ISSN 2704-3045

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Offcial Publication of the Society of Gynecologic Oncologists of the Philippines

Volume 17 Number 2 December 2020

EDITORIAL CORRESPONDENCE ADDRESS:
Editorial Office, Philippine Journal of Gynecologic Oncology
Society of Gynecologic Oncologists of the Philippines, Inc.
Unit 414, Manila Astral Towers, 1330 Taft Ave. corner Padre Faura St., Ermita, Manila, 1000 Phlippines
Telephone: 63-2-3531688; 63-932-7282864 • Email: phil.j.gyn.onco@gmail.com

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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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Perspective Article

Gynecologic Oncology Fellowship Training in the Time of COVID-19 Pandemic

Ana Victoria V. Dy Echo, MD, MHPEd, FPOGS, FSGOP[*] and Jennifer O. Madera, MD, FPOGS, FSGOP[**]

[*]*Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of the Philipines-Manila, College of Medicine, Philippine General Hospital*
[**]*Section of Gynecologic Oncology and Trophoblastic Disease, Department of Obstetrics and Gynecology, Jose Reyes Memorial Medical Center*

The COVID-19 Pandemic brought a lockdown, an Enhanced Community Quarantine (ECQ), to the whole nation starting March 16, 2020. While this lockdown significantly affected the lives of all Filipinos, it created a tremendous impact on gynecologic cancer care. It also resulted in the temporary disruption and subsequent adjustment of the training, service and research strategies of the two (2) gynecologic oncology accredited training institutions in the Philippines.

With the **Philippine General Hospital (PGH)** becoming a COVID referral center, there was an initial complete discontinuation of gynecologic oncology services – elective surgeries, inpatient care, outpatient clinics, chemotherapy, radiotherapy; all conferences were put on hold; and the fellows-in-training became part of the COVID health care team of the hospital. With this scenario, it was difficult for the Division of Gynecologic Oncology to give priority to subspecialty training. Service became the priority over training. After 2 weeks of ECQ, however, and with the resumption of limited services to non-COVID patients at the PGH Cancer Institute (CI), the Division slowly resumed the training activities for the fellows. Weekly small group discussions, via virtual platforms, were started; and by the middle of May, the weekly conferences (preoperative and postoperative conferences, journal reports, outpatient clinic census, ward report) were resumed via Zoom. The quarterly knowledge competency requirements were adjusted, and eventually the fellows were able to complete their quarterly written examinations and oral examination via online platform.

In terms of research, the ECQ provided the best opportunity for the fellows to complete their research proposals and interesting case papers. Their quarantine days off were utilized to complete their research requirements. With the limited number of patients, however, their researches focused on descriptive studies rather than experimental studies. Topics on the effects of the COVID-19 pandemic on gynecologic cancer care were likewise explored.

The greatest hurdle was the completion of surgical requirements. It was not until June when PGH resumed elective surgeries on non-COVID cases that the fellows were able to perform gynecologic oncology surgeries. In the first 2 months, all gynecologic oncology surgeries were assisted by the Division consultants, primarily to facilitate intraoperative decisions and limit morbidities and mortalities, and secondarily to help the fellows regain their confidence in performing surgeries after two months of hiatus. It was fortunate that gynecologic cancer surgery was of high priority that the fellows were able to make up for missed surgical procedures and were slowly able to complete their surgical requirements.

At the **Jose R. Reyes Memorial Medical Center (JRRMMC)**, gynecologic oncology care pursued during the acute phase of ECQ, but was limited to emergency admissions. Although not a COVID referral center, the fellows attended to a significant number of probable COVID and non-COVID gynecologic oncology cases, most of which are referrals from COVID centers. Fellows on duty attended to emergency consults, referrals and admissions, while the rest were doing telemedicine consultations.

Despite these challenges, training was uninterrupted. In the immediate weeks following ECQ, weekly written activities on various topics were assigned. Upon availability of online teleconferences, scheduled written and oral examinations, regular conferences, as well as special conferences with other subspecialties were conducted. Fellows were also able to complete their research requirements on time, despite initial delays such as difficulties in accessing patients' records, lack of patients for prospective studies and delays in institutional research board (IRB) approvals. As the ECQ eased up, gradual resumption of hospital services ensued. This started with resumption of brachytherapy, outpatient consultations, chemotherapy administration and eventually elective surgeries.

Gynecologic Oncology training involves being proficient in surgical skills. Hence, one measure made to address the limited number of surgical cases during the height of the pandemic was the inclusion of discussions of surgical videos of both basic and difficult gynecologic oncology cases in the conferences. Upon resumption of the elective surgeries, almost all cases are consultant-assisted to maximize the learning of the fellows, surgical and intraoperative decision making-wise. The fellows have yet to complete their surgical requirements in the months to come.

The COVID-19 pandemic has truly made an impact on the training in gynecologic oncology. For the fellows, the biggest challenge was to maintain a sense of purpose and normalcy when everything else was at a standstill. There was a constant sense of dread and fear that their pursuit of training would risk their own and their family's health. On the other hand, the experience taught the fellows to become adaptable and resilient despite the difficulties. For the two training institutions, the COVID-19 pandemic presented many difficult and unique challenges in implementing its training program. However, through the consultants' dedication, resilience and ingenuity, both institutions managed to not only continue training the fellows, but also made training more relevant and appropriate during this very trying time.

Correspondence to:
Ana Victoria V. Dy Echo, MD, MHPEd; email: anadyecho@yahoo.com
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of the Philippines-Manila, College of Medicine, Philippine General Hospital, Taft Avenue, Manila

Health system analysis on the implementation of community cervical cancer screening program-comparison between urban and rural health system

Jay-Ar T. Sorreda, MD and Maria Lilibeth L. Sia Su, MD, FPOGS, FSGOP

ABSTRACT

Introduction: The Department of Health (DOH) advocates the use of visual inspection with acetic acid (VIA) as a screening method for cervical cancer in primary health care facilities.

Objective: This study assessed and compared the implementation of cervical cancer screening between an urban and a rural health system using the health systems framework. Results of the study are vital as they provide baseline information on the status of community cervical cancer screening in the country.

Methods: A cross-sectional descriptive design was used to evaluate the implementation of cervical cancer screening for year 2017-2019, in public primary healthcare facilities in the National Capital Region (N=10) and Bicol Region (N=16). Self-administered questionnaires were distributed to program coordinators in the study sites. Descriptive statistical analysis was used to summarized the results.

Results: Results showed that the coverage of cervical cancer screening is 0.39% in rural areas and 5.5% in the urban areas. The rural health system has inadequate screening facilities (40%), low clinic to population ratio (1:9196), and low personnel to population ratio (1:1751). The urban health system has 100% screening facilities served by 244 clinics, with a clinic to population ratio of 1 per 869 and personnel to population ratio of 1 per 699. Improvements needed includes local policy to institutionalize cervical screening, an updated training of health personnel, constant supply of consumables and health promotion materials, budgetary support, and improved data recording and reporting.

Conclusion: The disparity in implementing cervical cancer screening programs between the rural and urban areas were evident and should be addressed with program interventions that will increase the use of VIA screening programs in the community.

Keywords: *cervical cancer screening, urban health system, rural health system*

INTRODUCTION

In the Philippines, cervical cancer remains to be the second most common malignancy among women and is the most common female genital tract malignancy. Approximately, 7,190 new cases were diagnosed in 2018, with an age-standardized national incidence rate of 14.9 per 100,000, and national standardized mortality rate of 8.8 per 100,000 translating to 4,088 cervical cancer deaths among Filipino women.[1]

Organized cervical cancer screening program that aims for early detection and management is crucial for preventing and controlling cervical malignancies.[2] The Department of Health (DOH) advocated cervical cancer screening as one of its preventive strategy. A study by Avila et al. in 2001 reported that less than 42% of the 389 Philippine hospitals offer screening and only 8% have dedicated screening clinics.[3] The 2003 WHO Health Survey reported a 9.2 % total Pap smear coverage of Filipino women aged 18-69 years old.[4]

In 2005, the DOH issued Administrative Order No 2005-2006 establishing the Cervical Cancer Screening Program (CCSP).[5] The cervical cancer screening policy shifted to the single visit approach using Visual Inspection with Acetic acid (VIA). VIA is an alternative screening method, especially in primary and secondary level health care facilities without Pap smear capability.[6] VIA entails brushing acetic acid (3-5 % vinegar) on a woman's cervix which makes precancerous lesions turn white. This method does not require laboratory processing and utilizes simple equipment and basic supplies.[7] With immediate results, clients can be screened and treated in the same visit using the cryotherapy method. All of these health services can be provided by trained health personnel.[8] However, the lack of cryotherapy capability among local health centers recommends that VIA as a triage method before pap smear can be done in higher level of healthcare facility.[6]

A recent cost-utility analysis study in the Philippines concluded that high VIA coverage targeting women aged 35-

Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines-Manila

This paper has been presented at 1. 6th Biennial Meeting of Asian Society of Gynecologic Oncology, Songdo Convensia, Incheon, Korea (October 10-12, 2019). 2. ESGO Congress 2019 - 21st European Congress on Gynecological Oncology, Athens, Greece (November 2-5, 2019)

Corresponding authors:
Jay-Ar T. Sorreda, MD; email: jay_sorreda@yahoo.com
Maria Lilibeth L. Sia Su, MD, FPOGS, FSGOP, FPSCPC
email: lilibethsiasu@gmail.com
Department of Obstetrics and Gynecology-Philippine General Hospital

Financial Disclosure
The authors did not report any potential conflicts of interest.

45 years old at five-year intervals would be the most efficient and cost-saving strategy in reducing cervical cancer burden. Shifting from the current low coverage of Pap smear to VIA at high coverage will result in a lower healthcare cost and a higher health benefit. VIA has shown dominant and cost-saving screening strategy with incremental cost-effectiveness ratio (ICER) of Php 61,059 (1443 USD) per QALY gained. The use of VIA as a screening method can reduce cervical cancer cases and deaths by 25%.[9] This study strengthens the current policy to scale up coverage of VIA screening in the country compared to the conventional Pap smear.

Documents reviewing status and coverage of cervical cancer screening in the Philippines are limited. There are few studies on cervical cancer that evaluated the primary healthcare provider's capacity and performance to execute community cervical cancer screening programs. The World Health Organization identified the building blocks of a health system to deliver its function, achieve its goals and improve health outcomes.[10] This study aims to increase the national coverage of cervical cancer screening by assessing and comparing the implementation of cervical cancer screening between an urban and a rural health system using the health systems framework. Results of the study are vital as they aid in the planning and development of strategies and activities that are geared towards improving local health systems performance in cervical cancer screening and prevention programs.

OBJECTIVES

This study evaluated the status of the community cervical cancer screening program among selected local health departments for calendar year 2017-2019. It specifically aimed to: 1) determine the coverage of Community Cervical Cancer Screening program particularly the use of Visual Inspection with Acetic Acid (VIA), and 2) compare the Community Cervical Cancer Screening program between an urban and a rural population using the health systems framework in terms of (1) leadership and governance, (2) health service delivery, (3) human resources for health, (4) technology and equipment, (5) health information systems; and (6) financing.

METHODOLOGY

The study protocol was approved by the UP Manila Review Ethics Board (UPMREB). A cross sectional study design was used. It involved assessment of public primary healthcare facilities in Metro Manila and Albay utilizing a facility self-administered questionnaire based on the 2018 WHO tool kit for cervical cancer prevention and control programs.[11]

The study population were public primary healthcare providers in either the city or municipal health office. Private healthcare facilities and hospitals were excluded in this study. The sample groups were predetermined purposively. These were chosen due to the proximity of the sites, familiarity of the investigator with the area, availability of health data from these providers and being the focus area of the investigator for future interventions. The urban group included 17 health facilities in Metro Manila. The rural health system group is composed of 15 municipalities and three cities in the province of Albay. A total of 35 public primary healthcare providers were recruited in this study.

Distribution and retrieval of the survey were approved and coordinated with DOH-National Capital Region Office, the DOH-Bicol Regional Office and facility heads. Consent was secured by the primary investigator either through correspondences (email or phone) or through personal appearance. Each facility was represented by only one respondent and may include the Facility Head or the Program Coordinator or whoever will be the best respondent to answer the self-administered questionnaire. Questionnaires not returned within four weeks after lifting of the enhanced community quarantine enforced in Luzon, despite continuous follow up, was considered a non-response.

Completed questionnaires were considered for completeness, accuracy and consistency prior to analysis. Each facility was designated with a facility code that provides anonymity during the data analysis. All responses were tabulated as datasets in Microsoft Excel. Target coverage was computed based on the 2015 Population Census of the Philippine Statistic Authority. The target computation was done as follows based on program manual from DOH:

VIA TARGET: 80% of WOMEN aged 21 years old and above for a period of 5 years computed as follows:

$$\text{Annual Target} = \frac{\text{TOTAL Population x 0.51 (Female) X 0.40 (≥ years old)}}{\text{X 0.80 (80\% Coverage in 5 years) X 0.2 (1/5 as annual target)}}$$

Descriptive statistics was used to describe the various domains of health systems between the rural and urban health system group. Numerical variables such as VIA coverage, budget allocation and cost of services were presented as medians and interquartile ranges. Other qualitative responses such as facility profile and healthcare providers profile were reported as frequencies and percentages.

RESULTS

Participants

Among 17 healthcare facilities in Metro Manila, only 10 (62.5%) were able to participate. One city heath office gave initial response not to participate in the study, while the remaining six city health offices were not able to fill out the questionnaire on the required period. For the rural health system group, the retrieval rate was 88.89 % with two health units in the province of Albay unable to participate. The reason for non-submission was their workload related to the Covid-19 response.

For the urban group, majority of the respondents were doctors (60%) compared to the rural group where majority were nurses (87.5%). The participants were predominantly female, whose age range from 31-63 years. Table 1 presents the demographic profile of the respondents.

Table 1. Profile of Respondents of the Survey

RESPONDENTS	ALBAY (n=16)	METRO MANILA (n=10)
Profession		
Doctor	1	6
Medical Technologist	1	0
Nurses	14	3
Midwife	0	1
Gender		
Male	0	1
Female	16	10
Age Range	31-63	32-56
Years Handling Program	2 months to 10 years	2 years to 5 years

Governance and Leadership

The urban group had all health facilities oriented to Cervical Cancer Screening Program (CSSP). The rural group had only 81.25 % (13) of the facilities with orientation to CSSP. On policies concerning CSSP, 20% of facilities in the urban group had a policy compared to none in the rural group. All facilities in the the urban group were noted to have a protocol on cervical cancer screening compared to 31.25% for the rural group. No local ordinance promoting cervical cancer screening and prevention in the urban and rural communities was enacted.

Service Delivery

Only four (25%) of the 16 facilities in the rural group were actively screening facilities for cervical cancer. One facility in the rural group offered Pap Smear instead of VIA as form of screening. All facilities in the urban group were screening providers, with 40% providing cryotherapy. None of the facilities

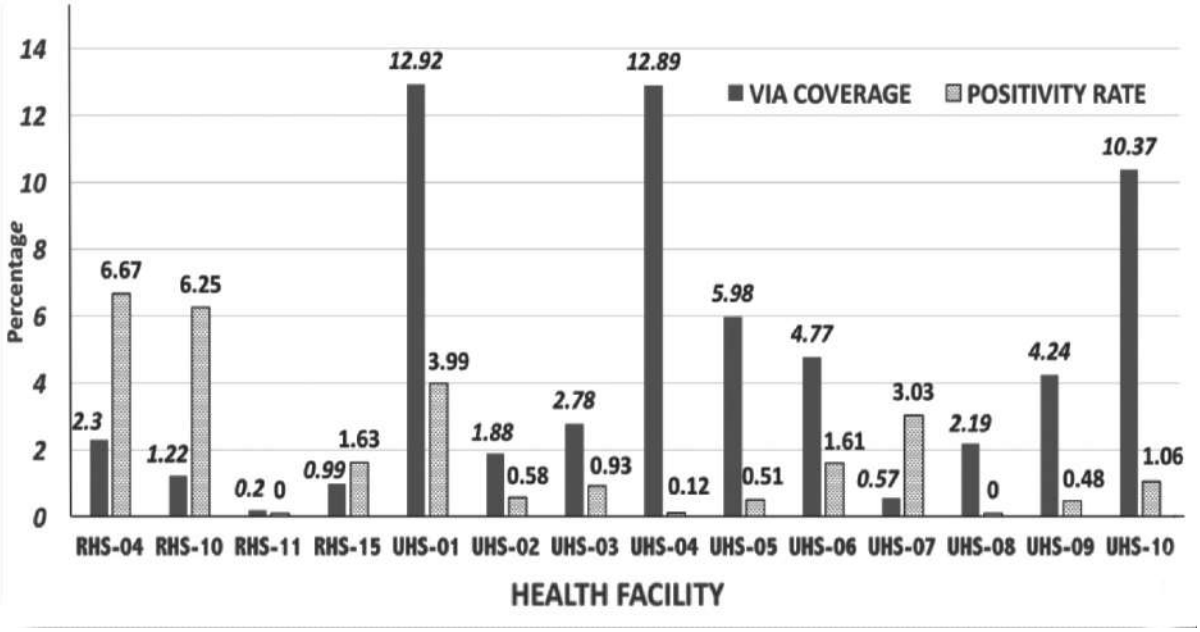

Figure 1. Screening Coverage and VIA-Positivity Rate among local health systems with Cervical Cancer Screening from 2017-2019

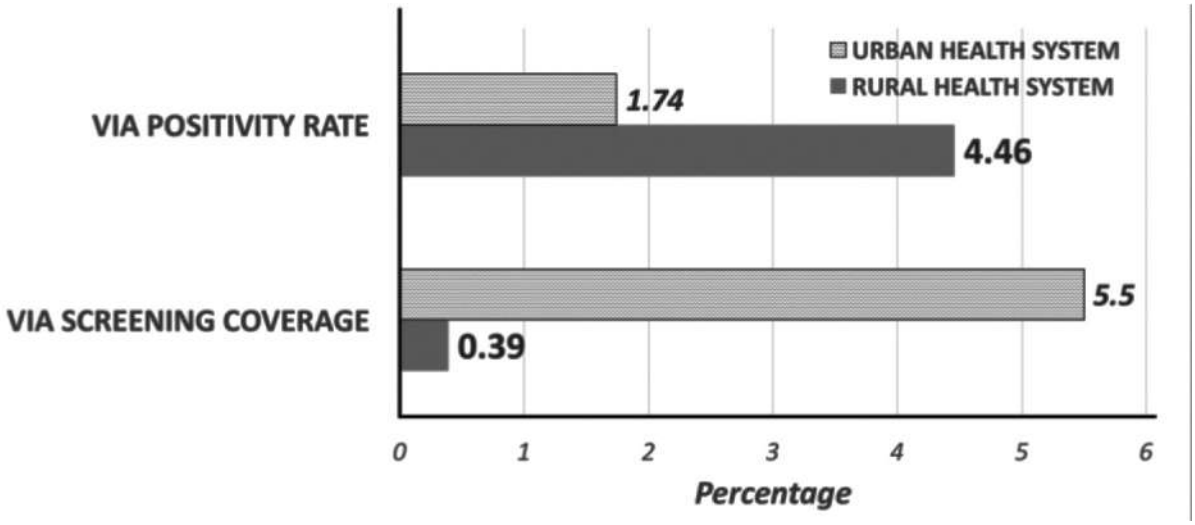

Figure 2. Comparison of Average Screening Coverage and VIA-Positivity Rate between a Rural and Urban Health System from 2017-2019

in the rural group had the capacity to provide cryotherapy.

