubes with lymphovascular space invasion; Metastatic Papillary Carcinoma of bilateral ovaries and external iliac lymph nodes. Final staging according to FIGO system was Cervical carcinoma Stage IB2 and fallopian tube carcinoma stage IIIB.

She completed 6 cycles of Carboplatin-Paclitaxel regimen. External beam radiotherapy at 50 Gy and intracavitary brachytherapy delivered in four fractions of 6 Gy was administered. Patient has remained in follow-up, and at 8 months post-diagnosis, there has been no documented evidence of recurrent disease.

Keywords: *case report, multiple primary malignant neoplasms, multiple gynecologic carcinoma, synchronous primary cervical and fallopian tube carcinoma*

INTRODUCTION

Multiple primary malignant neoplasms (MPMNs) are two or more independent primary malignancies arising from different sites and are of different origins in the same individual[3]. Research studies showed that multiple primary malignancies occur at 0.4-17%[14].

Only 0.5-1.7% of women with gynecological malignancies have synchronous primary cancers of the female genital tract[1]. Majority of these are endometrial and ovarian in origin. Primary fallopian tube carcinoma (PFTC) comprises 0.14 – 0.18% of female genital malignancies and it is more unusual to find a fallopian tube with a synchronous cervical carcinoma. Cervical carcinoma, however, is a frequent neoplasm in which 80% to 85% are squamous cell carcinomas[8]. While management for fallopian tube carcinoma is similar with epithelial ovarian carcinoma, standard treatment of cervical cancer involves surgery or radiotherapy or a combination of both. Overall survival rates for both malignancies are stage dependent.

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The authors did not report any potential conflicts of interest.

CASE REPORT

This is a case of a 64-year-old nulligravid, who presented with post-menopausal bleeding, described as brownish, non-foul vaginal discharge. Transvaginal ultrasound showed a slightly enlarged uterus with thickened dilated endometrium (7.8 mm) with possible hematometra. On pelvic examination, the cervix was nodular, about 3 cm in diameter; uterus was slightly enlarged; no adnexal mass nor tenderness noted; parametria were free and pliable. An abnormal uterine bleeding secondary to endometrial pathology with cervical involvement was considered.

Patient underwent cervical punch biopsy and fractional curettage. Histopathologic report showed Squamous cell carcinoma, Non- keratinizing, with associated Cervical Intraepithelial Neoplasia III (High Grade Squamous Intraepithelial Lesion); Endometrial fluid showed malignant cells consistent with Squamous Cell Carcinoma. Assessment was Squamous Cell Carcinoma, Large Cell Non- Keratinizing, cervix, Stage IB2 VS Primary endometrial carcinoma with cervical extension. A primary endometrial pathology was considered since patient was a nulligravid, had early menarche and the endometrial lining was thickened on ultrasound. She was advised to undergo radical hysterectomy with complete surgical staging.

Intraoperatively, peritoneal fluid was collected for cytology. Multiple fleshy implants were noted on the peritoneum and pelvic walls. The isthmic portion of the uterus was densely adherent to the bladder and to the recto-sigmoid area, obliterating the cul de sac. Multiple fleshy papillations were noted on fallopian tubes (Figure 1). There were multiple tan-

colored nodules and erythematous papillations on the bladder flap and in between loops of intestines and mesentery. Plan for radical hysterectomy was abandoned, instead proceeded with bilateral salpingo-oophorectomy and adhesiolysis, followed by biopsy of the implants noted on the cul de sac. There was a 2.5 cm x 1.5 cm nodular lymph node on the external iliac vein. Multiple erythematous nodules were noted on the omentum. Excision of the left external iliac lymph node and infracolic omentectomy was done. On further inspection, the liver surface, paracolic gutter and diaphragmatic surface were smooth and free of implants.

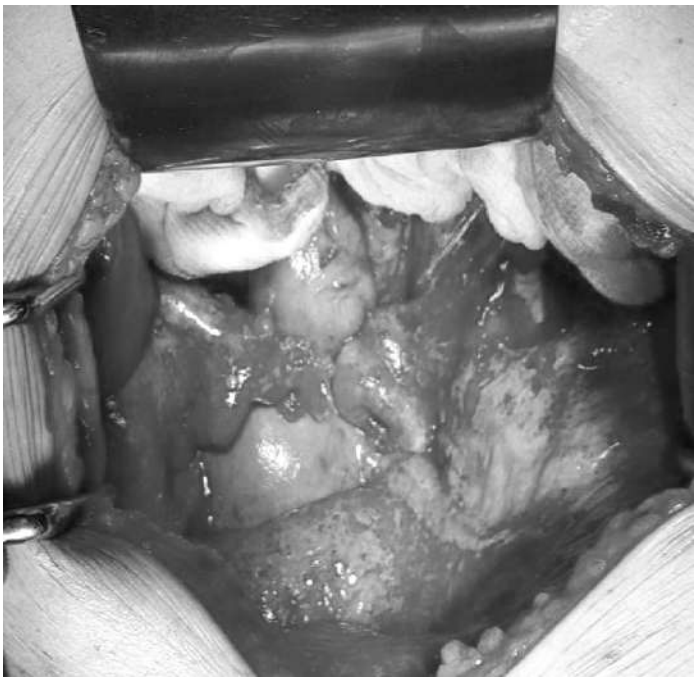

Figure 1. Multiple fleshy papillations on both fallopian tubes and multiple tan-colored nodules and erythematous papillations on the bladder flap and in between loops of intestines and mesenteries

Microsections of implants from fallopian tubes and ovaries showed sheets and nests of neoplastic cells forming short delicate papillary structures and eccentrically located hyperchromatic nuclei, some exhibiting hob-nailing and with variable amount of basophilic cytoplasm (Figure 2). The four pelvic lymph nodes recovered were positive for tumor metastasis. The smears and cell block from peritoneal fluid showed clusters of neoplastic cells with mostly eccentric hyperchromatic nuclei and variable amount of basophilic cytoplasm. Histopathology showed High-grade Papillary Serous carcinoma of the fallopian tubes with lymphovascular invasion; Metastatic Papillary Carcinoma of bilateral ovaries and external iliac lymph nodes.

Serial serum CA-125 level measurement was done on follow-up visits. Baseline serum CA-125 was elevated (449.6 U/mL) and returned to normal level after 2nd cycle of chemotherapy (27.68 U/mL). Patient underwent external beam radiotherapy. The whole pelvis was irradiated to 50 Gy, given in 1.8 Gy per fraction via 3D conformal techniques for 28 fractions with a 6-15MV linear accelerator.

Intracavitary brachytherapy was delivered in 4 fractions (5-6Gy at 0.5cm from the surface using 2.5-3.0cm cylinder blocks)

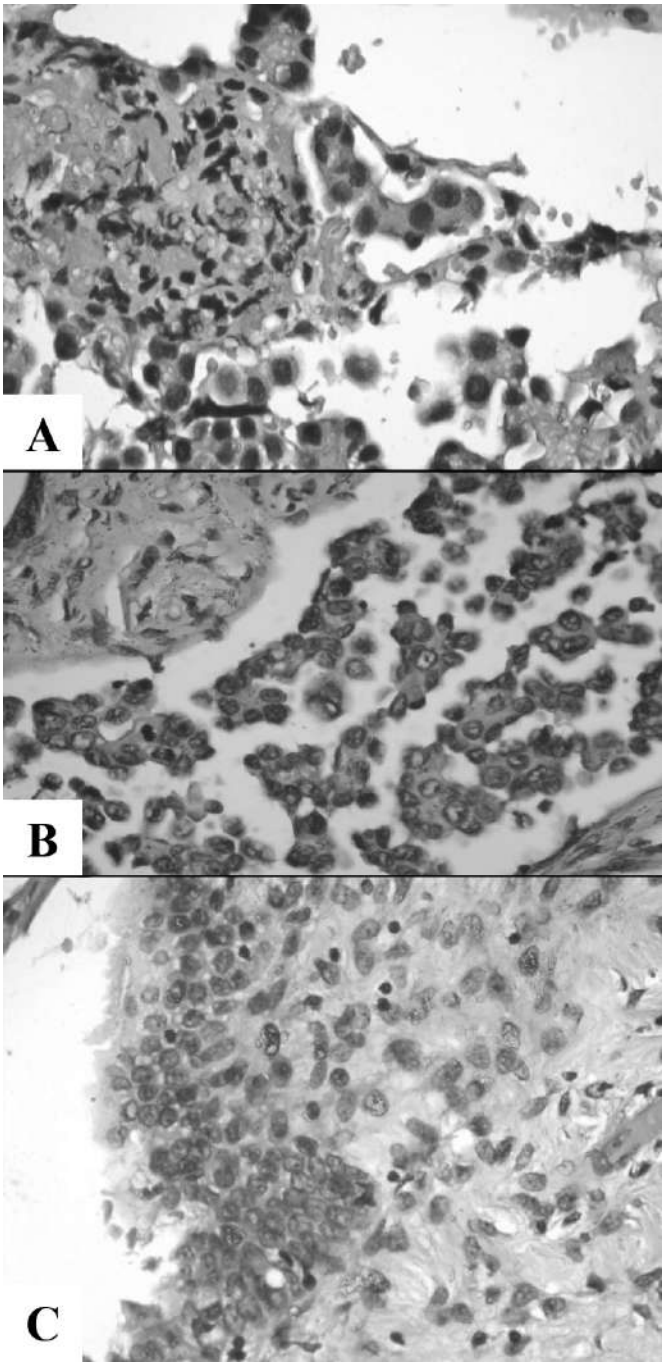

Figure 2. Microsections from the tumor implant (A), left fallopian tube (B) and right fallopian tube (C), showing sheets and nests of neoplastic cells with eccentrically located hyperchromatic nuclei, exhibiting hob-nailing and with variable amount of basophilic cytoplasm consistent with Papillary Serous Carcinoma. H&E, 40x

for a total of 23Gy to the cervix. Marked cervical stenosis and vaginal atrophy prevented insertion of tandem and ovioids (Henschke applicator). Overall treatment time was 56 days.

DISCUSSION

Multiple primary malignant neoplasms (MPMN) were first described by Warren and Gates in 1932. Neoplasms are “synchronous” when the second primary carcinoma is diagnosed within 6 months of the primary carcinoma; and

"metachronous", when the second primary carcinoma is diagnosed more than 6 months after the diagnosis of the primary carcinoma. The incidence of MPMTs ranges from 0.4-21%[7].

As explained by Tong Seo-Yun et al, embryologically similar tissues, when simultaneously exposed to hormones or carcinogens may develop synchronous neoplasms in genetically susceptible individuals.[21] The theory of "Secondary Mullerian system" proposed that the epithelia of cervix, uterus, fallopian tubes, ovaries and peritoneal surface have shared molecular receptors responding to carcinogenic stimulus leading to synchronous development of multiple primary malignancies.

Criteria proposed by Warren and Gates is used for the diagnosis of double primary malignant neoplasms. Following these diagnostic criteria for synchronous tumors, the endocervical tissue and fallopian tube showed different histopathologic report. Endometrial scrapings and endocervical tissue after fractional curettage, showed squamous cell carcinoma, non-keratinizing; with associated cervical intraepithelial neoplasia III (high Grade squamous intraepithelial lesion). Fallopian tubes showed papillary serous carcinoma, high grade, while ovaries and external iliac lymph node showed metastatic papillary carcinoma.

There are only few documented cases of synchronous fallopian tube and cervical carcinoma in the medical literature. Review of Philippine medical literature has not yet shown documented cases of synchronous fallopian tube and cervical carcinoma.

Primary fallopian tube carcinoma (PFTC) comprises approximately 0.14 – 0.18% of female genital malignancies. It occurs in women aged 18 to 88 years and usually occurs between 4th and 6th decades of life. In 40% to 50% of cases, nulliparity and lower parity are risk factors for PFTC. The survival percentage of patients with PFTC is low, from 20-50%, as its pre-operative diagnosis incidence is only about 4% and up to 50% are missed intra-operatively. Pre-operative diagnosis has been difficult due to its low incidence and differential diagnosis with ovarian tumors. Histologically and clinically, it shares similar characteristic with epithelial ovarian carcinoma (EOC). As explained in the case report done by Sahu et al (2014), the criteria for distinguishing PFTC from other gynecological malignancy include: (1) the tumor should arise from endosalpinx; (2) histological pattern should produce the epithelium of tubal mucosa (3) the tubal wall if involved, a transition from benign to malignant proliferation should be identified (4) ovary and endometrium should either be normal or with a tumor smaller than that in the tube. All of these criteria were fulfilled in our case.

The Latzko's triad of symptoms consists of intermittent profuse watery serosanguinous vaginal bleeding, colicky pelvic pain, and an abdominal or pelvic mass. In the literature review done by Lau et al (2013), most common clinical presentation was nonspecific pelvic pain (37.5%), followed by abnormal vaginal bleeding (31.2%), pelvic mass (18.8%) and gastrointestinal symptoms (12.5%). Patient's profile exemplified more of an endometrial pathology with a probable cervical involvement based on pelvic examination. According to Lobo et al (2012), 10% to 40% of women with fallopian tube carcinoma have abnormal cervical cytology results, which includes adenocarcinoma and or atypical glandular cells (AGUS). It was recommended that cancer antigen 125 (CA-125) level and transvaginal ultrasound to rule out ovarian and fallopian tube cancer should be done in women with such findings who have a negative workup for endocervical and endometrial carcinoma.

There are no specific guidelines regarding the management of synchronous primary gynecological neoplasms. Management should be largely individualized considering several parameters, such as age of patient, disease type, disease stage, disease grade, and extent of the neoplastic invasion.

Clinically, PFTC resembles epithelial ovarian cancer in terms of age of presentation, association with low parity, frequent infertility and genetic abnormality. It is also similar in surgical staging, its management and indications for adjuvant chemotherapy[3].

Surgery is the treatment of choice for PFTC. Surgical principles are the same as those used for ovarian cancer. Adjuvant chemotherapy is given prophylactically to patients after surgery[5].

Standard treatment of early-stage cervical cancer may involve surgery or radiotherapy or a combination of both. According to Lobo et al (2012), patients have equally good outcomes with radical surgery or radiotherapy. In this case, initial plan of radical hysterectomy with bilateral salpingo-oophorectomy was not done because of the adhesions on the vesicouterine area, hence proceeded with bilteral salpingo-oophorectomy with biopsy of implants and bilateral lymph node dissection.

Surveillance strategies for both malignancies should include serum CA-125 monitoring and regular pelvic examination. Serum CA-125 level, if initially elevated, should be every 2 to 4 months for the first 2 years, every 3 to 6 months for the following 3 years, and then annually after 5 years[8].

SUMMARY

A synchronous cervical and fallopian tube carcinoma is a more uncommon clinical entity with only a few documented cases worldwide. Low incidence of PFTC makes pre-operative diagnosis difficult, with most of the cases diagnosed with another carcinoma intraoperatively.

A case of a 65-year-old, nulligravid with squamous cell carcinoma of the cervix and fallopian tube carcinoma was presented. She underwent 6 cycles of carboplatin- paclitaxel regimen followed by complete radiotherapy after bilateral salpingo-oophorectomy, adhesiolysis and bilateral lymph node dissection. At the time of this report, patient is two months post-radiation. CA-125 levels are normal.