The catchment population of the health facilities was 1,126,940 for the rural group compared to 6,497,831 in the urban group. The target population of cervical cancer screening program was computed with an 80% coverage for a period of 5 years among the females aged 21 years old and above. Cervical cancer screening using VIA in the urban group had an average annual coverage of 5.50 % (35,020 individuals) compared to 0.39 % (388) for the rural group. Women in the urban group had a 1.74% (609 cases) positivity rate on VIA compared to 4.46% (19) in the rural group. Figures 1 (all health facilities) and 2 (average per health system) show the VIA coverage and positivity rate among the health facilities with cervical screening. Based on the number of clinics, the rural group serves 9,196 target population per clinic (total of 4 clinics) compared to only 869 target population per clinic (total of 244 clinics) in the urban group.

Human Resource Management

Five facilities (31.3%) in the rural group had no personnel trained in cervical cancer screening using VIA. The remaining 11 rural facilities had a total of 23 trained personnel composed of 11 doctors, 6 nurses and 6 midwives. All facilities in the urban group have trained personnel, composed of 60 doctors, 106 nurses and 137 midwives with a total of 303. The trained health personnel to population ratio was 1 per 1751 in the rural group compared to 1 per 699 in the urban group. Majority of the training of the rural group was done more than 3 years ago, with nine of the 12 facilities with training. For the urban group, 90 % were trained within the last 1-3 years.

Equipment and technology

All health facilities except one in the rural group had available instruments for VIA screening such as speculums, headlight, examination beds, etc. The sole facility with partial availability of instruments/equipment lacked an autoclave. For the consumables (acetic acid, cotton pledget, gloves, etc.), all the facilities with VIA screening capacities reported availability. For the stationary, 25% in the rural group and 90% in the urban group reported partial availability. The participants noted lack of VIA cards, Information Education and Campaign Flipcharts on cervical cancer screening program and VIA Registers.

Health information System

All four facilities in the rural group doing VIA screening activities utilized Logbooks in recording their patients' data. Sixty percent in the urban group used VIA registers to document patients screened and only 40% used logbooks. All screening facilities in both groups stored a medical record of patients after cervical cancer screening. The facilities in the rural group made quarterly reports of their screening activities while 60 % of health facilities in the for the urban group, generated their reports on a monthly basis.

Financing

Financial support for cervical cancer screening program relied primarily on the local health budget. All screening using the VIA method was offered for free. A facility in the rural group offered cervical screening by Pap Smear at a cost of PhP170 pesos.

Only two of the facilities, both belonging to the urban group, identified specific budget on cervical cancer screening included in the Local Annual Investment Plan for Health (AIP). Six facilities in the rural groups while eight facilities in the urban group identified that their budget for cervical cancer screening was aggregated with the general budget for health. Ten facilities (62.5%) in the rural group reported having no budget item for cervical cancer screening.

On accreditation to the Philippine Health Insurance Corporation (Philhealth) as a primary healthcare benefit provider, 100% of the urban group facilities were accredited compared to only 56.25% in the rural group. However, there is unavailable data on how much payment each facility has received in providing the primary care services.

Figure 3 highlights the health system indicators for implementing community cervical cancer screening. Table 2 summarizes the health components of VIA screening comparing the rural group from the urban group.

DISCUSSION

Various differences in the health system components can be noted between a rural and an urban health system. Based on the coverage of cervical cancer screening, the urban health facilities registered a higher performance at 5.5% compared to 0.39% among the rural health facilities. The 2003 WHO World Health Survey in the Philippines involving 4022 women from 25-64 years old noted the estimated coverage of cervical cancer screening within the last three years was low at 9.2%.[12] Indonesia utilizing VIA and cytology screening and Malaysia using cytology screening has more than twice screening coverage than the Philippines at 23% and 24.4% respectively.[13] Among Southeast Asian countries, Singapore, using cytology based screening program, has the highest cervical cancer screening coverage at 47.2%.[14]

The current national recommendation of the program is to target women 25-55 years with VIA done at five to seven year intervals with a target of 50% coverage within the year of implementation and to maintain at least 80% coverage thereafter.[5] WHO recommends 80% coverage for national screening programs to be successful.[15] Reduction in mortality from cervical cancer will be achieved if screening will reach 25% of the target population over a 5-10 year period.[16] With low screening coverage in the country, improving utilization of cervical cancer screening in the community can help achieve the target screening coverage in order to decrease mortality from cervical malignancy

VIA screening coverage depends on the capacity of the health facility. A range of personnel including doctors, nurses, midwives and paramedical health workers can be trained in VIA and cryotherapy. Availability of personnel in primary healthcare facilities can improve access to cervical cancer prevention

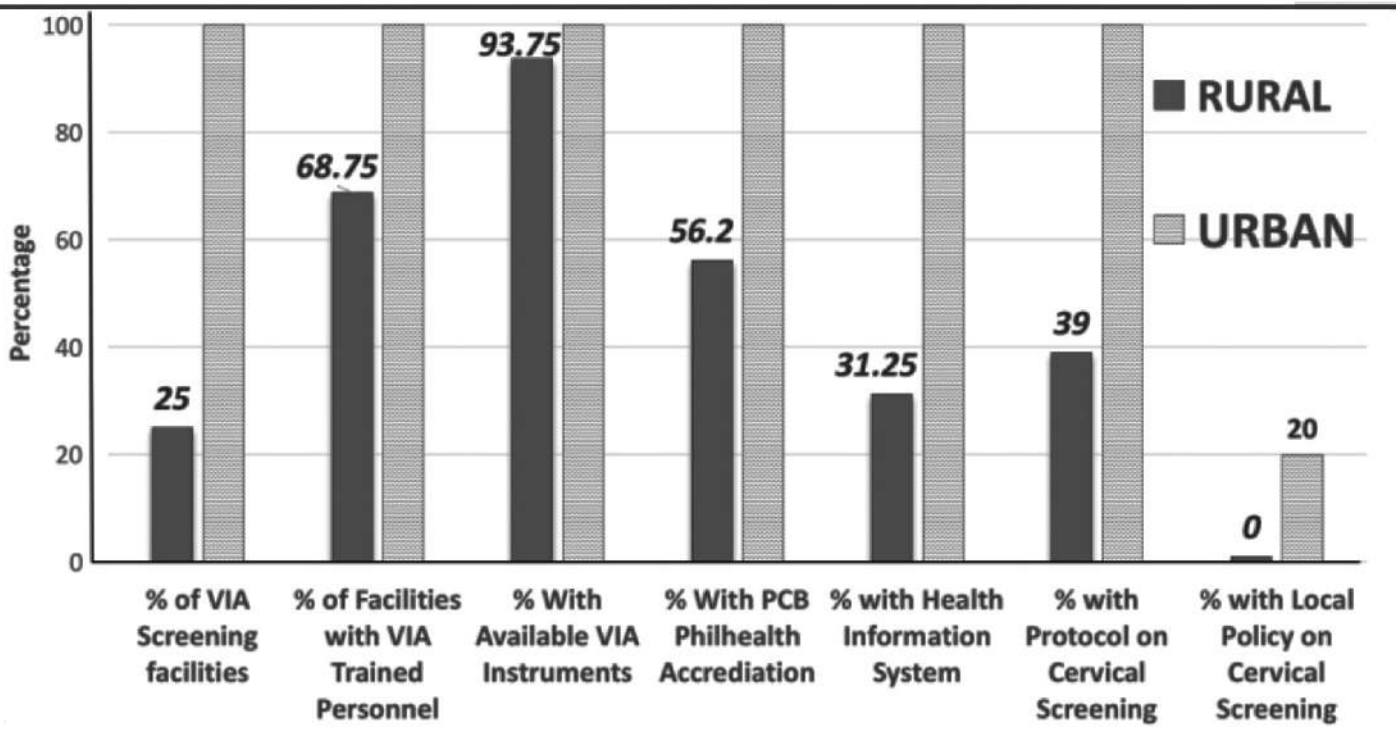

Figure 3. Status of Implementation of Cervical Cancer Screening between a Rural and Urban Health System from 2017-2019

services.[17] Only 25% (4) of health facilities in the rural group compared to 100% of the urban group provided VIA screening services. The access to screening facilities is one of the factors limiting VIA screening.[18] In this study, the clinic to population ratio at the urban setting was 1 per 869 population compared to 1 per 9,196 population in the rural setting. The availability of screening clinics in urban centers was 10 times more than those in the rural counterparts.

Five health facilities in the rural group did not have any trained personnel for VIA screening. The VIA training provided in Albay province were related to the Safe motherhood project back in 2013. No follow up monitoring and evaluation was done afterwards. Considering the number of trained personnel for VIA screening, the personnel-population ratio for the urban group was 1 per 699 compared to 1 per 1,599 in the rural health setting. The number of trained heath personnel among urban health units was twice more than those in the rural health units.

An important consideration in screening programs is to capacitate screening providers with adequate training. An updated training of health personnel among rural health units should be organized. The Alliance for Cervical Cancer Prevention (ACCP) recommended providing screener training using a competency-based curriculum, combining both didactic and hands-on approaches, and conducting the trainings in a clinical setting similar to service delivery conditions of the program.[19]

On the presence of equipment and technology to support VIA Screening, all facilities had the equipment. The only unavailable consumable was the acetic acid which is inexpensive. The other stationaries that needed support from DOH National Cervical Cancer Program include production of VIA registers, VIA cards as references for positive and negative cases, and flipcharts that will be useful during information dissemination activities.

Physical presence of screening infrastructure and human resources is limited in the rural setting compared to the urban counterparts. Findings of this survey are consistent with the previous studies of Turnball et al. in 2018 where they suggested that significant investment in healthcare workforce, improving healthcare worker density and improving training in the existing workforce are vital in attaining the cervical cancer screening goals.[20] Every unit increase in the number of healthcare providers available increased the likelihood of screening by 1%. The WHO minimum standard is 23 healthcare workers per 10,000 population.[21]

This study highlights that accessibility and availability of cervical screening services are crucial for a cervical cancer screening and prevention program. Decentralization of services by incorporating cervical screening in primary healthcare will ensure adequate rural-urban coverage.[22] Increasing access to screening services within communities is critical to address barriers such as long distances to health facilities and transport costs. An outreach model of service delivery with regular screening services extended to the community while building capacity at local health units will increase access. Integration of cervical cancer screening with other programs accessed by women such as prenatal care, family planning or postnatal care could also increase screening uptake.[23]

VIA cervical cancer screening is offered for free on all screening facilities surveyed. Financial support of the program is primarily dependent on the local budgetary

Table 2. Comparison of of Health System Components of Cervical Cancer Screening Program between a Rural and an Urban Health System from CY 2017-2019

HEALTH SYSTEM COMPONENT	ALBAY (n=16)	METRO MANILA (n=10)
I. LEADERSHIP AND GOVERNANCE		
A. Orientation to Cervical Cancer Screening Program	13 (81.25%)	10 (100%)
B. Policies on Cervical Cancer Screening	0	2 (20%)
C. Protocol on cervical Cancer screening	5 (31.25%)	10 (100%)
D. Local ordinance enacted to promote cervical cancer screening and prevention	0	0
II. SERVICE DELIVERY		
A. CAPACITY		
A.1 Screening	4 (25%)	10(100%)
A.2 Colposcopy	0	0
A.3 Treatment	0	4 (40%)
B. Years Screening Services in Place		
B.1 <1yr	0	0
B.2 1-3 years	0	2 (20%)
B.3 >3 years	4 (255)	8 (80%)
C. PERFORMANCE INDICATORS		
C.1 <1yr	1,126,940	6,497,831
C.2 1-3 years	110,349	636,267
C.3 >3 years	428 (0.39%)	35020 (5.50%)
C.3 >3 years	19 (4.9%)	609 (1.7%)
D. Number of Screening Clinics (RATIO)	4 (1:9196)	244 (1:869)
III. HUMAN RESOURCES MANAGEMENT		
A. TRAINED PERSONNEL	23	303
A.1 Medical Doctor	11	60
A.2 Nurse	6	106
A.3 Midwife	6	137
A.4 Target Population to Personnel ratio	1: 1599	1: 699
B. YEAR OF RECENT TRAINING		
B.1 within 1 year	0	1
B.2 1-3 years ago	2	9
B.3 >3 years ago	9	0
B.4 NO training	5	0
C. With monitoring and evaluation done after training?	0	6
D. Training Needs	175	273
D.1 Medical Doctor	20	90
D.2 Nurse	40	79
D.3 Midwife	115	104
IV. EQUIPMENT AND TECHNOLOGY		
A. Equipment and Instrument		
A.1 Available	15 (93.75%)	10 (100%)
A.2 Partial	1 (6.25%)	0
A.3 NONE	0	0
B. CONSUMABLES		
B.1 Available	4 (25%)	10 (100%)
B.2 Partial	12 (76%)	0
B.3 NONE	0	0
C. STATIONERY		
C.1 Available	0	1 (10%)
C.2 Partial	4 (25%)	9
C.3 NONE	12 (7 5 %)	0

HEALTH SYSTEM COMPONENT	ALBAY (n=16)	METRO MANILA (n=10)
D. AVAILABILITY OF SUPPLIES/ CONSUMABLES		
D.1 No stockouts	0	4
D.2 1-2 stockouts but replenished within 2 weeks	2	3
D.3 stockouts of 2 weeks duration to 3 months	2	3
V. HEALTH INFORMATION SYSTEMS		
A. Presence of Cervical Cancer Screening Registry		
A.1 Target Client List	0	6
A.2 Logbook	4	4
A.3 Electronic	0	0
B. With medical records of clients after cervical cancer screening	4	1
C. Reports of Coverage for VIA Screening		
C.1 Monthly	0	6
C.2 Quarterly	4	3
C.3 Annually	0	1
VI. FINANCING		
A. Budget for Cervical Cancer Screening in Annual Investment Plan		
A.1 Identified budget	0	2
A.2 Aggregated with budget for health	6	8
A.3 No budget item	10	0
B. Budget allotted for cervical cancer screening	UNSPECIFIED	216,800
C. Primary Care Benefit Provider	9 (56.25%)	10 (100%)
D. Reimbursement received from Philhealth for Primary Care Benefit	NO DATA	NO DATA

allotment. However, majority of the screening health facilities had no data on their actual budget for cervical cancer screening program. Being a primary care benefit provider, these facilities are required by Philhealth to offer VIA screening. Regulation through Philhealth circulars may reiterate the need to intensify VIA screening and incentives to facilities can be advocated to encourage adequate VIA screening coverage.

The VIA screening is just a component of the Cervical Cancer Control Program and Prevention. The most effective way to increase coverage is training screening providers and actively involve them to encourage screening participation. Further development of cervical cancer prevention may depend on organizational changes.[24] Based on this survey, urban health facilities are more oriented on the program and protocols on how to do VIA screening. However only two (2) health facilities in the urban group while none in the rural group reported the adoption of the program as a local policy. Scaling up the activities for community cervical cancer screening requires a solid program policy and actions within the healthcare facility that is adopted by the local government units through a legislation of local ordinance. A solid framework of the local cancer control and prevention program, fiscal and institutional mechanisms should be established to promote and sustain VIA screening in our communities.

The primary limitation of this study is its limited population hence inferential statistics was not utilized. Although the study involved two predetermined areas and results cannot be used to generalize for the whole country, the baseline data can be instrumental to the reform and progress of community cervical cancer programs and services.