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When Everything Turns to Black – MAN: A Sign of Impending Doom

Malignant Acanthosis Nigricans (MAN) in a Patient with Endometrial Carcinoma

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ABSTRACT

Being diagnosed with cancer can have a huge impact not only on patients, but also on their families. Physical symptoms, such as pain, nausea or fatigue limit one's ability to perform daily tasks thus altering social and work roles. Common physical manifestations of malignancy may also cause an altered self-image leading to lower self-esteem. Dermatoses, although rare, could cause significant distress especially if they are abrupt, widespread and generally noticeable.

Such is the case of our patient, CF, 44/G0, who presented with Malignant Acanthosis Nigricans, prior to being diagnosed with malignancy. She initially presented with a 3-month history of pruritic plaques on the neck and intertriginous areas followed by sudden and rapid spread of hyperpigmentation and thickening of areas of the skin from the face, chest and trunk down to the extremities. After a month, she had profuse vaginal bleeding with increasing abdominal girth, weight loss and anorexia. Her worsening condition prompted consult and she was eventually diagnosed with Malignant Acanthosis Nigricans (MAN) associated with Endometrial Carcinoma with extrauterine spread. The presence of bilateral femoral thrombi on CT Scan deterred the possibility of doing extended surgical staging/ tumor debulking until an IVC filter was placed. After three cycles of Carboplatin and Paclitaxel, there was no significant change in her symptoms. Her hyperpigmentation appeared darker and more diffuse, the fissures on her lips deeper, and her soles and palms more thickened and coarser. After her 3rd cycle of chemotherapy, she developed chemotherapy-induced diarrhea, markedly worsening her condition. She eventually succumbed to pulmonary embolism.

Malignant acanthosis nigricans associated with tripe palms is an early manifestation of internal malignancies. Thorough and prompt work-up for these patients may lead to early intervention and treatment. As gynecologic oncologists, we must be familiar with the multitude of symptoms that our patient can present with. Being the "monumental façade of the human body," the skin may serve as our guide in disease monitoring as it gives us clues as to what is happening inside our body.

Keywords: *Malignant acanthosis nigricans, paracutaneous neoplasia, endometrial cancer*

INTRODUCTION

Dermatologic manifestations of malignancy, although rare, could cause significant distress among cancer patients especially if they present abruptly, widespread and generally noticeable.

Paraneoplastic neoplasias, which include Acanthosis Nigricans, are a group of dermatologic lesions that may be benign but may also signal an underlying malignancy. Acanthosis nigricans (AN) is characterized by the presence of symmetric velvety hyperpigmented, verrucous plaques of the intertriginous surfaces of the axilla, nape, inframammary region, abdominal folds, groin, antecubital and popliteal fossae and of the mucocutaneous regions. It is associated with insulin-resistance, drugs, endocrine disorders, chromosomal abnormalities and malignancy. About 20% of Acanthosis Nigricans is said to be associated with intra-abdominal malignancies and are known as malignant acanthosis nigricans (MAN). Eighteen percent (18%) of these precede the malignancy while 61% occur simultaneously. MAN is most commonly associated with gastric adenocarcinoma, being extremely rare among gynecologic malignancies. Although the pathophysiology is poorly understood, it is postulated that cutaneous paraneoplasias parallel that of the behavior of the underlying malignancy.[1] Knowledge of the existence of such dermatologic manifestations, could lead to earlier diagnosis and intervention.

CASE REPORT

This is the case of CF (Figure 1), a 44-year-old, nulligravid, who initially presented with a 3-month history of pruritic plaques on the neck and intertriginous areas followed by sudden and rapid spread of hyperpigmentation and thickening of areas of the skin from the face, chest and trunk then to the extremities. Two months prior to consultation, she had profuse vaginal bleeding soaking 2 pads per day associated with increasing abdominal girth, weight loss and anorexia. This prompted consult at a local hospital wherein she was diagnosed to have an abdominopelvic mass with massive ascites and was advised surgery.

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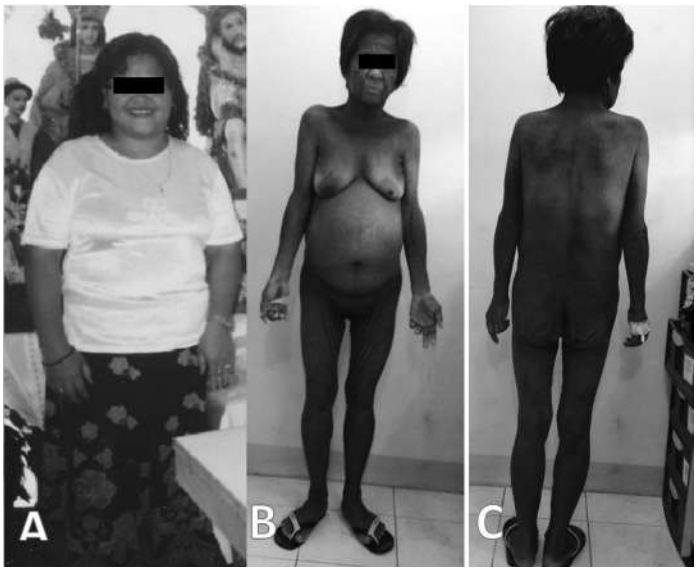

Figure 1. Comparison of CF before and after cancer diagnosis. A. Photo of CF taken 10 years prior to cancer diagnosis. B. Distribution of MAN taken upon admission (front). C. Distribution of MAN taken upon admission (back)

She presented in our institution, already with persistent abdominal pain, rapid abdominal enlargement, decreased caliber in stools, increased frequency in urination, as well as increasing infiltration and hyperpigmentation of the velvety plaques on her skin.

Review of her past medical history did not show any known comorbidities (thyroid problem, diabetes mellitus and bronchial asthma), nor did she take any maintenance medications or supplements. There was no family history of cancer, diabetes, bronchial asthma or any endocrine disorder.

On examination, the patient was ambulatory and not in cardiorespiratory distress. She was overweight with BMI of 25. There was generalized hyperpigmentation (Figure 2) with ill-defined velvety plaques more prominent over the face, neck, axillae, inter and inframammary areas and popliteal fossa. Minute examination of the skin showed hyperpigmented, soft, pedunculated papules, with corrugated thickening of the palms and hyperaccentuation of the ridges of the palms and gluteus. The vermillion border of the lips also showed verrucous and papillomatous overgrowths. She had an abdominal girth of 98 cm with note of fluid wave. There were 2 palpable abdominopelvic masses – 10 x 10 cm solid mass on the RLQ, and 8 x 8 cm vague mass on the LLQ. On internal examination, there was a 6 x 5 cm cystic mass at the right vaginal wall extending up to the lower third of the vagina. The cervix was smooth and measured 2 x 2 cm. The uterus was enlarged to 12 weeks size with note of 2 adnexal masses – the right seemed to be superior and anterior to but was densely adherent to the corpus and the left seemed posterior to the uterus.

Upon presentation at our institution, she underwent biopsy of the endometrium which showed **Endometrial Carcinoma (endometrioid type)** (Figure 3), while biopsy of the plaques on her nape and tripe palms showed **Acanthosis Nigricans** (Figure 4). Cytology of the peritoneal fluid did not show any malignant cell.