CONCLUSION

VIA screening was in place in the urban groups but is limited in the rural group. The average screening coverage using VIA among health facilities in urban health systems was at 5.5 % for the last 3 years compared to 0.39 % in rural health systems. Urban facilities were characterized by more screening clinics and higher trained personnel to populationn ratio to cater to a larger population. The rural healthcare facilities have a very limited coverage on screening as it is offered by few screening clinics due to limited healthcare personnel trained on cervical cancer prevention and control program. Additional training of workforce is needed in both healthcare setups to improve the capacity and attain the target coverage goals of the program to 80% in a 5-year period. Both health systems encountered challenges in the following key areas: local policy to institutionalize cervical screening in primary care, updated training of personnel, regular supplies of consumables to conduct VIA, specific budgetary mechanism to sustain the program, and improved data registry and reporting to provide status of the program. Supervision and monitoring mechanisms of the program must be put in place by DOH and their regional offices to be able to upscale screening coverage in communities, especially in the rural health systems.

RECOMMENDATIONS

This study presented the baseline characteristics of health system dimensions influencing community cervical cancer screening. Based on these results, interventions can be recommended to facilitate screening in areas with absent or limited coverage, or for improvement of performance in areas with screening facilities. The Department of Health must also provide clear policy and program support on the community cervical cancer screening, with specific goals that must be accomplished on an annual basis.

Studies related to influencing factors that promote the utilization of cervical cancer screening by the population can be done. Quality assurance studies on the conduct of VIA screening among primary healthcare workers can further be investigated to verify accuracy. Feasibility study of setting up cryotherapy units in primary healthcare facilities may also be done to improve service delivery for a single visit approach for screening and management.

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Laparoscopic approach to comprehensive surgical staging for clinical stage I endometrial cancer: An institutional review of operative outcomes, costs and its clinical implications

Gladdy Maura G. Facun, MD, DPOGS[1], Renee Vina G. Sicam, MD, FPOGS, FSGOP, FPSGE[1] and Doris R. Benavides, MD, FPOGS, FSGOP, FPSGE[1]

ABSTRACT

Background: Laparoscopy is considered as standard of care for early-stage endometrial cancer, however, the absence of local oncologic results utilizing this technique prevents its adoption in managing endometrial cancer in the Philippines.

Objectives: The purpose of this study was to determine the clinical profile, operative outcomes and costs of undergoing laparoscopic surgery for clinical stage I endometrial cancer.

Materials and Methods: Data from 28 patients who underwent TLHBSO, PFC, LND for presumed stage I endometrial cancer were collected retrospectively from May 2017 to May 2019 in a tertiary institution.

Results: Mean age of the patients was 46.7 (range, 25 to 71). Risk factors included obesity (53.5%), nulliparity (46.4%), diabetes mellitus (14.3%), primary infertility (14.3%), PCOS (7.1%) and dyslipidemia (3.6%). None of the cases were converted to laparotomy, one necessitated mini-laparotomy to deliver the uterine specimen. Median length of operations was 236 minutes and 281 minutes depending on whether para-aortic lymphadenectomy was included. Complications include blood transfusion (3), vaginal vault dehiscence (1) and lymphocyst formation (1). Mean hospital stay was 7 days. Blood loss was minimal (217.3 +/- 171.4 mL). Two out of the 28 cases were noted to have stage III disease intra-operatively. Median follow up was 13.5 months. Sixteen subjects (57%) had no evidence of disease on follow up while 2 (7%) already died of disease. The presence of LVSI and tumor size ≥2 cm were factors identified for progression. Average hospital cost was $1137.15 (range, $336.47 to $ 2,386.98). Interventions identified to make laparoscopic surgery available to the general population include: 1) increasing PhilHealth coverage, 2) sterilization and re-use of instruments, and 3) provision for medical subsidy from the government and other institutions.

Conclusion: Laparoscopic surgery is a safe and viable surgical option for carefully selected clinical stage 1 endometrial cancer patients.

Keywords: *laparoscopic surgery, early-stage endometrial cancer, minimally invasive surgery*

INTRODUCTION

Endometrial cancer ranks third among malignancies of the female genital tract following cervical and ovarian cancer.[1-3] From 2015 to 2019, we had an average of 210 newly diagnosed cases of endometrial cancer per year, approximately 52-60% of whom eventually undergo surgery.[4,5] The standard treatment performed consists of peritoneal fluid cytology, total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic lymphadencectomy with or without para-aortic lymph node sampling.[6-10]

Surgical staging for endometrial cancer has traditionally been done via laparotomy or open surgery. But with the positive results coming from 2 large randomized controlled trials -- the GOG LAP2 Study and the LACE Trial, laparoscopy is considered as standard of care as it results in fewer postoperative complications, lesser postoperative pain, shorter hospital stay, earlier return to work and better quality of life.

The use of laparoscopic surgery for endometrial cancer was introduced in 1993 when Childers JM and Surwit EA reported two cases of laparoscopic-assisted vaginal hysterectomy (LAVH).[11] Since then, studies have been undertaken to evaluate the role of laparoscopy in managing endometrial cancer. Advances in laparoscopy equipment and instruments led to the application of laparoscopic surgery to more complex operations. To date, a total of nine (9) randomized controlled trials comparing laparoscopy with laparotomy for early-stage endometrial cancer have been undertaken, and these have shown that laparoscopy should be the preferred treatment for early-stage endometrial cancer.[12-18]

The first randomized controlled trial to compare the survival outcomes of laparoscopy and open surgery was done in 2006.[12,13] Results from the Laparoscopic Approach to

[1] *Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of the Philippines-Philippine General Hospital*

Presented as a Poster at the 2020 International Gynecologic Cancer Society xDigital Annual Global Meeting, Sept. 10-13, 2020

Corresponding author:
Gladdy Maura G. Facun, MD, DPOGS
Tel. No.: (63) 9459752056
Email address: gladzfacun@gmail.com

Disclaimer: The views expressed in this article are the authors' own and do not reflect the views of the institution.

Source(s) of support: All expenditures related to the conduct of this study are all provided for by the authors.

Financial Disclosure:
The authors did not report any potential conflicts of interest.

Carcinoma of the Endometrium (LACE) Trial demonstrated a similar over-all survival [Total Abdominal Hysterectomy (TAH) 6.8%, Total Laparoscopic Hysterectomy (TLH) 7.4%, p=0.76] and recurrence free survival (TAH 7.9%, TLH 8.1%, p=0.93) among patients undergoing surgical staging for endometrial cancer. The disease-free survival after 4.5 years of follow up was higher in the laparoscopy group (TAH 81.3%, TLH 81.6%, $p < 0.007$). Findings from these early studies on laparoscopic surgery encouraged the utilization of laparoscopic surgery as treatment for early-stage endometrial cancer.

Compared with TAH, patients who underwent TLH had significantly greater improvements in quality of life (QoL) both at early (up to 4 weeks) and late (up to 6 months) post-recovery. During early recovery, patients who underwent TLH showed better physical (11% greater), functional (13%) and over-all well-being (7.5% greater). Body image (7.5%) was also better in the TLH group. There was no difference in the social and emotional components of QoL. A similar finding was noted during the late postoperative recovery phase.[12,17,18]

The Gynecologic Oncology Group LAP 2 (GOG LAP2) Study is the largest multicenter trial comparing laparoscopy and open surgery.[17,18] Findings from this study strengthened the results of the LACE trial in terms of survival outcomes (5 yr OS - TAH 89.8%, TLH 89.8%). However, a small difference was found based on 3-year recurrence rate favoring the open surgery than laparoscopy (TAH 10.2%, TLH 11.4%). Conversion rate was higher in the GOG LAP 2 study (25.8% vs 6% in LACE Trial) and this was attributed to the need for aortic lymph node dissection in the GOG LAP2 Study. The main reasons for conversion included poor visibility (14.6%), metastatic cancer (4.1%) and bleeding (2.9%). Patients who underwent laparoscopy had fewer postoperative complications / events and similar rates of intraoperative complications. Operative time was longer in this group TLH (204 minutes) versus TAH (130 minutes).

A Cochrane systematic review of these trials including 4389 women did not show any significant difference in the risk of death (HR 1.04, 95% CI, 0.86 to 1.25), risk of recurrence (HR 1.14, 95% CI, 0.9 to 1.43), perioperative complications (blood transfusion, bladder/ ureteral/ bowel / vascular injury) and rate of perioperative death between the two groups.[15,16] The length of hospital stay, however, was shorter in those who underwent laparoscopy.

Despite the presence of large scale randomized trials supporting the role of laparoscopy for early-stage endometrial cancer, the paucity of local experience prevents the adoption of laparoscopic surgery as procedure of choice in managing early endometrial cancer. Through this study, we reviewed the surgical outcomes and costs of laparoscopic surgery for clinical stage I endometrial cancer patients during the first two years of its implementation in a tertiary hospital. The results from this study may guide future undertakings in relation to minimally invasive surgery.

OBJECTIVES

The present study aims to determine the clinical profile of patients, operative outcomes and costs of undergoing comprehensive surgical staging by laparoscopy for clinical stage I endometrial cancer in a tertiary hospital. The specific objectives are the following:

1. To determine the clinical profile of patients who underwent laparoscopic surgery for clinical stage I endometrial cancer
2. To determine the surgicopathologic profile of patients who underwent laparoscopic surgery for clinical stage I endometrial cancer
3. To determine the average duration of laparoscopic surgery and the average length of hospital stay of patients who underwent laparoscopic surgery
4. To determine the incidence of intraoperative complications which include blood loss, ureteral / bowel / bladder / vascular injury, abdominal wall hematoma, subcutaneous emphysema and pneumothorax / pneumomediastinum
5. To determine the incidence of postoperative complications which include ileus, sepsis, febrile episodes requiring intravenous antibiotics, wound dehiscence, umbilical herniation, lymphocyst formation, deep vein thrombosis, pulmonary embolism and death
6. To determine the average cost of surgery and hospitalization of patients undergoing laparoscopy for clinical stage I endometrial cancer

METHODOLOGY

This is a descriptive study that involves a chart review of all patients admitted under the Charity Service of the Division of Gynecologic Oncology who underwent comprehensive laparoscopic surgery and lymphadenectomy for clinical stage I Endometrial Cancer at the Philippine General Hospital from May 2017 to May 2019. Data collection was carried out after approval from the institutional ethics review committee. The following clinical parameters were extracted during the chart review and recorded in a patient data form: age, gravidity, parity, body mass index (BMI), performance status, clinical stage of the disease at the time of diagnosis of endometrial cancer, comorbidities and risk factors, pre-operative surgical pathology, ultrasound report and laboratory results (hemoglobin, hematocrit, WBC). Peri-operative and post-operative outcomes which included operative time, blood loss, duration of hospital stay, peri- and post-operative complications and adverse events were also recorded. The rate of conversion from laparoscopy to laparotomy was also recorded. The acceptable failure rate was based on the GOG LAP 2 study which showed a conversion rate of 25.8%, 4.1% of which was from presence of metastatic disease. The current disease status of the patients were documented. Patients who did not follow up at the Cancer Institute were contacted through phone calls to confirm current disease status.

All information collated was encoded in a dedicated computer using Microsoft Excel. Data was processed and analyzed using Open Epi statistical software. Descriptive statistics were presented for baseline demographic and clinical information. Results were expressed using frequency and percentage for categorical variables, or mean and standard deviation for continuous ones.

RESULTS

From the period of May 2017 to May 2019, a total of 254

endometrial cancer patients underwent total hysterectomy with bilateral salpingo-oophorectomy, peritoneal fluid cytology, bilateral pelvic lymph node dissection and/or para-aortic lymph node sampling. Among these, 141 (55.5%) were clinical stage I patients, and 19.9% (28 out of 141) underwent laparoscopic surgery. Seventeen cases were done during the first year of implementation of laparoscopic approach to surgical staging in the institution, while 11 were done during the second year.

A total of 28 cases were included in the study. Table 1 shows the baseline characteristics of those included. The mean age was 46.7 +/- 12.9 years. Majority of these patients were pre-menopause (57.1%) who presented with heavy menstrual bleeding. Risk factors that were present in our subjects included obesity (53.5%), nulliparity (46.4%), diabetes mellitus (14.3%), primary infertility (14.3%), polycystic ovary syndrome (7.1%) and dyslipidemia (3.6%). Although only considered as an associated risk factor, hypertension co-existed in almost half of the patients (42.8%).

All patients were of good functional status having and ECOG score of 0 prior to surgery. Four patients had previous abdominal surgery and the mean BMI was 24.7 +/- 3.5. The highest BMI was 31.2. The mean uterine diameter was 6.0 +/- 1.6 cm and 129.3 +/- 88.2 cc in volume. There were 2 patients assessed to have 10-12 weeks uterine size on

Table 1. Pre-operative Characteristics of Endometrial Cancer Patients who Underwent Comprehensive Surgical Staging via Laparoscopy

	Laparoscopy (n=28) **(Mean/ median, SD/range, frequency*)**
Age, years	Mean (Range) = 46.7 (25 - 71)
Gravidity	Median (Range) = 1 (0-8)
Parity	Median (Range) = 1 (0-7)
Menopausal status	
Premenopause	16 (57.1%)
Perimenopause	2 (7.1%)
Postmenopause	10 (35.7%)
BMI, kg/m2	Mean (SD) = 24.7 (3.5)
Underweight	2 (7.1%)
Normal (18.5 – 22.9)	8 (28.6%)
Overweight (23 – 24.9)	3 (10.7%)
Obese I (25 – 29.9)	13 (46.4%)
Obese II (≥ 30)	2 (7.1%)
Performance status	
ECOG 0	28 (100.0%)
Tumor size, cm	Mean (SD) = 3.6 (1.9)
Tumor Grade	
Grade 1	18 (64.3%)
Grade 2	8 (28.6%)
Grade 3	-
Tumor depth / Myometrial invasion	
No myometrial invasion	16 (57.1%)
< 50% myometrial invasion	7 (25.0%)
≥ 50% myometrial invasion	5 (17.9%)
Uterine size (sonographic-diameter), cm	Mean (SD) = 6.0 (1.6)
Uterine size (sonographic-volume), cm	Mean (SD)= 129.3 (88.2)
Comorbidities / Risk Factors	
Diabetes mellitus	4 (14.3%)
Hypertension	12 (42.8%)
Dyslipidemia	1 (3.6%)
Polycystic ovary syndrome	2 (7.1%)
Tamoxifen use	-
Other medications	-
Previous abdominal surgery	4 (14.3%)
Others	Primary infertility = 4 (14.3%) Hepatitis B = 2 (7.1%) Hypothyroidism = 1 (3.6%) Cholecystolithiasis = 1 (3.6%) Nodular non-toxic goiter = 1 (3.6%)

pelvic examination, one of whom eventually had to undergo myomectomy prior to vaginal delivery of the specimen (uterine diameter = 10.3 cm). Majority of the patients had Grade 1 tumor (64.3%, n=18) while the rest had Grade 2 tumor (28.6%, n=8). The mean tumor size was 3.6 +/- 1.9 cm. Majority had no to less than 50% myometrial invasion (82.1%).

Out of the 28 laparoscopic procedures performed, none was converted to an exploratory laparotomy. The first case necessitated a mini-laparotomy due to the presence of a large uterine size (13.5 x 11 x 5.2 cm) which precluded vaginal delivery of the uterus. BMI and history of previous surgery were not risk factors for conversion. The average length of surgery, from cutting to last stitch was 244.5 minutes. Six patients had additional procedures such as sentinel lymph node mapping (2), myomectomy (1), infracolic omentectomy (1), frozen section for peritoneal implants (1) and cholecystectomy (1). The mean operative time was 235.7 minutes for TLHBSO, BLND and 281.1 minutes for those in whom an addition of PALS was performed. No surgical complications were noted intra-operatively. The mean blood loss for all patients was 217.3 +/- 171.4 mL which is compatible with the mean drop in hemoglobin of 4.7 +/- 5.1 g/dL. Post-operative complications were minimal. Only 3 (10.7%) patients required blood transfusion and one patient had vaginal vault dehiscence and lymphocyst formation. Patients who had blood transfusion include (1) patient who had an abdominal incision for delivery of an enlarged uterus (EBL=900 mL), (2) patient with enlarged lymph nodes noted intra-operatively (EBL = 400 mL), and (3) patient with peritoneal implants and who underwent biopsy of implants with frozen section (EBL = 350 mL).

The mean hospital length of stay was 7 days (168.4 +/- 30 hours), 4 to 5 days (115.3 +/- 32 hours) of which are spent in the hospital prior to the actual operation. Pre-operative stay was due to work up and clearance for surgery and availability of OR schedule. The mean post-operative hospital stay was 49 +/- 13.8 hours (2 days). The delay in the actual hospital discharge of a patient from the time she is cleared for home by the attending physician, if any, was primarily due to financial reasons. Patients with insufficient funds to pay for their hospital bill had to apply for financial assistance from the hospital's medical social services. Other factors contributing to the delay include clearance from co-managing services and processing of papers required to avail the Philippine's social health insurance (PhilHealth) coverage.

Twenty five (89%) patients had endometrioid histology. Pre-operatively, 18 out of the 28 cases (64.3%) had FIGO Grade 1 tumor while 8 (28.6%) had Grade 2 tumor. Six of the 18 patients (33%) with Grade 1 tumor prior to surgery had high grade tumors on final histopathology. While all of the patients were diagnosed as clinical stage 1 prior to surgery, 2 were upstaged to stage III disease (7.1%, n=2) for lymph node and adnexal involvement, respectively. One patient had no residual tumor and one case only showed hyperplasia with atypia, though both of them had pre-operative histologic diagnosis of endometrioid adenocarcinoma obtained through endometrial curettage. One case had proliferative endometrium in the definitive specimen with a pre-operative diagnosis based on an endometrial biopsy of endometrial hyperplasia with atypia cannot rule out endometrial carcinoma. The rest of the cases (89.2%, n=25) had stage I disease (89.2%, n=25). Median lymph node counts were as follows: right pelvic = 7, left pelvic = 7, para-aortic=5.