Serologic studies which included blood chemistry, CBC with

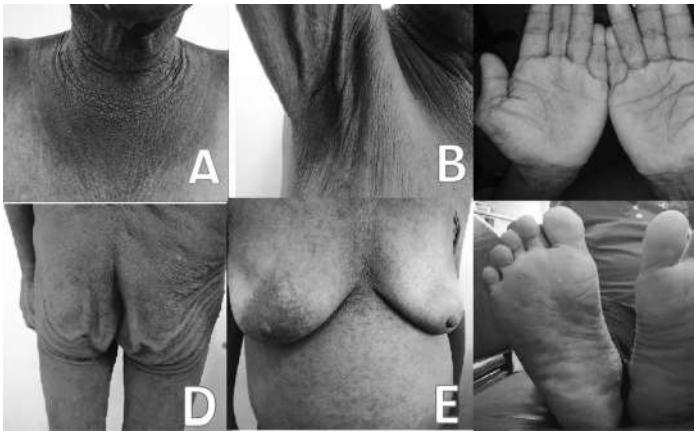

Figure 2. Cutaneous manifestations of CF: Multiple hyperpigmented velvety plaques with prominent ridges on the (a) neck, (b) axillary area, (c) palms, (d) sacrum, (e) inframammary area and (f) soles of the feet.

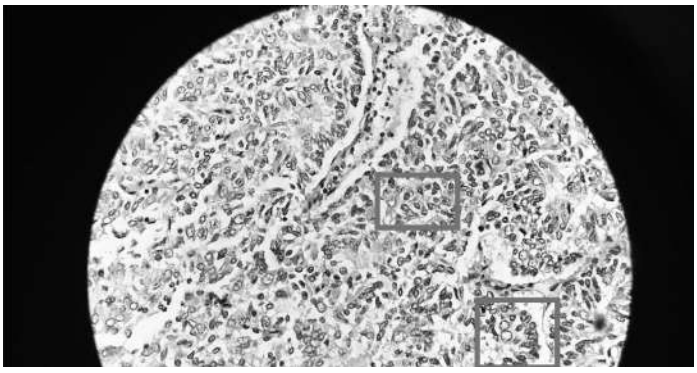

Figure 3. Histopathologic examination of the endometrial biopsy showed endometrioid adenocarcinoma showing irregular glands lined by columnar epithelium with pseudostratified nuclei and mild cytologic atypia.

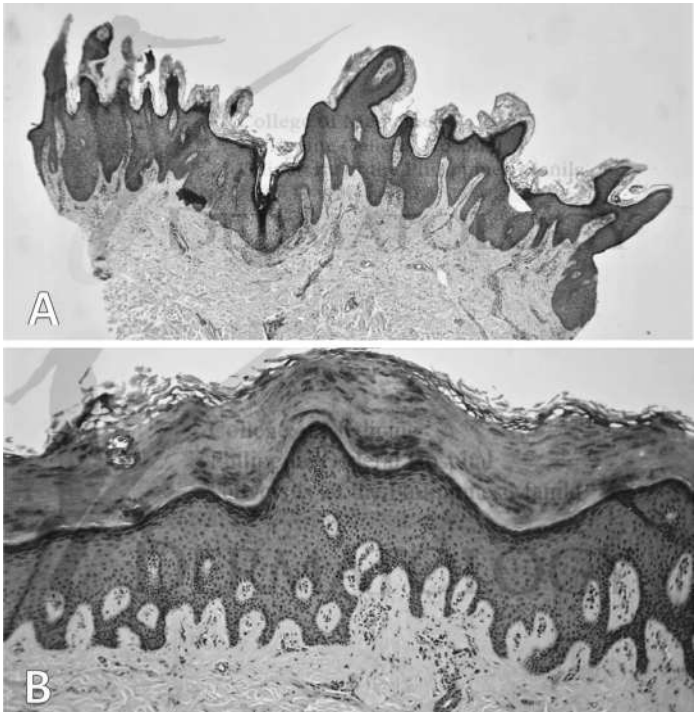

Figure 4. A. Histopathologic examination of the plaque on the left shoulder showed acanthosis, papillomatosis with basal layer pigmentation. B. Sections of the plaque on the left palm also revealed acanthosis, papillomatosis with overlying compact orthokeratosis

differential count, tumor markers, coagulation studies and liver functions tests were all within normal limits. CA-125 (2245 U/mL) and CA 19-9 (7024 U/mL) were both elevated, while CEA (4.27 ng/mL) was within normal range. Screening tests for hyperandrogenic and hyperestrogenic states (glucose, plasma insulin, estradiol and testosterone), which are the common causes of Acanthosis Nigricans, only showed dyslipidemia.

Initial imaging studies (Figure 5) showed an 8.9 x 3.4 x 4.2 cm endometrial mass (with almost full thickness myometrial invasion) with extrauterine spread to the ovaries (RAM – 6.8 x 7.2 x 4.6 cm, LAM – 8.8 x 8.9 x 9.4 cm) and pelvic lymph nodes. Extended surgical staging was initially contemplated. However, her abdominopelvic CT Scan showed bilateral femoral thrombi which required insertion of IVC filter prior to the surgery.

In the interim, our patient underwent two cycles of

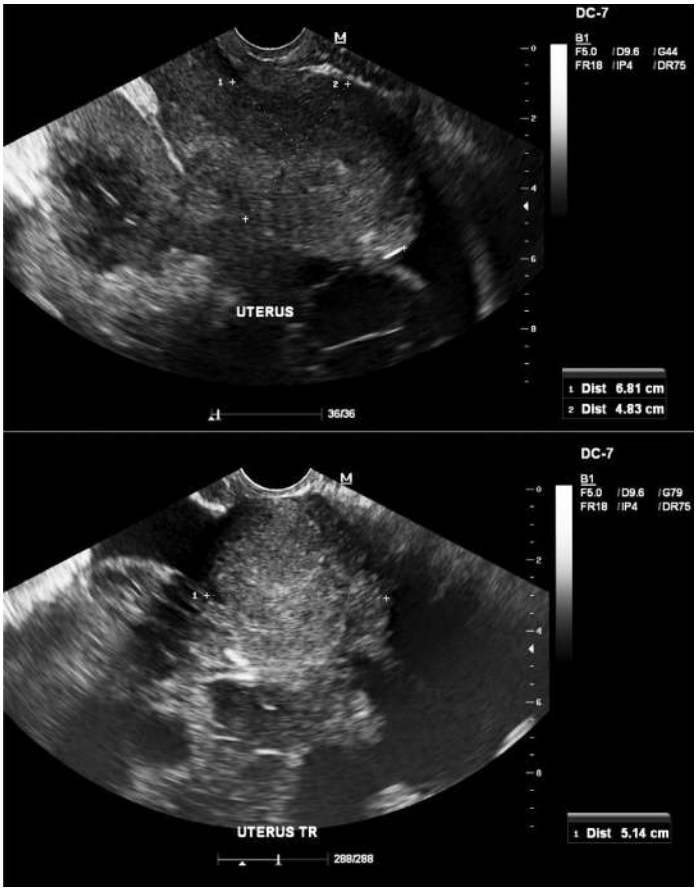

Figure 5. Transvaginal Ultrasound showing endometrial cancer with ovarian involvement

Carboplatin and Paclitaxel which did not result to any significant change in her symptoms. Prior to her 3rd cycle of chemotherapy, her hyperpigmentation appeared darker and more diffuse, the fissures on her lips deeper, and her soles and palms more thickened and coarser.

After her 3rd cycle of chemotherapy, she developed chemotherapy-induced diarrhea resulting in generalized weakness and multiple electrolyte abnormalities for which she was subsequently admitted. During this admission, she was noted to have shortness of breath attributed to pneumonia and bilateral pleural effusion. She underwent paracentesis obtaining 2.5 liters of brownish fluid which afforded temporary relief of symptoms. She was maintained on IV antibiotics to address her pneumonia and was also maintained on Enoxaparin. An attempt to optimize her to undergo the planned surgery was done as funds for her IVC filter had already been obtained.

Her shortness of breath persisted despite being maintained on O2 support. Chest ultrasound showed mixed echoes on the left lung and 150 cc pleural effusion on the left lung with no safe window for thoracentesis. ABG showed respiratory alkalosis. Evolving pulmonary embolism and pulmonary metastasis were considered, hence, Warfarin was also started. CA-125 at this point was 1736 U/mL.

Unfortunately, CF suddenly developed acute respiratory failure with chest pain and eventually succumbed to pulmonary embolism.

DISCUSSION

I. Acanthosis Nigricans

Paracutaneous neoplasia are a group of dermatoses that arise secondary to an underlying malignancy elsewhere in the body. Malignant acanthosis nigricans (MAN) is a form of paraneoplastic syndrome which is much less common but more aggressive than the other types of such syndrome. It is characterized by dark, coarse thickened skin with a velvety texture that symmetrically affects the neck, axillae, groin, antecubital and popliteal fossa.[2] It can be broadly categorized into benign (obesity-associated, syndromic, acral, drug-induced, hereditary), malignant and mixed type forms. Benign AN which comprises 80% of cases is insidious in onset and less widespread in distribution.[3] In contrast, malignant acanthosis nigricans (MAN) is rapid in onset, more widespread and has a predisposition to include oral manifestations.[3]

Diagnosis of AN is largely clinical with histopathology needed only for confirmation. Typical findings include papillomatosis, hyperkeratosis and hyperpigmentation of the basal layer. [3]

MAN is clinically indistinguishable from the benign forms. However, a review of patients by Curth showed that criteria for the association of dermatoses and neoplasia include :

1. The malignancy and the skin disease are of concomitant onset – this means that the neoplasm is diagnosed at the same time as the diagnosis of malignancy or shortly following the diagnosis.
2. The course of the skin disease and malignancy run parallel – therapy of the malignancy results in resolution of the dermatosis and recurrence of the dermatosis signals recurrence of the malignancy.
3. There is a uniform relationship between the specific skin disease and the malignancy.
4. There is a statistically significant association between the specific skin disease and the malignancy.
5. A genetic association exists between the two.

Ortega-Loayza reports that fulfilling the first 2 criteria is sufficient to consider a dermatosis as neoplastic.[4] Malignant acanthosis nigricans was considered in our case due to 1) the sudden and rapid progression of the cutaneous lesions, 2) the temporal relationship of MAN and diagnosis of endometrial cancer, 3) the absence of benign conditions that could explain her cutaneous manifestations.

Table 1. Review of Cases of Malignant Acanthosis Nigricans

Author, Year	Type of Malignancy	Presentation	MAN Distribution	Treatment	Treatment Response
Dingley, 1957	Ovarian	Warts presenting on arms, legs, and trunk; dry/sore tongue and cheeks	Arms, legs, trunk, face, oral, palms, soles,anus, groin, axillae	Laparotomy, deep Xray pelvic therapy	No obvious change in the skin lesions after laparotomy; while ongoing Xray pelvic therapy, a number of lesions had flattened, hands and perianal area were smoother and less thickened
Requena, 1995	Ovarian	Increasing hyper-keratosis of palms, anorexia and weight loss, night sweats	Palms, dorsum of hands, axillae and groin		
Oh, 2010	Ovarian		Neck, axillae, groin, oral, forearms, palms and soles	THBSO, PALS followed by Carboplatin and Paclitaxel for 6 cycles	Skin lesions gradually resolved after the third cycle of chemo; Malignancy in remission after 6 cycles
Singh, 2013	Ovarian	Fatigue, weight loss and night sweats	Face and body	THBSO, BLND, PALS, IO, RPB; chemotherapy planned post surgery	Not indicated
Garzitto, 2015	Ovarian	Vitiligo and AN	Axillary, inframammary region, inguinal, genital, perioral, tripe palms	Tumor excision of poorly differentiated large cell adenocarcinoma	AN and vitiligo persisted after tumor excision
Curth, 1962	Endometrial	Vaginal discharge, postmenopausal bleeding	Dorsa of hands, forearms, back, trunk, legs, umbilicus, axillae, perianal and vulvar	Data unavailable	Data unavailable
Gorisek, 1997	Endometrial	Postmenopausal menorrhagia	Tripe palms, dorsal neck, axilla, inframammary region, abdominal folds, inguinal and forearms; oral	Wertheim's hysterec-tomy followed by intra-vaginal radiotherapy; Etretinate; PUVA	Regression of MAN and TP 2 within 2 months post-Etretinate; No essential mitigation of the pruritus from PUVA
Meckhail, 2002	Endometrial	Hypothyroidism, obesity	Tripe palms, face, neck, axillae, groin and inframammary region	TAHBSO followed by Carboplatin and Paclitaxel for 6 cycles	Significant improvement of the skin, especially that of the palms after 2 cycles; NED after 6 cycles with a brief flare of acanthosis 4 months post treatment
Longshore, 2003	Endometrial	Anorexia, weight loss	Face, axillae, groin, hands, soles, inframammary folds	TAHBSO, PALS followed by Taxol and Carboplatin for 6 cycles	Skin findings improved, but did not resolve completely; Malignancy in remission
Chu, 2014	Endometrial	Previous endometrial carcinoma	Face, elbows, pudendum, groin, axillae, Nipples	THBS 9 years before onset of symptoms; palliative treatment for stage IVB	Patient died 4 months after recurrence
Deen, 2017	Endometrial	Pruritus, hyperpig-mentation, menorrhagia	Axillae, arms, abdominal folds, face, ears	Hysteroscopy with D&C; Mirena insertion	Not indicated
Mikhail, 1979	Cervical	Condyloma of the perineum	Face, oral involvement, palms and soles, perineal region, inframammary region, vulva, anus, gluteal cleft, upper thigh, axillae	Melphalan (Alkaran) ; recurrence was treated with Fluorouracil	Dramatic improvement of skin lesions after 9 months of treatment; remission lasted for 1 year; patient died 3 years post-Melphalan
Tsai, 2004	Cervical	Cervical cancer	Palms, dorsum of hand, soles, thighs, neck, axillary, waist	Surgical excision fol-lowed by 6 courses of chemotherapy; liquid nitrogen for lesions that appeared 3 years post initial surgery	With note of improvement of skin lesions after chemotherapy

II. Malignant Acanthosis Nigricans (MAN)

Literature has shown that the malignant form of acanthosis nigricans precedes the diagnosis of malignancy in 18% of patients, 61% simultaneous with cancer and 21% after tumor detection.[6] It is most commonly associated with intra-abdominal malignancies particularly gastric adenocarcinoma, but has also been linked with pancreas, colon, lungs, intestines, liver, kidneys and bladder.[6] Although very rare, it may occur in association with gynecologic malignancies. MAN often coexists with other markers of malignancy: the sign of Leser-Trelat, florid cutaneous papillomatosis, and hyperkeratosis of the palms and soles. The presence of tripe palms (AN of the palm) is associated with internal malignancy 90% of the time and it often preceded the diagnosis of cancer by as long as 15 months.[7] Survival after discovery of MAN is less than 2 years.[8]

III. Malignant Acanthosis Nigricans and Gynecologic Malignancy

On review of available literature, a total of 14 cases of MAN have been reported – 6 cases of ovarian carcinoma, 6 cases of endometrial carcinoma and 2 cases of cervical carcinoma.[3] The patients were aged 28 – 83 years old and they usually present with tripe palms and MAN in the axillae.

Acanthosis nigricans is caused by factors that stimulate the proliferation of epidermal keratinocyte and dermal fibroblast. In the benign form, this is probably the insulin-like growth factor α (IGF-1). In the malignant form, 5 cytokines (TGF α, IGF-1, epidermal growth factor, fibroblast growth factor and melanocyte stimulating hormone α) have been theorized to be the link between MAN and gynecologic malignancy.[2] These theories have been strengthened by cases in which the skin improved following treatment of the malignancy (Table 1).