Adjuvant treatment for endometrial cancer is stratified based on the risk of disease recurrence. No adjuvant treatment is given for low risk patients (FIGO grade 1 or 2 and <50% myometrial invasion) while radiotherapy and/or chemotherapy is given for those with intermediate (>50% myometrial invasion, age >60, tumor size >2cm), or high risk (FIGO Grade 3, stage II-IV, poor tumor histology). In our study, almost half (46.4%. n=12) of the patients were stage IA with low risk for recurrence, hence they were advised to undergo observation. The remaining half (57.1%, n=16) warranted adjuvant treatment. Out of 16, nine (32.1%) were classified as intermediate risk and underwent vaginal brachytherapy. One case was classified as high risk for recurrence (FIGO Grade 3, stage IB) and was advised EBRT, though did not comply.

Systemic chemotherapy with or without radiation was recommended to two patients with stage III disease (7.1%) and 4 other patients who had LVSI (14.3%). However, only 1 out of the 6 was able to complete treatment and 2 died of the disease without completing treatment.

Data on patient follow-up and disease status were completed until January 31, 2020. The median follow up of patients was 13.5 months (1 - 29 months). Sixteen patients (57.1%) were alive without evidence of disease while 5 (17.9%) were lost to follow up. The patient who was diagnosed as stage IIIA did not consent for adjuvant treatment but had no evidence of disease after 9 months of follow-up. Two patients (7.1%) had tumor progression and were documented dead without completing treatment.

Most low and middle income countries are slow to adopt laparoscopic surgery in their practice due to its associated high cost.[19-24] The total hospital charges in our study ranged from Php 17,718.75 ($336.47) to Php 125,698.50 ($2,386.98) with an average of Php 59,882.31 ($1,137.15). The lowest charge of Php 17,718.75 ($336.47) was incurred during the first laparoscopic procedure when all the instruments and the use the laparoscopic unit were provided free of charge. The highest charge was attributed to a 90 thousand ($1709) worth of use of anesthetic machine which was an error in hospital billing. The wide variation in costs may be attributed to the number and type of laparoscopic instruments/consumables being procured during each surgery. Several items such as trocars (2), suction irrigation device (1), bipolar electrosurgical vessel sealing device (1) and an ultrasonic dissector (1) comprised the bulk of one procedure which amounted to Php 111,401.25 ($2,115.48). The cost of laparoscopic surgery was brought down to Php 23,980.50 ($455.38) when no new laparoscopic instruments were procured and reusable instruments were sterilized and utilized.

The total hospital charges and the amount covered by PhilHealth for each patient, ranging from Php 18,500 to Php 21,400 is insufficient to subsidize the cost of laparoscopic surgery. The hospital then utilizes other government funding such as Department of Health medical assistance funds, Office of the President's funds, and guarantee letter from the local government. Only 1 in 28 patients had out of pocket expenditures for the surgery and hospitalization.

DISCUSSION

A 19.9% rate of utilization of laparoscopic approach for early-stage endometrial cancer and the actual count of 28 procedures in a span of 2 years is low. Factors that explain the low frequency include 1) limitation in the number of trained surgeons that can perform advanced laparoscopic surgery, 2) high cost of surgery, and 3) preference of patients to undergo surgery using an open technique.

PATIENT SELECTION

The zero conversion rate in our study, which is significantly lower than reported in previous studies, reflects the proper selection of patients who underwent laparoscopic surgery. [13,16,17] Our patients were screened using the criteria for laparoscopic surgery cited in the 2018 SGOP Clinical Practice Guidelines: endometrioid histology, BMI < 35 kg/m2, uterine diameter < 10 cm, mobile uterus, no severe cardiopulmonary disease, no previous pelvic and abdominal radiation, with clinical stage I and II disease and those with no bulky lymph node on imaging.[10,25] Though, there was one case that required an abdominal incision to facilitate extraction of an enlarged uterus (13.5 x 11.0 x 5.2 cm). Major reasons for conversion reported in literature include poor exposure and intraperitoneal lesion requiring laparotomy for resection, were not encounterd by proper patient selection.

Two out of the 28 patients (7.1%) included in the study had extra-uterine spread which was not detected pre-operatively. The addition of PET-CT or CT Scan as part of pre-operative imaging should be considered to improve detection of lymph node and distant metastasis and, thereby, optimize treatment planning.

SURGICAL OUTCOMES AND SAFETY

Operative time

The median operative time for TLHBSO, PFC, BLND, PALS in the GOG LAP 2 Study was 204 minutes. Bennich et al reported a median length of surgery of 60 minutes when BLND was performed and 120 minutes when both BLND and PALS were done.[26] Our study showed a mean operative time of 235.7 minutes and 281.1 minutes, respectively. There was no trend observed based on the number of cumulative cases performed and the length of surgery. The number of cases included in the study might not be enough to demonstrate this efficiency of performing the surgical procedures as may be reflected by a decreasing trend in the operative time and an increasing trend in the number of lymph nodes harvested. A few studies looked into the minimum number of cases needed to achieve surgical proficiency in laparoscopic surgery. Rosen found that the learning curve for a trainee laparoscopic surgeon was after 16 cases, while with the experienced laparoscopic gynecological surgeon, the plateau was seen after about 10 procedures.[28] Lim et al found that proficiency was only achieved after 49 cases of endometrial cancer.[29] Melendez et al found that statistically significant reductions in operative time occur and continue to occur after 125 cases were performed and after five years of doing this procedure.[30] The learning curve required to learn a new technique may account for the variation in the operative time. Fellows-in-training served as 2nd (camera) and 3rd (vagina) assists. The differences in the technical skills, dexterity and accuracy of movement of the camera-assist and the vaginal assist also affect the duration of the operation.

Because of the steep learning curve in acquiring advanced laparoscopic skills, it is suggested that oncologists follow the criteria for patient selection for laparoscopic surgery set by SGOP and to choose the easy cases during the early years of integration of laparoscopy in their institution. It is recommended to increase recruitment of patients undergoing laparoscopy to achieve surgical proficiency. Apart from observation in the operating room, fellows-in-training may also practice their laparoscopic skills using surgical trainers, simulators and animal models.

Complications

The mean blood loss for our patients was 217.3 mL without any significant drop in Hgb (4.7 g/dL), and only 3 required blood transfusion. The blood transfusion rate of 10.7% in our study is consistent with that reported in literature.[13,15,17] The increase in magnification that allows for more precise dissection, as well as the level of expertise of the surgeons could account for the minimal blood loss in our procedures.

There were no intra-operative complications. Vaginal vault dehiscence and lymphocyst formation were experienced by 1 out of the 28 patients (3.6%). The reported incidence of lymphocysts in patients undergoing gynecologic cancer surgery is 1-58%, 96% of these occur within 6 weeks after surgery but there have been cases that developed more than 1 year from surgery. Only 5-18% are symptomatic, and intervention in the form of drainage is only indicated in these subset of patients.[31] A local study by Sia Su et al showed a lymphocyst prevalence of 3.44 per 100,000 gynecologic malignancy cases.[32] Several factors have been associated with lymphocyst formation such as BMI, type of lymphadenectomy performed, number of nodes harvested, number of positive lymph nodes and surgery type, but data has remained controversial up to date. The median number of nodes harvested in this study is 7 on the left and 5 on the right. The patient who developed lymphocyst did not have lymph node metastasis, the total number of nodes harvested on the left was 7.

Number of Nodes Harvested

The value of lymphadenectomy in early-stage endometrial cancer is controversial. Nevertheless, pelvic lymph node dissection was done in all subjects included in the study. Para-aortic lymph node dissection was not included as part of standard surgical staging because it lengthens operative time, increases risk for vascular injury and the risk of para-aortic involvement in stage 1 endometrial cancer is very low (0.8%)[33]. The decision to proceed with PALS was based on the presence of 1) deep myometrial invasion 2) tumor grade 3, and 3) intraoperative findings beyond stage I. The definition of adequate lymphadenectomy has not been standardized but at least 10 pelvic nodes sampled from each side of the pelvis[25], and 5 from the para-aortic area[34] have been suggested to constitute adequate lymphadenectomy. Our median lymph node counts were as follows: right pelvic = 7 (0-16), left pelvic = 7 (1-17), and para-aortic=5 (0-10). Comparing the average number of harvested pelvic and para-aortic lymph nodes in our study to the results obtained by Co and Sicam in their review

of endometrial cancer patients who underwent laparotomy showed a lower yield for pelvic lymph nodes (7 versus 16) for laparoscopy but with higher yield (5 versus 1) for para-aortic lymph nodes.[35] Although the therapeutic benefit of lymphadenectomy for early-stage endometrial cancer can be argued, steps to achieve adequate lymphadenectomy should be undertaken especially in intermediate and high-risk endometrial cancer patients, as it will help us determine those at increased risk of developing recurrence.

Sentinel lymph node mapping with ultrastaging has been associated with less morbidity than complete or systematic lymphadenectomy, and has been shown to improve detection of micrometastasis to the lymph nodes. However, data on this procedure are not generalizable due to limited statistical power[36-38]. The addition of SLND in two of our patients did not affect the number of nodes harvested.

Hospital Stay

Studies on laparoscopic and open surgery showed a significant difference in postoperative hospital stay favoring the open approach. In the GOG LAP 2 study, a smaller proportion of patients who underwent laparoscopy needed more than 2 days of hospitalization after surgery (52% versus 94%, p<0.0001), the median length of post-operative stay for these patients is 2 to 4 days.[17,18] Our local data is consistent with these findings, with median length of postoperative stay of 2 days (49 hours). However, the mean length of stay from admission to actual discharge was 7 days (168.4 hours), which has no difference in those who undergo exploratory laparotomy. The total hospital stay is not entirely accounted for by the actual hospital care and surgical management. The prolonged duration of admission was primarily due to the pre-operative work-up, waiting time for OR scheduling/queuing and pre-operative medical clearance clearance which takes an average of 4 to 5 days. Shifting all of these in the outpatient setting will significantly decrease the length of hospital stay translating to decrease in total cost of hospitalization.

SURVIVAL / RECURRENCE

Most women with endometrial cancer have a good prognosis with a 5-year overall survival rate of 80-85%[39]. Several prognostic factors have been identified such as age, stage, histologic type and grade, extrauterine involvement and presence of LVSI.[2,40-42]

Stage is the most important prognostic factor in endometrial cancer, with a 5-year survival rate of 81-91% for a stage I disease and 30-52% for a stage III disease. In our study, 2 patients (7.1%) were upstaged to stage III, one due to the presence of positive para-aortic lymph nodes, the other due to adnexal involvement. The patient with lymph node involvement died of disease 1 year after surgery. The other patient did not consent for adjuvant treatment but with no evidence of disease for 9 months. Close follow-up of this patient is necessary as the probability of recurrence was 7.5 times higher in late stages than with stage I disease. A recurrence rate of 3.8% for stage IA endometrial cancer was reported by Co and Sicam in 2018.[35]

The presence of LVSI has also been shown to be a significant and consistent poor prognostic factor for lymph node involvement and recurrence. Overall recurrence can be as high as 17% in LVSI-positive patients while lymph node involvement can be as high as 25%.[40,41,43] In our study, LVSI was present in both cases that had local recurrence and subsequently died of cancer.

COST

The total hospital charges in our study ranged from Php 17,718.75 ($336.47) to Php 125,698.50 ($2,386.98) with an average of Php 59,882.31 ($1,137.15). The wide variation in expenses was due to the number and type of laparoscopic instruments being procured during each surgery. The total cost of single use/ disposable instruments is Php 108,143.00 ($2,053.61). Other instruments such as the graspers, endoshear and suction irrigator are re-usable and part of the basic lap package purchased by the hospital. Single use/ disposable type of these instruments are available but are only purchased depending on surgeon's preference.

The cost of surgery was decreased by 79% [Php 111, 401.25 ($2,115.48) to 23, 980.50 ($455.38)] when no new laparoscopic instruments were procured and old instruments, whether disposable or re-usable, were sterilized for re-use. Presently, disposable instruments are being sterilized and re-used up to 3-4x prior to being discarded. Concerns regarding transmission of infections, instrument inefficiency and lack of durability when instruments are re-sterilized have been addressed in several studies[44,45]. The cheap alternative of re-sterilizing instruments especially in low to middle income economies are feasible and acceptable.

Estimates of the amount needed to perform laparoscopy for endometrial cancer was done based on data gathered in the study. The following cost estimates may serve as a guide in establishing health packages that could benefit majority of our patients (Table 2).

Using the computations given, a patient with endometrial cancer needs Php 127,667.00 ($2,424.36) to undergo laparoscopic surgery, which is a far cry from the Php 21,400 ($406.38) maximum PhilHealth coverage being given to patients. Majority of Filipinos with average monthly income of Php 16,110.00 ($305.92), based on a minimum daily wage of Php 537.00 ($10.20) will not be able to afford laparoscopic surgery as this is equivalent to 6 months-worth of salary.

In this study, we identified 3 possible steps to make laparoscopic surgery, which is the standard of care for endometrial cancer, available to the general population: 1) PhilHealth coverage must be increased, 2) instruments may be sterilized and re-used, and 3) other alternative sources of funding both from government and/or private donors must be identified.

INTEGRATION IN THE GYNECOLOGIC ONCOLOGY PROGRAM

Only a handful of gynecologic oncologists have been trained in laparoscopy and all of these oncologists received training from oncologists in high resource settings. The integration of laparoscopic surgery in the gynecologic oncology fellowship training program in our country provided hands-on exposure on gynecologic laparoscopy techniques to the trainees and made it accessible to the service patients. This is an integral step in promoting and adopting laparoscopy as standard of care for endometrial cancer. This also opens the possibility that the availability of skilled laparoscopic surgeons will no longer be a limiting factor in the future.[46]

Table 2. Estimated Perioperative Cost of Laparoscopic Surgery for Endometrial Cancer

PRE-OPERATIVE COSTS	Php 2,790.00 *($52.98)*
CBC with platelet and differential count	75.00 *($1.42)*
PT / PTT	250.00 *($4.75)*
Blood chemistry (FBS, Crea, K, Mg, Ca, alb, AST, ALT, Na, Cl, alk phos)	710.00 *($13.48)*
Lipid profile (Triglyceride, total cholesterol, HDL, LDL)	170.00 *($3.22)*
Urinalysis	240.00 *($4.56)*
Blood Typing	125.00 *($2.37)*
12-lead ECG	70.00 *($1.33)*
Chest X-ray PA	140.00 *($2.66)*
Holoabdominal Ultrasound	275.00 *($5.22)*
Transvaginal Ultrasound	300.00 *($5.70)*
Hepatitis screening (HBSAg)	215.00 *($4.08)*
Blood Typing	125.00 *($2.37)*
Crossmatching	95.00 *($1.80)*
OPERATION-RELATED COSTS	Php 127,667.00 *($2,424.36)*
Basic OR Fee	1,500.00 *($28.48)*
Laparoscopy (operative)	690.00 *($13.10)*
OB OR Machine and Equipment (LigaSureTM)	2,000.00 *($37.98)*
OR Anes Equipment	905.00 *($17.19)*
Basic Machine / Instruments	10, 884.00 *($206.68)*
Laparoscopic Instruments	108,143.00 *($2,053.61)*
PACU / Recovery Room Fee	545.00 *($10.35)*
Room and Boarding	3,000.00 *($56.97)*
POST-OPERATIVE COSTS	Php 1,305.00 *($24.78)*
12-lead ECG	70.00 *($1.33)*
CBC with platelet and differential count	75.00 *($1.42)*
PT / PTT	250.00 *($4.75)*
Crea, K, Na, Cl, Mg	395.00 *($7.50)*
Tissue Biopsy	515.00 *($9.78)*
TOTAL PERIOPERATIVE COSTS	Php 131,762.00 *($2,502.12)*

CONCLUSION

The results of this study support the incorporation of laparoscopy as standard of treatment for early-stage endometrial cancer. Data gathered confirm the benefits reported in the GOG LAP 2 Study, the LACE Trial and the Systemic Cochrane Review which include minimal blood loss, minimal complications and short recovery time. Proper patient selection using the following criteria: endometrioid histology, BMI < 35 kg/m2, uterine diameter < 10 cm, mobile uterus, no severe cardiopulmonary disease, no previous pelvic and abdominal radiation, with clinical stage I and II disease and those with no bulky lymph node on imaging is recommended. The addition of PET-CT/CT Scan as part of pre-operative imaging should be considered to improve detection of lymph node and distant metastasis.

Modifications in our current practice, such as outpatient pre-operative medical evaluation, 1 day admission prior to surgery, outpatient screening for medical subsidy and increase in the number of PhilHealth personnel for processing insurance claims, should be adopted to decrease the length of hospital stay. This may also translate to a decrease in the cost of laparoscopic surgery.

Surgical efficiency was not yet demonstrated in this study because of the small sample size. Increasing the number of laparoscopic procedures and instituting measures that would help make this procedure accessible will increase surgical proficiency, decrease its cost, and improve health gain. Key steps include: popularization of the safety and benefits of the technique, increasing PhilHealth coverage, sterilization and re-use of instruments, and provision for medical subsidy.