TGF α produced by cancer cells is structurally similar to EGF-α and both stimulates growth and differentiation of normal keratinocytes by activation of the Mitogen Activated Protein Kinase (MAPK) ERK pathway. Fibroblast growth factor, particularly FGFR3, also acts on the MAPK ERK pathway to induce proliferation. [9] An increase in melanocyte-stimulating hormone alpha (MSH-α) will directly cause darkening of the skin. More recently, a role for a tyrosine kinase receptor in the basal cell of the epidermis has been proposed.[10]

The development of MAN in our patient could be due to the increased expression of TGF α, IGF-1 and FGF1 among patients with endometrial cancer.[11]

Based on Curth's postulates, the course of cutaneous paraneoplasia parallels that of the underlying malignancy. A review of the available literature on MAN (Table 1) have shown that most patients experienced improvement in their symptoms after receiving at least two cycles of chemotherapy or months after radiation therapy. Total resolution of both the MAN and the malignancy were also seen in some of the cases reported. In this regard, the progression of skin lesions of our patient and her worsening clinical condition was actually a reflection of the behavior of her internal malignancy. Had our patient consulted upon the early manifestation of her skin lesions, we could have intervened earlier. She could have benefited from primary debulking surgery followed by chemotherapy. This case illustrates the need for having a keen clinical eye and an aggressive approach for patients presenting with paraneoplastic dermatoses.

D. CONCLUSION AND RECOMMENDATIONS

A cancer diagnosis causes significant physical, psychological, emotional and social distress, not only on the patient but also to their families. As such, timely diagnosis and appropriate treatment may translate to a favorable outcome in cancer management.

As gynecologic oncologists, we must be familiar with the multitude of symptoms that our patient can present with. Being the "monumental façade of the human body," the skin gives us clues as to what is happening inside our body.[9] Malignant acanthosis nigricans along with tripe palms has been identified as an early manifestation of internal malignancies. A thorough work-up for possible causes should be instituted after such lesions have been identified.

The sudden onset of hyperpigmentation in our patient could have given us a clue of a developing malignancy. The progression of her cutaneous lesions despite undergoing systemic chemotherapy and a decreasing trend of CA-125, could have warned us of the impending doom that our patient was facing. The presentation of our patient already gave us a clue on what is happening inside her body, which is congruent with literature findings that MAN's course parallels that of the disease. Had we intervened earlier, she could have had better outcomes.

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Small Cell Neuroendocrine Tumor of the Vagina: A Case Report

Niña Kriste P. Mendoza, MD and Divina Ghea B. Mata-Carrillo, MD, FPOGS, FSGOP

ABSTRACT

Primary cancer of the vagina is rare and constitutes less than 2% of all gynecologic malignancies. Primary vaginal small-cell neuroendocrine tumor is even rarer and highly aggressive. It is a condition with substantial clinical challenges because of the tumor heterogeneity and rarity leading to a lack of standard guidelines for therapy. This is a case of a 65 year-old female with a vaginal mass associated with bleeding. On physical examination, a polypoid mass attached to the distal third of the anterior vaginal wall was noted. Treatment modalities include surgical excision of the mass, followed by radiation therapy. Histopathology showed a picture suggestive of high-grade small cell neuroendocrine tumor of the vagina. The patient achieved complete response and remission for eight months post primary treatment. There have been only 28 reported cases in literature. This is the first documented case in this institution.

Keywords: *neuroendocrine tumor, postmenopausal bleeding, vaginal cancer*

INTRODUCTION

Primary small cell neuroendocrine tumor of the vagina was first reported by Scully et. al. in 1984. This is a rare neoplasm with only 28 cases reported in literature. This type of tumor exhibits aggressive clinical behavior and has a poor prognosis. Since the disease is so rare while being highly aggressive, there is still no consensus regarding the optimal therapy. This is a case report of a postmenopausal woman with a malignant polypoid vaginal mass which was managed conservatively by primary surgical approach and adjuvant pelvic external beam radiotherapy. There was complete regression of the lesion after the primary treatment, and the patient was disease free for 8 months after radiation therapy.

CASE PRESENTATION

E.M. is a 65-year-old female, widow, G6P6 (6005), Roman Catholic from Bacolod, Lanao del Norte who was admitted for vaginal mass associated with vaginal bleeding.

Six months prior to admission, the patient noted a peanut-sized mass at the introitus associated with intermittent vaginal bleeding soaking 2 pads per day, lasting for 7 days. Three months prior to admission, the patient noted rapid enlargement of the mass reaching approximately the size of a fist. It was still associated with vaginal bleeding soaking 8 pads per day, lasting for 10 days. Three weeks prior to admission, there was recurrence of vaginal bleeding associated with dizziness and body malaise. This prompted consultation and subsequent admission at a private hospital as a case of severe anemia. She was transfused with 4 units of packed red blood cells and further work-up was done including CT scan of the pelvo-abdominal area. Sharp incision biopsy under IV sedation of the vaginal mass was also done, which revealed Rhabdomyosarcoma on histopathologic examination (Fig. 1). She was advised surgical management, thus she was subsequently referred to a public tertiary hospital due to financial constraints.

On bimanual pelvic examination at the outpatient clinic of the government tertiary hospital, there was a polypoid pedunculated mass measuring approximately 4 x 5 x 2 cm, attached to the distal third of the anterior vaginal wall, with no subvaginal tissue involvement.The mass was located 1 cm from

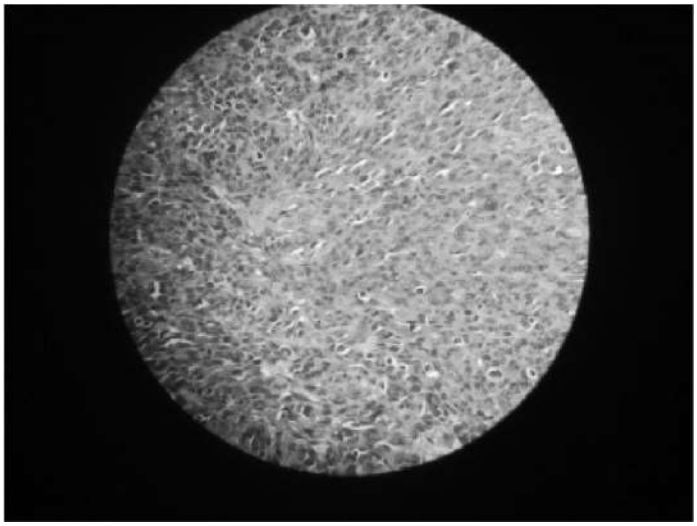

Figure 1. The mass composed of spindle cells and epitheloid like cells. Focal area shows alveolar-like pattern. Higher magnification shows spindle cells with eosinophilic cytoplasm. Some cells appear round with abundant cytoplasm. Pleomorphic enlarged cells are noted with high grade nuclei. Mitotic figures are numerous. Necrosis and hemorrhages are noted. The histologic picture of the soft tissue malignancy was suggestive of rhabdomyosarcoma. (H&E stain, LPO, x100)

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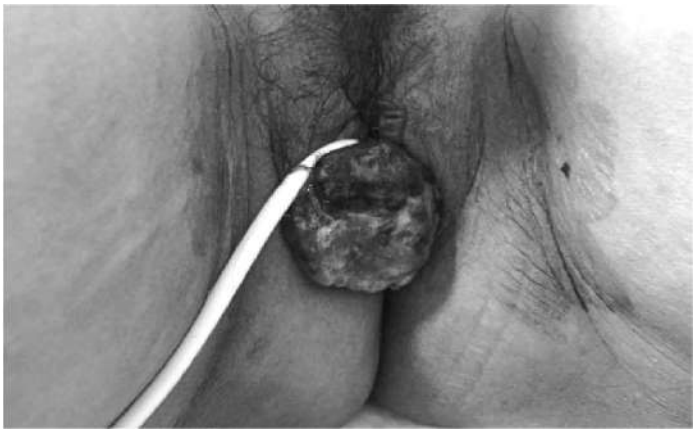

Figure 2. The mass is prolapsing out of vaginal canal on examination. And a foley bag catheter was in-place

the urethral meatus with active bleeding upon manipulation (Fig. 2). The cervix measured 1 x 1 cm, smooth, closed with no motion tenderness and was 4 cm from the vaginal mass. The uterus was small. There was no tenderness and there was no mass noted on both adnexa. On rectovaginal examination, the sphincter tone was tight. There was no intraluminal and extraluminal mass palpated. The parametria were free and pliable.