LIMITATIONS AND RECOMMENDATIONS

Given the retrospective nature of the study, we were limited to the small number of patients who underwent comprehensive surgical staging from May 2017 to May 2019. Survival and recurrence rates of patients who underwent laparoscopic surgery were not included due to the short follow-up from date of surgery. Direct non-medical and indirect costs of laparoscopic surgery, which include transportation costs, paid caregiver time, productivity loss and the associated post-hospitalization costs were also not included.

It is suggested that future studies look into the long term outcomes of these patients. Local studies comparing the surgical and long-term outcomes of open versus laparoscopic surgery is recommended. Cost effectiveness and safety of re-use of laparoscopic instruments is another aspect that may be looked into.

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Incidence of HIV infection among cervical cancer patients in a tertiary government hospital from August 2019 - April 2020

Diorelle Rose G. Malaque, MD and Helen R. Amorin, MD, FPOGS, FSGOP

ABSTRACT

Introduction: Human immunodeficiency virus (HIV) disease continues to be a serious global health issue. As of January 2019, there were 1,249 newly confirmed HIV-positive individuals reported to the HIV/AIDS & ART Registry of the Philippines (HARP). The Centers for Disease Control and Prevention has expanded the AIDS surveillance case definition to include the addition of invasive cervical cancer as an AIDS-defining illness (ADI).

Objective: To determine the incidence of HIV infection among cervical cancer patients in a tertiary government hospital from August 2019 to April 2020.

Materials and Methods: This was a descriptive, cross-sectional, facility-based study design. Collection of data was made through a one-on-one interview. Participating patients were screened for HIV according to the institution protocol for routine HIV testing services. The data collected was entered and analyzed by descriptive statistics using statistical software SPSS version 22.

Results: All 95 participants diagnosed with cervical cancer were not co-infected with HIV.

Conclusion: Although HIV/AIDS may predispose a woman to developing cervical cancer, this study showed that there was no co-infection with HIV among cervical cancer patients treated in a tertiary government hospital from August 2019 to April 2020.

Keywords: *AIDS, cervical cancer, coinfection, HIV, incidence*

INTRODUCTION

On December 18, 1992, the Centers for Disease Control and Prevention had expanded the Acquired Immunodeficiency Syndrome (AIDS) surveillance by including pulmonary tuberculosis, recurrent pneumonia and invasive cervical cancer to the 23 clinical conditions cited in the 1987 definition. Invasive cervical cancer is the third malignancy in the list of AIDS Defining Illnesses (ADI) which includes Kaposi's Sarcoma and Non-Hodgkin's Lymphomas.[1]

HIV disease continues to be a serious global health issue. In 2017, 1.8 million new cases of HIV and 940,000 deaths from AIDS related illnesses were reported globally.[2] As of Jan 2019, the HIV/AIDS & ART Registry of the Philippines (HARP) reported 1,249 new HIV cases, 16% of which had advanced HIV infection. Sixteen percent (196) had clinical manifestations of advanced HIV infection at the time of diagnosis.[3]

Department of Obstetrics and Gynecology, Vicente Sotto Memorial Medical Center, B. Rodriguez St., Cebu City

This paper has been presented at: 1. Research Paper Presentation, Philippine Obstetrical & Gynecological Society Cebu Chapter (July 23, 2020) online; 2. Society of Gynecologic Oncologists of the Philippines, Inc. (SGOP) 6th Dr. Luciano Sotto Research Paper Contest, Philippines (6 November 2020) online

Corresponding author:
Diorelle Rose G. Malaque, MD
Department of Obstetrics and Gynecology, Vicente Sotto Memorial Medical Center, B. Rodriguez St., Cebu City
Email address: diorellemalaque@gmail.com

Financial Disclosure
The authors did not report any potential conflicts of interest.

Cervical cancer is a leading cause of cancer and cancer-related deaths among women worldwide.[4] Nationally, it ranks second to breast cancer as the top leading cause of new cancer and cancer deaths.[5]

A meta-analysis found 41% of HIV positive women with high grade squamous intraepithelial lesion (HSIL) had more than one type of HPV compared to 7% of women in the general population. They are less likely to have oncogenic HPV type 16 and more likely to have other high risk HPV types.[6] Invasive cervical cancer (ICC) can develop in both HIV-infected and non-infected women. Its incidence can be seven times greater in women with HIV.[7] Various studies concluded that HIV positive women are more likely to develop cervical intraepithelial neoplasia, vulvar, vaginal and perianal lesions compared to HIV negative women.[8-9] Strickler HD, et al observed the strong association between incident HPV and immune status of HIV positive women, characterized by their CD4 T-cell count and plasma HIV RNA levels.[10]

The documentation of HIV status prior to treatment is an important prognostic factor in patients with cervical cancer. It will facilitate the early commencement of treatment for HIV positive cases. This will be associated with lesser cancer-related treatment toxicity, better treatment compliance and outcome.[11] This study can increase awareness on the incidence of HIV in cervical cancer patients, and aid in the development of policies on HIV testing and early initiation of treatment.

STUDY OBJECTIVE

This study was conducted to determine the incidence

of HIV infection among cervical cancer patients in a tertiary government hospital from August 2019 to April 2020.

MATERIALS AND METHODS

This was an institutional Research Ethics Board-approved, descriptive, cross-sectional, facility-based study design conducted in a tertiary government hospital. HIV counselling and testing services were done by the HIV/AIDS Core Team (HACT) in the same institution.

Study Population

Women between 18-80 years of age seen at a tertiary government hospital with biopsy-proven cervical cancer who were evaluated by a gynecologic oncologist and consented to the study were included. The study excluded women below 18 or above 80 years of age and those who did not give consent for participation in the study.

Data Collection Procedure

Collection of data was made through a one-on-one interview between the researcher and the respondent. The researcher assessed socio-sexual characteristics of the patients and their history of cervical cancer screening uptake. Both the English and Visayan dialects were used depending on which language the participant was most proficient with.

The HIV status of the subjects was determined upon enrollment to the study. Participating patients with unknown HIV status but who consented to have HIV testing were referred to the HACT of the hospital. They were screened for HIV according to the institution protocol for routine HIV testing services.

The data collected was entered and analyzed by descriptive statistics using statistical software SPSS version 22. Summary statistics, such as frequencies, means and percentages, were used to summarize variables.

Data Analysis

Descriptive statistics such as Mean with Standard Deviation (SD), Mode, Minimum and Maximum were reported to describe the different numerical variables under socio-sexual characteristics of cervical cancer patients.

Frequency and percentages were computed to summarize results for the different categorical variables. Frequency distribution and percentage were also used to report the proportion of cervical cancer patients with history of HIV testing as well as the results of the HIV testing conducted in this study.

Minitab, a statistical software package, was used in the statistical computations and analysis of data. Data were entered with Microsoft Excel Spreadsheet and were then analyzed with Minitab version 19.0 for Mac Mojave OS.

Data Sampling

Sample size computation was done using OpenEpi version 3.01. The desired a margin of error was to be no more than 5%. A similar study done in UP-PGH wherein a 0 percent prevalence rate was observed was used for sample size computation.[12] A total of 95 participants from a population of 195 were needed for a 95% confidence interval with a 5% margin of error in statistical analysis. Potential respondents were approached based on a set of inclusion criteria, i.e., purposive sampling.

RESULTS

A total of 95 subjects diagnosed with cervical cancer participated in this study. Table 1 presents the various socio-demographic and clinical factors of cervical cancer patients included in this study. The mean age of these women is 48.80 with a standard deviation of 10.12 years, indicating a varied group in terms of age. The youngest in this study was aged 24 years old while the oldest was 75 years old at the time of data collection. Majority of the participants (64.21%) were married, leaving a third of the sampled population as either single (21.05%) or widowed (14.74%). About 24.21% of the subjects finished elementary education, 48.42% finished high school and the remaining 27.37% of the population completed college.

Majority (80%) of the participants had gravidity of 5 and below and only 20% of the study population got pregnant >6 times. Majority of the study subjects had their sexual debut between the ages of 16-20 (49.47%). Only 6.32% had sexual contact at the age of 15 and below. There were 42 subjects (44.21%) with only 1 lifetime sexual partner while the rest of the study population (N=53; 55.79%) had two or more sexual partners.

Majority (76.84%) of the subjects denied any history of STI while the rest were previously diagnosed with an STI. All of the subjects had prior cervical cancer screening.

Also shown in Table 1 are the FIGO stage and histologic types of the study subjects. Majority had advanced stage of cervical cancer (80%) at the time of diagnosis. The most common histologic type was squamous cell carcinoma, accounting for about 73.68% of the sample population. Second in rank was adenocarcinoma (17.89%). Other histologic types included the following: clear cell adenocarcinoma (2.11%); adenosquamous carcinoma (2.11%); small cell carcinoma (1.05%) and undifferentiated carcinoma (1.05%).

Table 2 presents the proportion of cervical cancer patients with history of HIV testing and results of the HIV test conducted in this study. Majority of the patients (74.74%) never had prior HIV screening. Of the 24 patients (25.26%) who were previously screened, 21 declared they were non-reactive. Three patients however refused to share the results of their previous test for unknown reasons.

Since this study wanted to determine the HIV status of cervical cancer patients, the participants were asked to undergo HIV screening regardless of their history of prior testing. The HIV test conducted in this study reveals that all 95 subjects were non-reactive.

DISCUSSION

Because cervical cancer is caused by persistent HPV infection, cervical cancer is observed to be uncommon in the 25-29 age group.[13] According to the Philippine Cancer Facts and Estimates, cervical cancer among Filipino women starts rising steeply at age 30.5 The mean age of the participants studied was 48.80 with a standard deviation of 10.12 years. On the other hand, ninety-two percent of newly diagnosed HIV female cases since 1984 were in the reproductive age group (15-49 years old) at the time of testing.[14]

Table 1. Socio-demographic and Clinical Factors

Patients' Clinical Profile	(N=95)	
	Mean (SD)	Min-Max
Age (years)	48.80 (10.12)	24-75
	n	%
Marital status		
Single	20	21.05
Married	61	64.21
Widowed	14	14.74
Highest educational attainment		
Elementary	23	24.21
Secondary (High School)	46	48.42
Tertiary (College)	26	27.37
Gravidity		
0	4	4.21
1	11	11.58
2	20	21.05
3	17	17.89
4	15	15.79
5	9	9.47
6 and up	19	20.00
Coitarche		
less than 15 years old	6	6.32
16-20 years old	47	49.47
21-25 years old	32	33.68
26-30 years old	10	10.53
Number of sexual partners		
only one	42	44.21
two	17	17.89
three	14	14.74
four	8	8.42
five	6	6.32
more than 5	8	8.42
History of sexually transmitted infection		
with	22	23.16
without	73	76.84
Prior cervical cancer screening		
with	95	100.00
Patients' FIGO Clinical Stages		
Early		
IA	1	1.05
IB	10	10.53
IIA	8	8.42
Advanced		
IIB	19	20.00
IIIA	1	1.05
IIIB	54	56.84
IVA	1	1.05
Patients' Histological Findings		
Squamous cell carcinoma	70	73.68
Adenocarcinoma	17	17.89
Clear cell adenocarcinoma	2	2.11
Adenosquamous	2	2.11
Small cell carcinoma	1	1.05
Undifferentiated carcinoma	1	1.05
Others	2	2.11

Table 2. HIV testing of cervical cancer patients: history of testing and recent results

HIV Testing of Cervical Cancer Patients	(N=95)	
	Mean (SD)	Min-Max
Coitarche		
less than 15 years old	6	6.32
16-20 years old	47	49.47
21-25 years old	32	33.68
26-30 years old	10	10.53
Prior cervical cancer screening		
with	95	100.00

Only 27.37% of the study population was able to finish college. Women with low socio-economic status are vulnerable to preventable illnesses, such as cervical cancer, because of their restricted access to health care, lack of knowledge on preventive measures and poor nutrition.[15]

High parity may increase the risk of cervical cancer because it maintains the transformation zone on the ectocervix for many years facilitating the direct exposure to HPV. Also, hormonal changes induced by pregnancy (increased levels of estrogen and progesterone) may also modulate the immune response to HPV and influence risk of persistence or progression.[16-18] However in this study, majority of the participants (80%) reported gravidity of 5 and below and only 20% of the study population got pregnant >6 times. These participants might have other factors particularly having a low immune system response to clearing an oncogenic infection.

Early sexual activity of less than 14 years old or within 1 year of menarche is a risk factor in acquiring cervical cancer since the transformation zone is susceptible to HPV during this period.[19] The risk of invasive cervical carcinoma is increased with the number of lifetime sexual partners.[13] In this study, most of the subjects had their sexual debut between the ages of 16-20 (49.47%) and only 6.32% had sexual contact at the age of 15 and below. Moreover, there were 42 subjects (44.21%) with only 1 lifetime sexual partner while the rest of the study population (N=53; 55.79%) had two or more sexual partners.

These findings do not support the literature mentioned. However, these subjects may have other risk factors that predisposed them to the development of cervical cancer.

Women who have co-infection with HPV and other sexually transmitted infections are more likely to develop cervical cancer than women who are not co-infected.[13] This observation was not evident in our study since only 23.16% of our participants had prior STI.

About 2/3 of cervical cancer in the Philippines are diagnosed in advanced stage, leading to a high mortality rate.[13] This is similar to the findings in our study wherein majority of the subjects had advanced stage of cervical cancer (80%) while only less than a third (20%) were in the early stage of the disease at the time of diagnosis.

Approximately 80% to 85% of cervical cancers are squamous cell carcinomas, and 15% to 20% are adenocarcinomas.[4] These findings are similar to our study as 73.68% of our participants had the squamous cell carcinoma subtype. Second in rank was adenocarcinoma (17.89%).

The HIV test conducted in this study revealed that all 95 subjects were non-reactive. Our result is similar to the UP-PGH study where there was no reported HIV infection among the 394 cervical cancer patients enrolled from 2012 to 2014.12 Based on the data documented by DOH-HARP from January 1984 to March 2020, ninety-four percent (72,855) of those diagnosed with HIV were male and only 6% (4,759) were female. Of the 4,759 females reported with HIV, 585 (12%) were from Region 7. From 1984 to 1990, 62% (133 of 216 cases) of those diagnosed were female. However, since 1991 the proportion of diagnosed males has been greater than that of females because of males having sex with males. Geographically, from January 1984 to March 2020, Region 7 ranked fourth nationwide with 6,798 (9%) cases. Although heterosexual intercourse was the most common mode of transmission among diagnosed females, 99% of reported cases are among intravenous drug users.[14]

CONCLUSION

Although HIV/AIDS may predispose a woman to developing cervical cancer, this study showed that there was no co-infection with HIV among the cervical cancer patients in a tertiary government hospital from August 2019 to April 2020.

RECOMMENDATIONS

Individualized rather than routine screening for HIV should be done among cervical cancer patients.

Future researchers should take into account other variables such as history of oral contraceptive use and cigarette smoking. Sexual partners of participants must be further investigated for any history of STI, illicit drug use, and history of sexual contact with other male individuals or high-risk women, as these factors could highly contribute in acquiring cervical cancer and HIV.

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Laparoscopic sentinel node biopsy in early endometrial cancer using indocyanine green: A report of the first two cases in the Philippines

Bernadette C. Yap, MD, Renee Vina G. Sicam, MD, FPOGS, FSGOP, FPSGE and Doris R. Benavides, MD, FPOGS, FSGOP, FPSGE

ABSTRACT

Standard surgical staging for endometrial cancer is extrafascial hysterectomy, bilateral salpingo-oophorectomy with retroperitoneal lymph node dissection. Sentinel lymph node (SLN) biopsy allows the surgeon to selectively remove and analyze the most relevant nodes, thereby minimizing complications. Herein we report the first two cases of laparoscopic SLN biopsy using near-infrared fluorescence (NIR) with indocyanine green (ICG) for endometrial cancer in the Philippines. Both cases were diagnosed with endometrial cancer, endometrioid type, confined to the corpus. Identified sentinel nodes were negative for metastasis on ultrastaging. Final histopathology of harvested nodes was negative. Peritumoral lymphovascular space invasion was identified only in the first case. Sentinel lymph node biopsy using ICG in laparoscopic staging for endometrial cancer is an easily performed and reproducible procedure in experienced hands. Standardization of histopathologic analysis of sentinel nodes should be implemented before adapting this method as standard of care in endometrial cancer.

Keywords: *Sentinel lymph node, indocyanine green, endometrial cancer, laparoscopy*

INTRODUCTION

Endometrial cancer is the most commonly occurring female genital tract malignancy worldwide. In the Philippines, it is the 7th leading site among women (4%). It is estimated that one out of 100 hundred women will have endometrial cancer before age 75.[1]

Endometrial cancer spreads lymphatically or hematogenously. The major pathway of lymph node metastasis from the endometrium is through the obturator node, or the internal iliac node with or without parametrial involvement, into the para-aortic chain. Surgical staging involves removal of the pelvic and para-aortic lymph nodes through systematic lymphadenectomy. Lymphedema, as a consequence of lymphadenectomy, varies widely from 5% to as high as 38%.[2] Achouri et. al. observed an incidence of 34.5% of symptomatic postoperative lymphocysts and lower-limb lymphedema in 11.5% of patients who underwent systematic lymphadenectomy for gynecological cancers. They recommend a restrictive use of lymphadenectomy through the sentinel lymph node biopsy.[3]

The sentinel lymph node (SLN) is defined as the first lymph node draining from the tumor. It presupposes an existence of an organized and predictable pattern of lymphatic drainage, such that when the sentinel lymph node is negative for metastasis, the nodes in the secondary nodal basin will be negative as well. Centers such as the Memorial Sloan Kettering Cancer Center have applied an algorithm using sentinel lymph node biopsy to triage patients diagnosed with early stage endometrial cancer. If the harvested sentinel lymph node is negative for tumor, systematic lymphadenectomy is not performed. If positive, systematic lymphadenectomy is completed. SLN allows the clinician to individualize management, preserve physical appearance and functionality, while minimizing complications.