Transperineal ultrasound report showed an irregular mass measuring 4.5 x 4.1 x 1.9 cm, which exhibited moderate color flow on mapping. No extension of the mass to the mid-upper third of the vaginal wall was noted. CT scan also showed a poorly delineated inhomogenously-enhancing polypoid vaginal mass lesion from the introitus to the lower half of the vaginal vault measuring 5.1 x 5.0 x 4.0 cm. The liver was normal in size with normal parenchyma. Chest radiograph showed no significant pulmonary abnormalities. Pap smear of the cervix was negative for lesion or malignancy. However, colposcopy was not available at the time of examination, thus it was not done.

With an admitting impression of Rhabdomyosarcoma, vagina, stage I, the plan was to perform simple excision of the vaginal mass followed by radiation and chemotherapy.

Intra-operatively, the mass was excised using a sharp linear dissection, 0.5 cm from its tumorous borders with a 1 cm depth. (Fig. 3). The lines of resection extended from the inferior aspect of the urethra to the distal third of the anterior vaginal wall. The edges were closed using an absorbable suture by continuous interlocking technique (Fig. 4). Estimated blood loss was 50 cc.

The histopathology report revealed a picture suggestive of high-grade small cell neuroendocrine tumor (Fig. 5). Immunohistochemical staining for chromogranin and synaptophysin was recommended but was not done due to financial constraints and unavailability of immunohistochemical staining in the local setting.

The patient received 28 days of external beam radiation therapy three weeks after she underwent surgery. She was advised to undergo 6 cycles of chemotherapy with cisplatin and etoposide, however the patient refused due to financial constraints and intolerance to possible side effects. The patient returned for follow-up a week post-radiation therapy with no

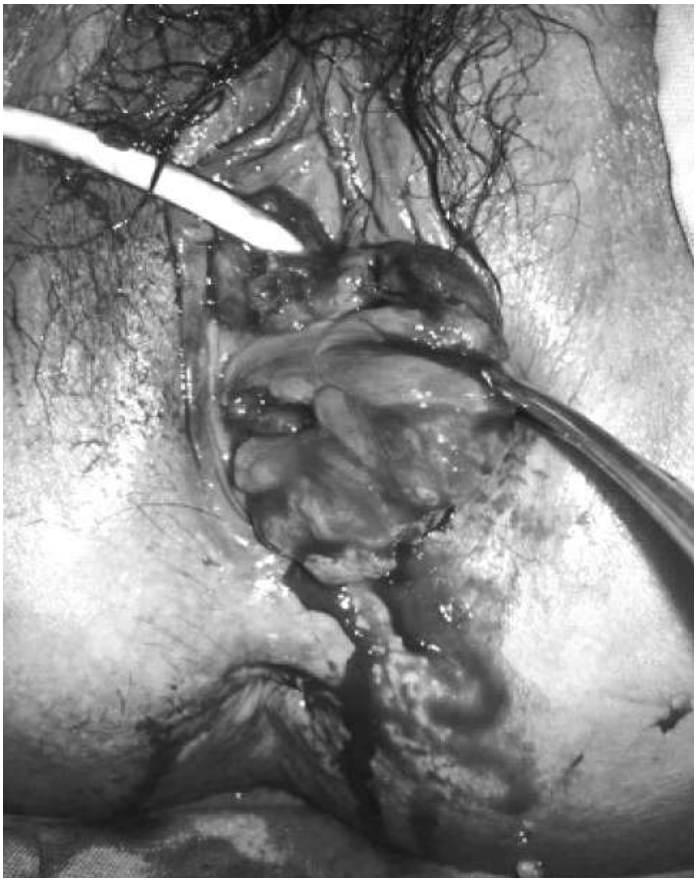

Figure 3. The prolapsing vaginal mass pre-operatively

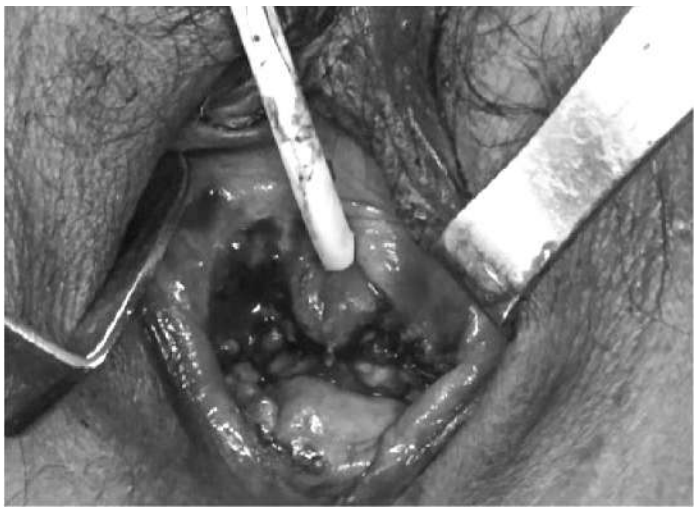

Figure 4. Appearance of vagina post-excision

subjective complaints and in apparent good condition. She achieved complete response to both surgery and radiation therapy. (Fig. 6)

Eight months post-radiation therapy, the patient had productive cough associated with hemoptysis and dyspnea. She was admitted at a private institution for pneumonia, with an incidental finding of multiple lung nodules on chest radiograph. She was advised for further workup and palliative chemotherapy, but the patient refused due to financial limitations and opted for palliative care. The patient expired 11 months post-radiation therapy.

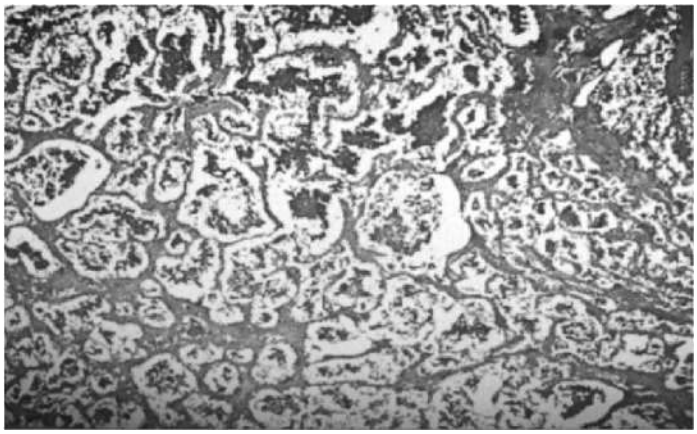

Figure 5. Microscopic description of the malignant neoplasm made up of small tumor cells, possessed with a round to oval hyperchromatic nuclei, surrounded by scanty cytoplasm. They are seen to diffusely infilrate and invade the surrounding stroma, including the vascular wall, leading to hemorrhages and necrosis. A histologic picture of vaginal mass suggestive of high-grade small cell neuroendocrine tumor (H&E stain, HPO, x400).