Herein we report the first two cases of laparoscopic sentinel lymph node biopsy using near-infrared fluorescence with indocyanine green dye for endometrial cancer. The procedure was described.

CASE REPORT

Case 1

A 52-year old Gravida 5 Para 5, Filipino woman presented with postmenopausal bleeding. Past medical history was unremarkable. All her pregnancies were carried to term via spontaneous vaginal delivery. Menopause was at 49 years old. She underwent dilatation and curettage that revealed endometrial adenocarcinoma, endometrioid type, moderately differentiated. On internal examination, she had normal external genitalia and smooth vagina. The cervix was smooth measuring 3 x 3 cm. The corpus was small, with no adnexal mass or tenderness. Bilateral parametria were smooth and pliable. Transvaginal ultrasound showed an anteverted uterus with smooth contour. Within the endometrial cavity was a

Section of Gynecologic Oncology, Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines – Manila

Corresponding author:
Bernadette C. Yap
Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines-Manila, Taft Avenue, Ermita, Manila 1000
Email: bernadetteyap8@gmail.com

Presented as a Poster at the 2020 International Gynecologic Cancer Society xDigital Annual Global Meeting, Sept. 10-13, 2020

Financial Disclosure
The author did not report any potential conflicts of interest.

hyperechoic mass measuring 1.6 x 2.0 x 2.7 cm with its inferior pole at the level of the internal os. Doppler studies of the mass showed abundant vascularity with a color score of 4.

She underwent operative laparoscopy, peritoneal fluid cytology, sentinel lymph node biopsy, total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic lymphadenectomy. The conduct of the surgery was as follows: The patient was placed in modified dorsal lithotomy position under general anesthesia. Indocyanine green dye powder (25mg) was dissolved in 10 cc of sterile water. Under direct visualization, 1 cc of the diluted solution was injected superficially at the 3 o'clock position of the cervix, then 1 cc deeply into the cervical stroma, using a 1 cc syringe attached to a spinal needle. The same was done at the 9 o'clock position of the cervix. After ICG injection, a 12mm blunt trocar was inserted at the umbilicus using the Hasson technique. Abdominal survey with a 10 mm zero degree scope showed no ascites or extra uterine spread. Two 5 mm accessory trocars were placed 3 cm above the bilateral anterior superior iliac spines and one left paramedially, at the level of the umbilicus. The pelvis was visualized using normal light then under NIR fluorescence (Figures 1A and 1B) Peritoneal fluid washing was collected for cytology. The right pelvic peritoneum was carefully opened. The right external iliac node lighted up with the ICG dye and was identified as the sentinel lymph node and subsequently harvested. (Figures 2A and B). The left external iliac and left parametrial nodes were the sentinel nodes harvested on the left pelvis (Figures 2C and 2D).

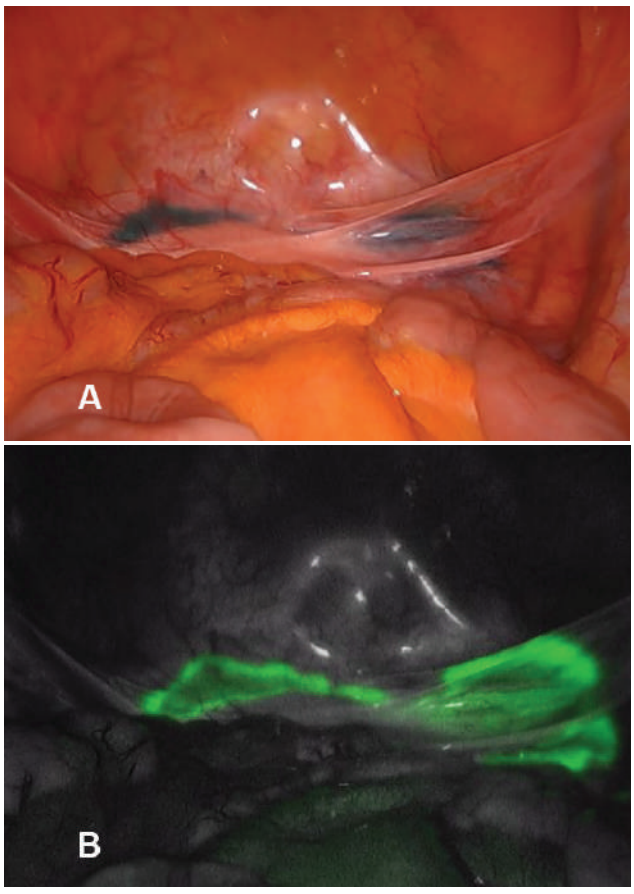

Figure 1. Case 1 A) Caudad view of the pelvis in normal light B) Caudad view of the pelvis in near infrared light

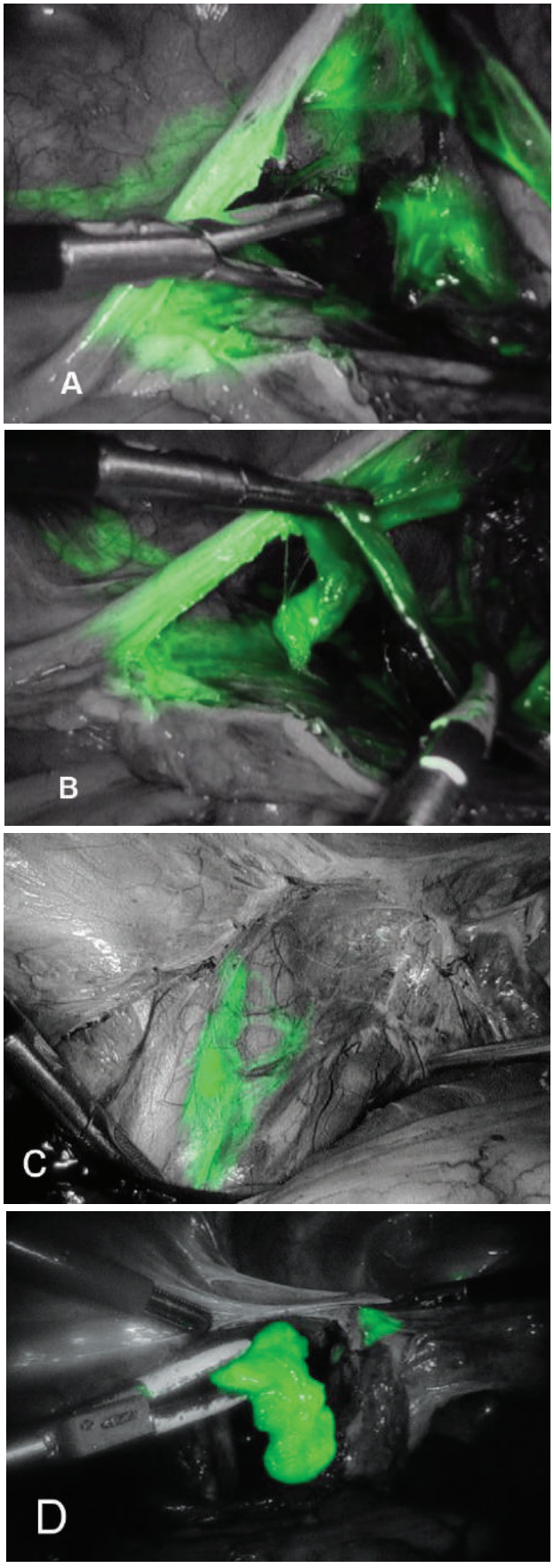

Figure 2. CASE 1 A) View of the right sentinel lymph node prior to harvesting B) Harvesting the right sentinel Lymph node using near infrared light C) View of the left sentinel lymph node prior to harvesting D) Harvesting the left sentinel lymph node using near infrared light

Total laparoscopic hysterectomy with adnexectomy was performed using standard techniques. Systematic bilateral pelvic lymphadenectomy was completed. Total operative time was 152 minutes with less than 100 cc blood loss. The patient was discharged on the third post-operative day.

Histopathological examination of the uterus showed endometrial adenocarcinoma, endometrioid type, FIGO grade 2 with 1.7 centimeters in greatest tumor dimension. The tumor invaded less than 50% of the myometrium. It also showed peritumoral lymphovascular space invasion (LVSI) (Figure 3B). Sentinel lymph nodes were sectioned in 3mm serial cuts and stained with Hematoxylin and Eosin. Systematic lymph nodes were sectioned and blocked in a cassette for complete examination. A total of five right pelvic and five left pelvic lymph nodes were harvested. All were negative for malignancy.

She was advised to undergo adjuvant chemotherapy in the form of Carboplatin and Paclitaxel for peritumoral LVSI. Although well advised, the patient was lost to follow-up. Four months after surgery, she returned for vaginal spotting. She had a 2 x 2 cm firm mass at the apex of the vaginal stump on internal exam. Transvaginal ultrasound showed a 2.3 x 2.3 x 2.4 cm mass superior to the vaginal stump. Chest and abdominal imaging did not show distant spread. Pelvic external beam radiotherapy was recommended. She is currently undergoing pelvic radiotherapy.

Case 2

A 63-year old Gravida 3 Para 3, Filipino woman presented with postmenopausal bleeding. She was a known hypertensive for 5 years with good control. All her pregnancies were carried to term via spontaneous vaginal delivery. Menopause was at 48 years old. She underwent office endometrial sampling which revealed endometrial adenocarcinoma, endometrioid type, FIGO grade 1. On internal examination, she had normal external genitalia and smooth vagina. The cervix was smooth measuring 2 x 2 cm. The corpus was small, with no adnexal mass or tenderness. Bilateral parametria were smooth and pliable. Transvaginal ultrasound showed an anteverted uterus with smooth contour. Within the endometrial cavity was an irregular heterogenous mass measuring 3.3 x 2.9 x 2.0 cm. Doppler studies of the mass showed moderate scattered vascularity with a color score of 3.

She underwent the same procedure as the previous case. Sentinel lymph node mapping and biopsy were also done (Figure 4A-D). The tumor measured 4 cm in greatest dimension and invaded less than 50% of the myometrium. Total operative time was 133 minutes with 150cc blood loss. She was also discharged on the third post-operative day. Histopathological examination of the uterus showed endometrial adenocarcinoma, endometrioid type, FIGO grade 2, negative for LVSI (Figures 3C and D). Sentinel lymph nodes were also sectioned in 3mm serial cuts. Systematic lymph nodes were sectioned and blocked in a cassette for complete examination. All lymph nodes were negative for malignancy. The patient was asymptomatic post-operatively and underwent vaginal brachytherapy as adjuvant therapy since the tumor size exceeded 2cms. She is on regular follow-up for monitoring.

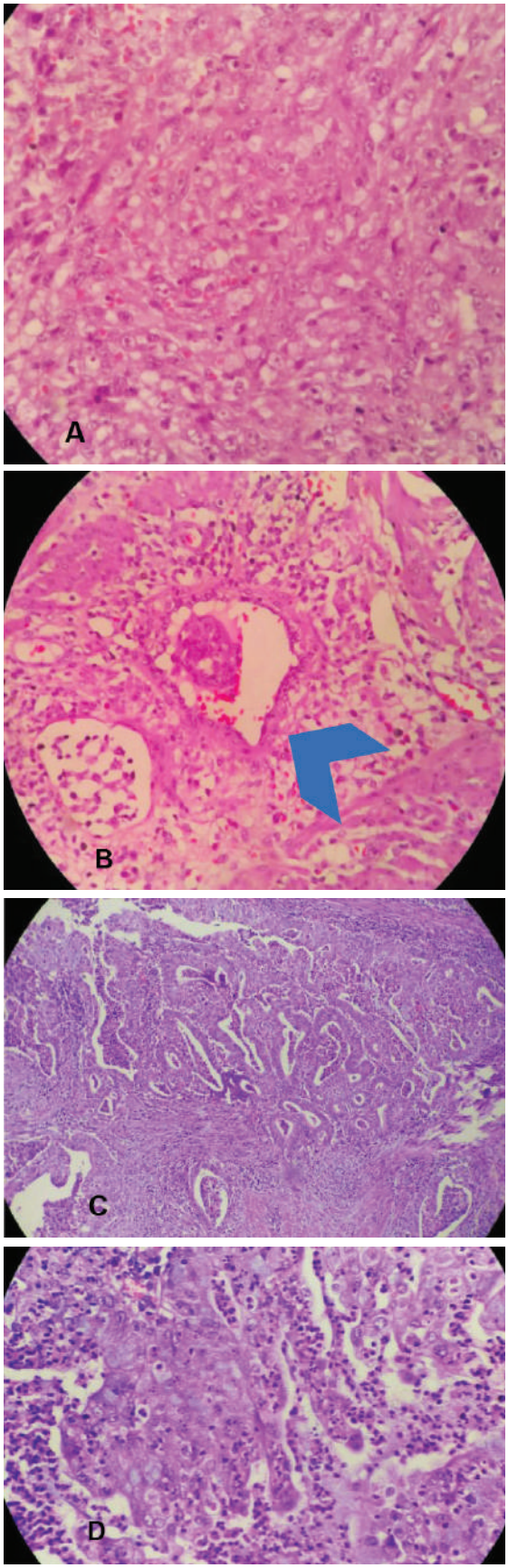

Figure 3. A) Endometrial carcinoma, Endometrioid type, FIGO Grade 2 in Case 1 (HPF) B) Presence of tumor cells in a lymphatic vessel with blue arrowhead (OPF) in case 1, C) Endometrial carcinoma, Endometrioid type, FIGO Grade 2 in Case 2 (LPF), D) Endometrial carcinoma, Endometrioid type, FIGO Grade 2 in Case 2 (HPF)

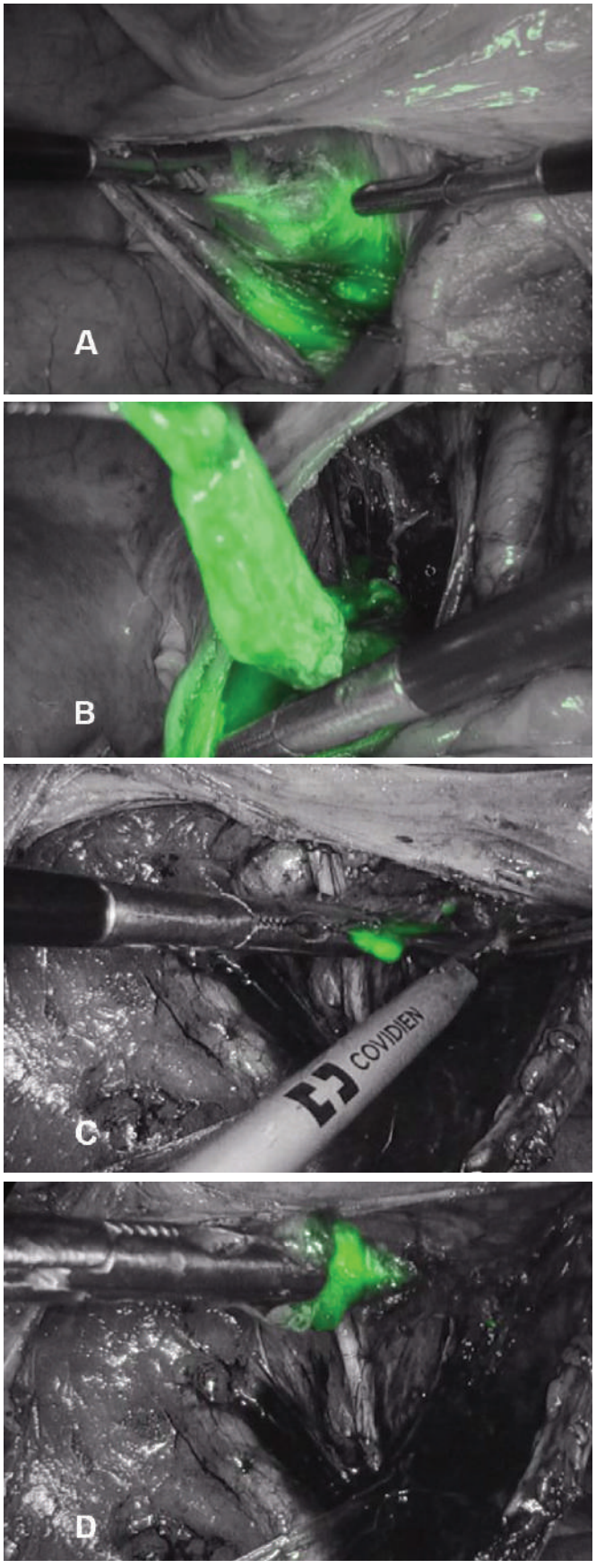

Figure 4. CASE 2 A) View of the right sentinel lymph node prior to harvesting B) Harvesting the right sentinel Lymph node using near infrared light C) View of the left sentinel lymph node prior to harvesting D) Harvesting the left sentinel lymph node using near infrared light

DISCUSSION

Laparoscopic hysterectomy is now advocated for well-selected patients as early stage endometrial carcinoma can be treated with laparoscopy with excellent surgical outcome, improved quality of life, reduced pain score and hospitalization stay and earlier return to daily activities. Gynecologic Oncology Group LAP2 Study also states the minimal potential for increased risk of cancer recurrence with laparoscopy versus laparotomy was quantified and found to be small at 1.4%.[4] Minimal access surgeries are becoming the preferred approach.

Determining lymph nodal involvement preoperatively is difficult and its involvement is one of the best prognostic factors. Sentinel lymph node mapping identifies lymph nodes with micro metastases. Detection methods to visualize sentinel nodes are continually developing. The first technique described in literature involves the intraoperative peritumoral injection of a methylene blue dye that disperses over the lymphatic system and allows selective dissection and excision of the sentinel lymph node. The second method uses preoperative injection of a radiolabeled albumin solution, usually Tc99m, where a lymphoscintigraphic photo will be taken after an hour prior to surgery.[5] Sentinel lymph nodes will light up allowing the selective dissection. A newer technique using indocyanine green dye (ICG) is now being popularized. The ICG dye was first developed by Kodak Research Laboratories in 1955. It has the advantage of a good safety profile. It is a non-toxic, non-ionizing dye bound to lipoproteins and has a short lifetime in blood circulation. Some disadvantages of the ICG dye would be that it needs a near infrared imaging device for it to be visible. The solution contains sodium iodide thus the small possibility of an allergic reaction (0.7-1.9%).[5] After the dye is injected preoperatively, the ICG dye accumulates in the lymphatic pathway due to the high protein content of lymph. It fluoresces with near infrared (NIR) light range at 806nm five minutes after the administration until 60 minutes after. This provides specific lymphadenectomy. SLN mapping and biopsy can easily be added to the procedure of TLHBSO with minimal added surgical time, given the available facility, instrument, machine and surgeons.

Nodes obtained in the sentinel lymph node mapping are subjected to ultra- staging. The processing of the sentinel nodes is not yet standardized. There is no consensus protocol for optimal pathologic handling of the sentinel lymph nodes. This technique allows no more than 3mm cuts of specimen to detect micro metastasis. Different institutions apply their own method of processing of the SLN. The sectioning of the SLN ranges from 1.5mm-3mm cuts. Some use immunohistochemistry with Pancytokeratin.[5] A large study by Holloway demonstrated an increase in detection two- fold, from 30.3% vs 14.7% in mapped vs. non-mapped group in early stage endometrial cancer.[6] In the SENTI-ENDO study, negative predictive value of SLN is 97% while sensitivity is 84%.[7] The main objective and goal of SLN biopsy is to decrease radicality of procedures and provide women benefit with a good quality of life.

Most women with early stage endometrial cancer have good long-term survival with a 95% 5-year survival for stage IA or IB endometrioid tumor. Several prognostic factors are

well-recognized in endometrial cancers such as patient age, tumor grade and stage, histologic type. Across all stages and grades, the prevalence of lymphovascular space invasion (LVSI) is 25% and much lower for those stages IA and IB.[8] LVSI is defined as the displacement of tumor into the vascular and lymphatic channels. Its positivity has been shown to have a higher risk for lymph node involvement. LVSI is not included among the prognostic indicators of the Federation of Obstetrics and Gynaecology (FIGO) staging classification. Internationally, several guidelines already do not recommend lymphadenectomy in early-stage, well- to moderately-differentiated endometrial cancers.

Early-stage endometrial cancer has a low recurrence rate of 7% at 3 years.[9] The presence of the poor prognostic factor of lymphovascular space invasion in the first case puts the patient at high risk for recurrence. A cohort study by Weinberg states that overall recurrence of LVSI positive early stage endometrial cancer is at 17%. The study suggests LVSI as a significant and consistent poor prognostic factor for recurrences and survival. It claims to be better predictor of recurrences than other risk factors.[9] Another study by Narayan showed that even in node-negative intermediate to high-risk patients, the presence of LVSI may be a more powerful prognostic marker of recurrence than grade and histological subtype. Moreover, multiple studies are already available dictating LVSI as high risk for lymph node metastasis (25%).[10]

Since there is still no standardized protocol on SLN mapping and biopsy in our institution, systematic lymphadenectomy was also performed along with the SLN biopsy. The biopsy of SLN was accurate since no lymph node turned out to be positive. Lymphovascular space invasion should be emphasized to the patients clearly. It should entail that adjuvant treatment be given since recurrence in vaginal cuff are as high as 8%. Even when lymph nodes obtained are negative such as in this case, LVSI is considered an isolated and consistent prognostic factor for both recurrence rates and overall survival. It may even be a better predictor than other risk factors.[9]

CONCLUSION

Sentinel lymph node mapping and biopsy in endometrial cancer is feasible, reproducible, and has a reasonable result in other countries. These 2 cases described the technique of sentinel lymph node mapping and biopsy using ICG dye. The procedure is simple and does not need special patient preparation but requires special machines along with operators and highly trained surgeons. Prospective research and further investigation will benefit the development of guidelines for the SLN biopsy in endometrial cancers. In addition, a standardized protocol for handling sentinel lymph nodes should be developed before the SLN biopsy can be validated as a standard of care in our country.

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Familial Swyer Syndrome associated with mixed germ cell tumor: A case report

May B. David, MD and Carolyn R. Zalameda-Castro, MD, MSc, FPOGS, FSGOP

ABSTRACT

Swyer syndrome is a rare type of complete gonadal dysgenesis characterized by an XY karyotype, female phenotype, and hypoplastic gonads. Presenting complaint for most reported cases is primary amenorrhea. It is associated with an increased risk for development of neoplastic tumors, hence, the recommendation to remove both gonads upon confirmation of the diagnosis. In this paper, we present a case of a 14-year-old with primary amenorrhea and delayed puberty who consulted at our institution for an abdominopelvic mass. Family history is pertinent for an older sister having a confirmed XY karyotype who succumbed to an abdominopelvic mass of unknown histology two years prior. Clinical, hormonal, and karyotyping analyses confirmed the diagnosis of Swyer syndrome for our patient. Histopathologic and immunohistochemistry studies of the abdominopelvic mass showed a mixed germ cell tumor. This is the first local report, to our knowledge, of a familial Swyer syndrome.

Keywords: *Familial Swyer syndrome, 46 XY, complete gonadal dysgenesis, mixed germ cell tumor*

INTRODUCTION

Swyer syndrome is a pure gonadal dysgenesis and is one of the more uncommon forms of disorders of sexual differentiation (DSD). This condition is characterized by a phenotypically female appearance, unambiguous female genitalia, normal Müllerian structures, delayed puberty, and an XY chromosome.[1,2,3] Local studies are currently limited to few case reports.[4,5]

A high incidence of gonadal neoplasms has been associated with Swyer syndrome, with about one third developing a tumor in their lifetime.[2] Gonadoblastoma and dysgerminoma are the two most common neoplasms linked to the condition. Because of this significant risk, the general recommendation is to proceed with gonadectomy upon diagnosis.

Since it was first described more than 60 years ago, much is still not understood about Swyer syndrome. Current practice recommendations are based on individual case reports and a few small case series. In this paper, we report a rare case of familial Swyer syndrome associated with malignant germ cell tumor, the first to our knowledge, in the local setting.

Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Philippine General Hospital, University of the Philippines – Manila

Corresponding author:
May B. David, MD
Department of Obstetrics and Gynecology, Philippine General Hospital, Taft Avenue, Ermita, Manila, 1000
Phone number: (02) 855-48-400 local 2300
Email: mayb.david@gmail.com

Presented at the 2019 Society of Gynecologic Oncologists of the Philippines (SGOP) Interesting Case Contest, Nov. 10, 2019, Manila

Presented and won 3rd place at the University of the Philippines – Philippine General Hospital, Department of Obstetrics and Gynecology's Annual Fellows' Interesting Case Contest, Oct. 27, 2020, Manila

Financial Disclosure
The author did not report any potential conflicts of interest.

Index Case

Our patient is a 14-year-old nulligravid who initially presented at our institution for abdominal enlargement over three months, with undocumented weight loss, anorexia, and early satiety. She has no co-morbidities and no previous hospitalizations. She is the youngest of a brood of five, four of whom are phenotypically female.

Notable on her family history is that her third eldest sibling expired two years prior, also 14 years old then, from an unspecified malignancy. This sibling, with normal phenotypic female appearance, also presented with a huge abdominopelvic mass with delayed secondary sexual development, and an XY karyotype. She underwent excision of the mass and contralateral gonadectomy, but unfortunately, the biopsy of the excised tumor was no longer retrieved by the family.

A 27-year-old paternal cousin, also unable to achieve menarche, was diagnosed with dysgerminoma at 20 years old. However, no karyotyping has been done as she is prioritizing treatment for her progressive disease. Our patient's second eldest sibling, presently 20 years old, still amenorrheic, with delayed puberty, and underdeveloped uterus and streak gonads on imaging, currently has no consent for further diagnostic work up.

Upon presentation at our institution, our patient has still not had menses. On physical examination, her height was 146 cm, within normal for her age, with eunuchoid habitus, no appreciable axillary hair, and breasts at Tanner stage II. There was a palpable 20 x 15 x 10 cm predominantly solid abdominopelvic mass with limited mobility and no note of ascites. Pelvic examination showed normal external genitalia with Tanner stage I pubic hair, and no evidence

of clitoromegaly. Digital rectal examination showed no intraluminal masses with good sphincteric tone, and no palpable mass at the cul de sac.

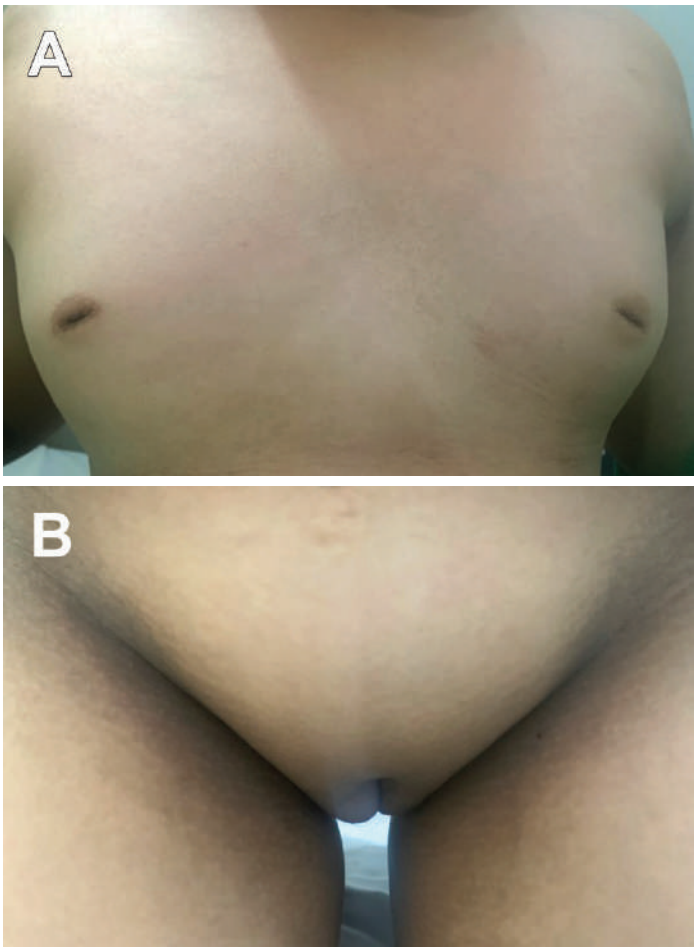


Figure 1. A. Breast at Tanner stage II; B. Normal female external genitalia with sparse pubic hair

Transrectal ultrasound revealed an irregular, lobulated predominantly solid mass measuring 12.4 x 10.2 x 10.0 cm, densely adherent to the posterior wall of the hypoplastic uterus. No ovaries were identified. On abdominopelvic CT scan, there was a large, fairly-circumscribed lobulated, mixed-attenuating heterogeneously-enhancing solid mass measuring 12.9 x 14.3 x 10.2 cm, intimately-related to the rectosigmoid, with note of secondary obstructive uropathy.

Tumor markers showed the following results: elevated LDH 1389 (266-500 IU/mL), bHCG 109.83 (5-25 mIU/mL), AFP 20.82 (0.74-3-7.3 IU/mL), and normal CA 125 25.3 (0-35 U/mL), CA 19-9 37.82 (<37 U/mL), and CEA 2.36 levels (<5 ng/mL), pointing to a probable mixed germ cell tumor. At this time, there was already a consideration of a DSD so that the following laboratories were also done and produced the following results: post menopausal FSH level of 78.6 (normal ovulatory peak values 4.0 – 13.5 mIU/mL), and normal LH 42.9 (normal ovulatory peak values: 25 – 94 mIU/mL) and estradiol 125.7 (consistent with middle follicular values: 57 – 227) levels.

She was then scheduled for exploratory laparotomy for

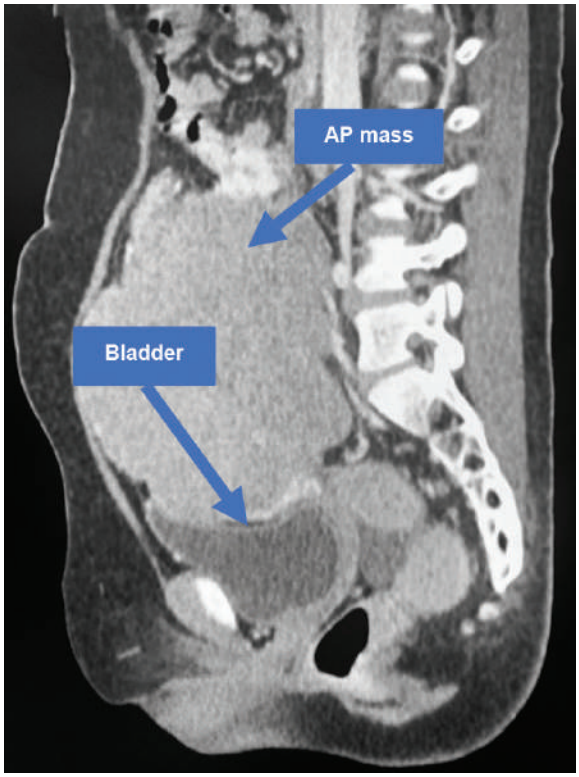


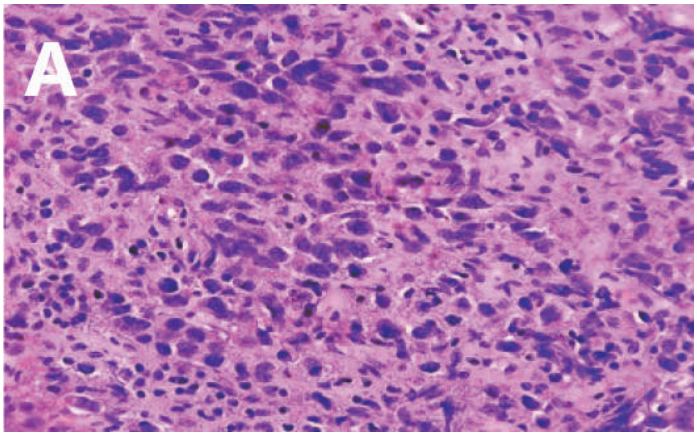
Figure 2. CT scan in sagittal view showing abdominopelvic mass in relation to the bladder, hypoplastic uterus, and rectum

excision of the abdominopelvic mass and surgical staging. Intraoperatively, what seemed to be the left gonad was converted to a complex predominantly solid mass measuring ~15 x 15 x 10 cm, densely adherent to the rectosigmoid and was deemed non debulkable. A biopsy of the tumor was taken and on final histopathology and immunohistochemistry report, it showed elements of both dysgerminoma and choriocarcinoma.

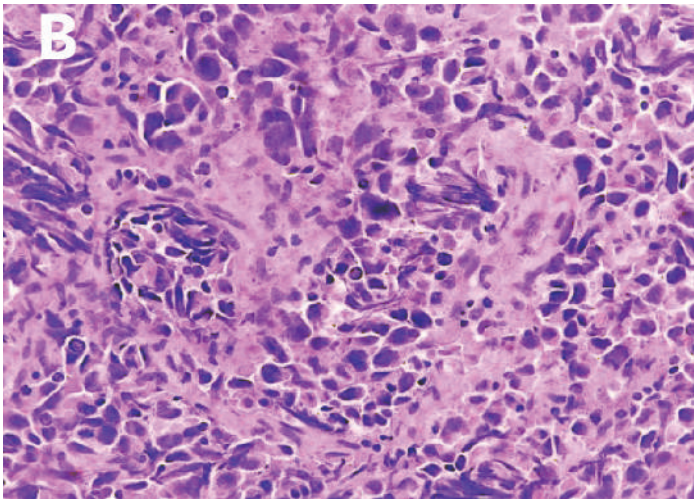
The right adnexa, grossly free of disease, was appreciated with the strip-like right gonad stretched over the abdominopelvic mass. The infantile uterus as well as the right fallopian tube were also grossly free of tumor. The intraoperative stage was IIIC due to omental caking.

The patient underwent three cycles of neoadjuvant Carboplatin-Etoposide-Bleomycin (JEB) under the Pediatric Hematologic Oncology service followed by re-exploration, left gonadectomy, tumor debulking, and infracolic omentectomy by the Gynecologic Oncology service. Intraoperatively, the remaining tumor was a solid mass measuring 7 x 5 x 3 cm which on cut section showed mostly areas of necrosis and hemorrhage. Histopathology of the mass showed ovarian teratoma with necrotic and degenerative changes, probably due to previous chemotherapy, with no viable malignancy present. All other specimens were negative for tumor.