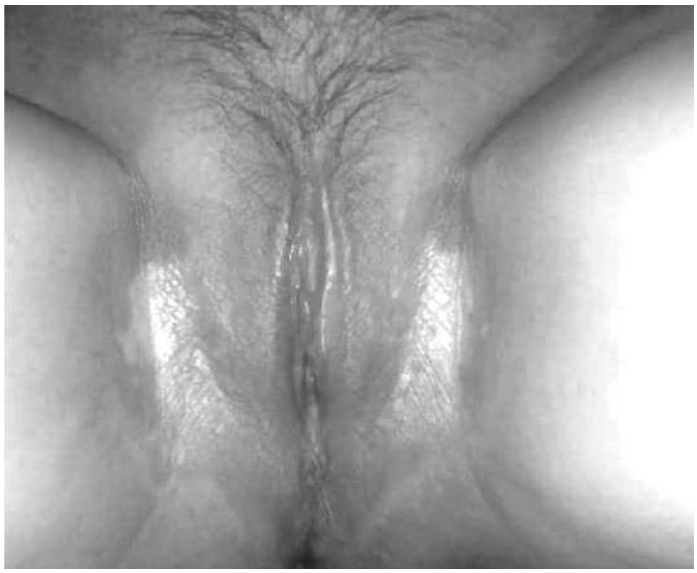

Figure 6. A picture of a cancer free perineum one week post-radiation therapy

DISCUSSION

Neuroendocrine tumors are abnormal growths that begin in the neuroendocrine cells, which are distributed widely throughout the body. The estimated incidence is 2.5 – 5 per 100, 000 persons per year.[1] Clinical and pathologic features of these tumors are unique to the site of origin. Neuroendocrine tumor arising in any organ is rare. They are commonly identified in the lungs, gastrointestinal tract, pancreas, liver and thymus. Gynecologic neuroendocrine tumor is a rare entity with an aggressive clinical behavior and a poor prognosis.

Primary small cell neuroendocrine carcinoma of the vagina is a rare neoplasm with only 28 reported cases in literature as of 2013. It was in 1972 that Albores-Saavedra et al. documented the first case of small cell neuroendocrine tumor of the female lower genital tract, primarily from the cervix.[2,4] In 1984, Scully et al. reported the first case of primary small cell neuroendocrine tumor of the vagina.[2,4,9] To date, there is still no reported case in the Philippines. This is the first case of neuroendocrine tumor in this institution.

Neuroendocrine tumor of the reproductive tract is a rare type of tumor which may arise from the neuroendocrine cells that are distributed in the normal epithelium of the female genital tract. Occurrence of primary vaginal small-cell neuroendocrine tumor is seen in postmenopausal females, with a mean age of 59 years old [11]. Our patient was menopausal and was diagnosed at the age of 65. These women usually present with localized pain, an introital mass, and vaginal bleeding, as in this case.[3,5,9]

The tumor can be accepted to be of neuroendocrine character when presence of neuroendocrine granules can be demonstrated on ultrastructural examination or tissue expression of at least two neuroendocrine markers other than neuron-specific enolase (NSE), particularly synaptophysin and chromogranin, are detected [14]. The patient was initially diagnosed as rhabdomyosarcoma due to the presence of spindle cells with eosinophilic cytoplasm and focal areas showing an alveolar-like pattern on initial tissue biopsy. Furthermore, there was an extensive differentiation of the rhabdomyoblast, with round to spindled shaped tumor cells.[10] On histopathologic examination of the entire tumor, it revealed presence of small tumor cells with hyperchromatic nuclei and scanty neoplasm suggestive of a high-grade small cell neuroendocrine tumor. Small cell carcinoma may have similar histopathologic findings of those of primary small cell carcinoma of the lung. Microscopically, these tumors are composed of sheets and nests of packed small cells, hyperchromatic nuclei, numerous mitotic activity and scanty cytoplasm. The nuclear shape may vary from round to spindle shaped with a characteristic of nuclear molding.[10]

Because of the rarity of the disease, histopathologic diagnosis is often difficult and overlapping of the histologic findings with other tumors does happen.[5] Detection of at least two of the following immunohistochemical neuroendocrine markers - neuoro-specific enolase, synaptophysin and chromogranin - confirms the histopathologic diagnosis of the disease.[2-9] In this case, immunohistochemical staining was not done due to financial constraints and unavailability of the staining at the local setting. Thus slide reviews from two different institutions, by different pathologists, were done, with a common finding of small cell carcinoma.

Complete work up to confirm the primary location of the malignancy was done. The lung is commonly the primary site in 95% of cases followed by the gastrointestinal tract.[2,9] In this case, chest radiograph, computed tomography of the pelvo-abdominal area and transvaginal as well as transperineal sonography confirmed the primary site of the lesion to be the vagina.

Staging by clinical examination showed early stage I for this case as the patient presented with a polypoid mass attached to the distal third of the anterior vaginal wall without further invasion to the urethra and urinary bladder.

Multimodality treatment through surgical resection with adjuvant radiation and systemic treatment in the form of chemotherapy significantly improves the survival rate in these cases. Chemotherapy with cisplatin or carboplatin and etoposide has a 70% overall response rate and is recommended.[3,6,8] In a report by Zivanovic et al., early stage patients who received post-

operative etoposide and cisplatin experienced an 83% three-year recurrence-free survival, compared to none for those who did not receive adjuvant chemotherapy[16]. Etoposide-cisplatin regimen is considered less toxic as compared to the vincristine-adriamycin-cyclophosphamide regimen.

However, small-cell neuroendocrine tumor of the vagina has a propensity for early widespread dissemination[12]. The prognosis is poor and most patients die within two years because of metastasis even at an early stage. It was reported by Gardner et al. that 85% of patients die within a year after being diagnosed.[9] One patient who received radiotherapy alone died after 3 months while another patient who received both chemotherapy and radiation therapy died after 11 months. Another patient who received local resection followed by chemotherapy and radiation therapy died after 23 months. [1,8]

Regardless of the extent of disease during the time of diagnosis, most patients die due to distant metastasis [12,13]. There was no association between survival and involvement of a particular vaginal segment or amount of vaginal structure involved with tumor[11]. Because of the rarity, there is no single approach to treatment which may be considered optimal. In this case, the poor prognosis as well as consideration of patient factors such as financial limitations and desire for a good quality of life, were taken into account in the plan of management. Thus, the patient underwent surgical resection followed by radiation therapy. These treatment modalities were chosen as the patient's goals were relief from her symptoms and avoidance of adverse effects from adjuvant therapy, particularly chemotherapy. Chemotherapy with cisplatin and etoposide was recommended, however the patient and her family no longer consented to chemotherapy. At the onset, the goal of treatment was palliation, that is, management of physical symptoms.

Treatment options for cancer care, especially in dealing with rare and aggressive malignancies such as primary vaginal small-cell neuroendocrine tumors, are often personal, depending on the goals of the patient as discussed with an oncologist [15]. In this case, the patient and her family decided that the side effects or other burdens, mostly financial, of aggressive cancer treatments particularly extensive surgery and chemotherapy, outweigh the possible benefits; thus the choice of treatment modalities.

CONCLUSION

Small cell neuroendocrine tumor of the vagina is a rare tumor with aggressive behavior and has a poor prognosis. It is commonly seen in postmenopausal women as in this case. Its clinical behavior is usually aggressive with early widespread dissemination. Most patients, as in this case, present with a vaginal mass associated with vaginal bleeding. Mortality is usually secondary to distant metastasis regardless of the extent of the tumor upon diagnosis. Standard therapy has not been established for this disease condition because of its rarity. This requires more cases for further investigation and discussion. The choice of treatment modality in this case report was geared towards patient's choice and goals of therapy.

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