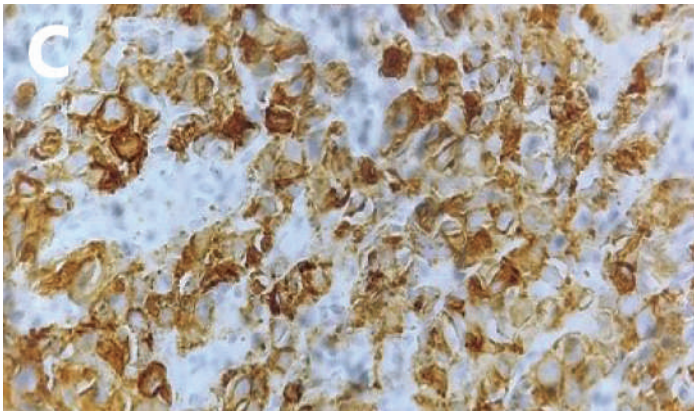
Karyotyping was also requested initially prior to the first surgery, however, due to repeated blood transfusions, treatment for various infections, and chemotherapy, the blood samples were rejected by the laboratory and the result of XY was only revealed after the second operation. Postoperatively, the patient received three additional cycles of JEB. Disclosure of the chromosomal analysis was made by



Round to ovoid-shaped cells with hyperchromatic nuclei and osinophilic cytoplasm



Occasional multinucleated giant cells are seen, which may represent syncytiotrophoblasts



Immunohistochemistry studies with PLAP (Placental Alkaline Phosphatase), positive in most GCTs

Figure 3. Microscopic picture of the abdominopelvic mass, consistent with mixed germ cell tumor

the patient's attending physician at the time, together with a Genetics specialist. The patient, an honor student in school and with strong family support, has decided to continue identifying with the female gender without any hesitation.

She was advised re-operation to remove the contralateral gonad, however, there was no consent initially as the patient wanted to recover from her treatment and to go back to school. She is currently free of disease and asymptomatic for over two years and on close follow up at the Gynecologic Oncology clinic, with active co-management by the Pediatric and Psychiatric services.

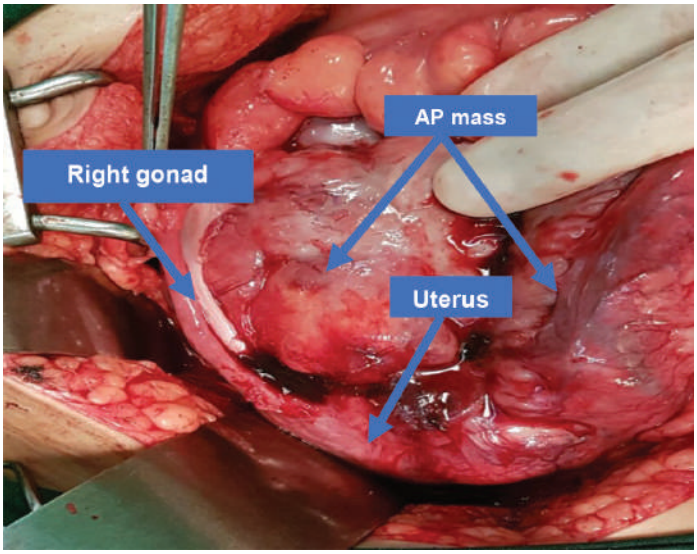


Figure 4. Mass adherent to the hypoplastic uterus and strip-like right gonad

DISCUSSION

Disorders of sexual differentiation (DSD) are uncommon congenital conditions wherein there is atypical development of chromosomal, gonadal, or anatomical sex. These occur in about 1 in 4500 births.[1] Swyer syndrome is a form of complete gonadal dysgenesis that was first described in 1955 and named after Dr. Jim Swyer when he reported on two individuals presenting with primary amenorrhea, tall with eunuchoid habitus, normal female external genitalia, vagina, and cervix, no palpable adnexa, and an XY karyotype. Since the first described cases, Swyer syndrome remains to be a rare condition, the exact incidence being unknown but is estimated to occur in approximately 1 in 80,000 to 100,000 births.[1,2]

Because of the normal pre-pubertal phenotype, there is usually a delay in the diagnosis, with a mean age of 18 to 23 years old, with as much as 90% of patients consulting because of delayed puberty.[1,3] The rest are diagnosed incidentally for other complaints like an abdominopelvic mass, as was seen in our patient and her sibling. Review of case reports in the Philippines revealed that majority consulted for a finding of a pelvic mass[4,5] and only one sought assessment due to primary amenorrhea (de Cadiz, et al, 2016, unpublished paper).

The definitive diagnosis of Swyer syndrome is made on the basis of clinical findings, hormonal analysis, gonadal histology, chromosomal analysis, and genetic testing. It is characterized by a phenotypic female appearance, 46 XY karyotype, hypoplastic or streak gonads, normal Müllerian structures, primary amenorrhea, and normal to tall stature. There may be some development of secondary sexual characteristics and a few, mild episodes of uterine bleeding. Minimal breast enlargement may be secondary to peripheral

aromatization of androgens while menstrual function may suggest tumor development with estrogen production in the streak gonad.[6] In our patient, she presented with primary amenorrhea, delayed secondary sexual development, hypoplastic gonads, normal stature, an XY karyotype, and at a relatively younger age due to development of a malignant tumor.

As primary amenorrhea is the most common complaint, differential diagnoses of patients with this initial presentation must also be considered and excluded. These include Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKHS; 46, XX), characterized by varying degrees of Müllerian duct abnormalities and absent or rudimentary uterus, as well as Androgen Insensitivity Syndrome (AIS; 46, XY), characterized by normal breasts, vagina ending in a blind pouch, undescended testes, and absent uterus.[7]

Swyer syndrome is caused by an error in sex determination during the process of embryogenesis. Molecular and genetic abnormalities in various genes have been implicated in the development of the condition which include ARX, ATRX, CBX2, DHH, DHRT1, GATA4, MAMLD, MAP3K, NROB, NR5AI, SOX9, WNT4, WT1, WWOX, and SRY.[2] Of these, modifications in SRY are the most common; the gene being deleted in 10-20% of cases and mutated in an additional 10-15% of tested individuals.[1,2,7] In 80-90% of cases, the SRY gene is normal and mutations or deletions in the other genes are likely implicated.

Hormonal analysis is part of the initial work up for Swyer syndrome and the panel usually consists of LH, FSH, prolactin, TSH, FT4, SHBG, estradiol, testosterone, and androstenedione. Patients would typically exhibit a hormonal assay showing hypergonadotropic hypergonadism. For our case, she had postmenopausal levels of FSH and LH but normal estradiol levels, the latter probably due to the neoplastic process.

Majority of identified cases of Swyer syndrome have no family history and current literature shows that only about 4% have an affected sibling.[1] Ates, et al (2014), presented a case of two sisters with underdeveloped uterus who both consulted for primary amenorrhea while Gupta et al described two siblings with primary amenorrhea and infertility, and later able to achieve successful pregnancies.[8] In 2017, Banoth, et al reported on three siblings with Swyer syndrome, two consulting for an abdominopelvic mass and the other for primary amenorrhea.[7] Bagci et al, meanwhile, presented a familial case involving two siblings as well as a maternal aunt; all with main concern of primary amenorrhea.[9]

Familial cases may be inherited in an autosomal dominant (WNT4, MAP3K1, NR5A), autosomal recessive (DHH), X-linked (NROB1) or Y-linked manner (SRY mutations).[7] However, most result from new mutations and have an unknown origin. In the case reported by Bagci et al, the pedigree showed a possible X-linked recessive pattern.[9] For our case, it appears that the gene is inherited in a Y-linked manner, as confirmed and suspected cases are all related on the paternal side. Hines et al studied the presence of mosaicism in sperm DNA and discussed how a normal father can have two populations of sperm with one normal and the other carrying the mutation in SRY gene.[5] Sequencing of specific causative genes is not routinely done nor is it widely available, but for familial cases, this might be particularly useful. This remains a challenge in resource-limited settings such as the Philippines.

The significant risk of development of ovarian neoplasms underscores the importance of early diagnosis of Swyer syndrome. About 15-35% will present with neoplasia, with gonadoblastoma being the most common.[1-3,8] Gonadoblastoma is unique to intersex states like Swyer syndrome and though a benign tumor, may be a precursor to malignant germ cell tumors like dysgerminoma, endodermal sinus tumor, embryonal and choriocarcinomas. They are believed to arise from clonal expansion of surviving germ cells in undifferentiated gonadal tissue.[7] The youngest case reported is in a 9-month-old infant[3] and the cumulative risk of developing gonadoblastoma is 30% by age 40 years which further increases with age.[7]

Dysgerminoma is found in 22-66% of those with neoplasms, occurring either in pure form or co-existing with other types of germ cell tumors.[1] Our patient had a mixed germ cell tumor - predominantly dysgerminoma with elements of choriocarcinoma. Compared to the general population, dysgerminoma in patients with Swyer syndrome behaves similarly and has the same prognosis stage per stage. In literature, 65% of patients presented with stage I disease; 80-95% had tumor limited to one ovary, while the rest involved both ovaries. Survival rates at 5 and 10 years exceed 90%.[10]

Because of this propensity for tumor development, the recommendation is to perform bilateral gonadectomy upon confirmation of diagnosis. This is in contrast to other DSDs like AIS which have lower malignant potential, so that waiting until 18 years old to remove the gonads is the common practice. In those where the contralateral gonad was preserved, there is a 5-10% chance of developing the disease over the succeeding 2 years[10], thus close follow-up is required.

As mentioned, bilateral gonadectomy upon diagnosis is recommended to prevent the development of neoplasms. For young patients, it is not always imperative that the uterus is also removed, even in association with germ cell tumors, as these are highly chemosensitive. The extent of surgery is dictated by the histology, stage, and the patient's age and reproductive desires. Hormonal therapy to effect secondary sexual maturation and uterine development may be given after surgery and treatment of the malignancy. Estrogen therapy is also necessary for adequate bone formation and to achieve adequate peak bone mass. Patients with Swyer syndrome are prone to osteopenia, hence, a baseline bone densitometry is recommended.[3]

Successful pregnancies with assisted reproductive technology and donor oocytes have also been documented. Current literature reports that except for a higher incidence of cesarean section for various reasons, pregnancy outcomes are similar to those with 46, XX ovarian failure and other in vitro fertilization (IVF) pregnancies.[7]

The diagnosis and management of patients with Swyer syndrome is complex. Only a few cases have been reported in literature, perhaps for two major reasons; one, that it is

an inherently rare condition, and second, because of the stringent criteria that must be satisfied for the diagnosis to be made. Especially in adolescents, psychological support must be given upon disclosure of the diagnosis. It is recommended that a trained genetic counsellor be the one to divulge the condition to the patient and the family. This is particularly important in those with familial clustering, as in our case. Family members with clinical signs suggestive of Swyer syndrome must be properly advised on the necessary work up to establish the diagnosis and the importance of the subsequent management. Currently, despite adequate counselling, the patient's other sibling with clinical signs of Swyer syndrome has no consent to proceed with the work up.

Finally, patients have to be reassured that it is a manageable condition and that a long, disease-free, and productive life is achievable, even among those who develop any of the associated gonadal tumors.[2,3]

CONCLUSION

Early diagnosis of Swyer syndrome is vital due to its association with the development of gonadal tumors. Hormonal and chromosomal analyses should be carried out in adolescents presenting with primary amenorrhea and an abdominopelvic mass. Bilateral gonadectomy is recommended upon confirmation of the diagnosis. This is followed by estrogen supplementation to induce puberty, fertility, and increase bone mineral density. The patients must also be counseled that despite an underdeveloped uterus and removal of both gonads, successful pregnancy may still be achieved through ovum donation and IVF. The management of patients with Swyer syndrome is complex, particularly the extremely rare familial type, as in our case. It requires a team of multidisciplinary specialists to give appropriate psychosocial support and proper counselling not only to the patient, but the entire family.

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Malignant transformation of a mature teratoma with cervical metastasis versus cervical carcinoma with ovarian metastasis versus synchronous tumors: A diagnostic dilemma

Ina Felize A. Ramajo, MD, Andrea M. Gaddi, MD, FPOGS, DSGOP, and Cynthia G. Gueco, MD, FPOGS

ABSTRACT

Ovarian mature cystic teratoma may occur in up to 20% of women. It is usually benign, but 2% of them may go through malignant transformation. The histological types of this transformation include squamous cell carcinoma, adenocarcinoma, small cell carcinoma, among others. On the other hand, squamous cell carcinoma (SCCA) of the cervix occurs more commonly at ages 45-55. This tumor spreads to lymph nodes and can have hematogenous spread to bone and lungs, but rarely to the ovaries. This report is of a 75-year-old grand multipara with an enlarging pelvoabdominal mass, initially managed as a case of ovarian new growth. The patient underwent exploratory laparotomy, total abdominal hysterectomy with appropriate surgical staging. The cervix and ovarian mass were found to be grossly malignant intraoperatively. Specimens were submitted for biopsy which revealed squamous cell carcinoma of the cervix, lower uterine segment, left ovary, and omentum along with malignant transformation of the mature cystic teratoma to SCCA. The detection of cervical carcinoma in a setting of a pelvoabdominal mass with normal preoperative cervical findings poses difficulty. Cervical SCCA rarely metastasize to the ovaries, while malignant transformation in mature cystic teratoma is rare. Adenocarcinomas are more predisposed to metastasize to the ovaries compared to the squamous cell variants. Meanwhile, SCCA from a mature teratoma metastasize via peritoneal spread similar to that of typical ovarian cancers. In cases such as this, where there is diagnostic dilemma with the primary carcinoma, the need for ancillary studies, such as immunostaining can be beneficial.

***Keywords**: mature cystic teratoma, squamous cell carcinoma, malignant transformation*

INTRODUCTION

Mature cystic teratoma (MCT) of the ovary, commonly known as a dermoid cyst, has been known for a long time. This teratoma is the most common type of ovarian germ cell neoplasm and is seen frequently. It includes approximately 20% of all ovarian neoplasms[1]. It is easy to diagnose grossly. This usually appears as a grey-colored ovoid cystic mass which contains yellow to brown sebaceous material and hair. Other tissues also found within are bone, fat, brain and cartilage. The cyst appears to be lined by keratinized epithelium with sebaceous glands, sweat glands, and hair follicles[2]. Malignant transformation of an MCT is an unusual complication which can arise in approximately 0.17–2% of all mature cystic teratomas. Any of the tissues of teratoma can potentially undergo malignant transformation. However, squamous cell carcinoma is the most frequently related cancer.[3] Squamous cell carcinoma (SCC) of the cervix is one of the most common gynecological malignancies and usually presents with vaginal or postmenopausal bleeding. This can involve the uterus by direct extension or by lymphatic invasion through the parametrium to the uterine wall. In most cases, the spread is restricted to the endometrium with very few cases of spread to fallopian tubes or ovaries[4].

From the Department of Obstetrics and Gynecology, Jose B. Lingad Memorial General Hospital, San Fernando, Pampanga

Corresponding author:
Ina Felize A. Ramajo, MD; email: inaramajo@gmail.com
Andrea M. Gaddi, MD, FPOGS, DSGOP, FPSCPC
email: drei_2006@yahoo.com
Department of Obstetrics & Gynecology, Jose B. Lingad Memorial General Hospital, San Fernando, Pampanga

This paper was presented as a finalist in the Online POGS Interesting Case Contest on September 17, 2020 and as an E-poster Presentation during the POGS Annual Convention on November 10-14, 2020

Financial Disclosure
The author did not report any potential conflicts of interest.

CASE REPORT

This is a case of a 75-year old Gravida 9 Para 9 (9009), Filipino, Roman Catholic, who consulted at the outpatient department due to a palpable pelvoabdominal mass. Family and past medical histories were non-contributory. She was a known smoker with 6 pack years.

She had her menarche at 13 years old occurring irregularly lasting for 3 days, soaking 3 pads per day with no associated dysmenorrhea, and had her menopause at the age 48. She had her coitarche at 17 years old with only one sexual partner only with no reported history of sexually transmitted diseases.

One year prior to consult, the patient noticed a palpable pelvic mass about 10 x 10 cm in size with no other associated symptoms. She consulted a private OB-GYN. A transvaginal ultrasound revealed a unilocular cystic pelvic mass measuring 11.7 x 10.6 x 9.0 cm with benign sonographic features. Other

structures were sonographically unremarkable. She was advised to undergo surgery but due to financial constraints, the patient refused and was lost to follow up.

Two weeks prior to consult, the patient still complained of a palpable abdominal mass now associated with on and off hypogastric pain, with a pain scale of 6/10, and associated with rectal discomfort. She consulted at the local health center and was advised surgery but she and her family were undecided.

One week prior to consult, due to the persistence of the above symptoms, and worsening pain of 8/10, the patient consulted at the outpatient department. Workup was done revealing slightly elevated CA-125 of 36.2 U/mL and normal alpha fetoprotein of 1.50 ng/mL. On physical examination, the patient was ambulatory, conscious, coherent, afebrile, normotensive, non-tachycardic, and non-tachypneic. Her abdomen was flabby, soft, had normoactive bowel sounds, and with a 15 x 12 cm cystic, movable, non-tender, pelvic mass palpable on the left lower quadrant. External genital examination showed normal-looking female genitalia. Speculum examination showed pink and smooth vaginal wall and cervix with no lesions or erosions. On internal examination, the cervix was closed, smooth, and pulled up; the uterus could not be assessed due to the pelvoabdominal mass. The rectovaginal septum was intact, with fullness at the cul de sac; parametria were free and pliable. On transvaginal ultrasound, the cervix measured 2.94 x 1.75 x 1.56 cm, uterus measured 3.54 x 2.62 x 1.03 cm anteverted, with homogenous abnormalities of calcified myometrial vessels. Endometrium was thin, intact, isoechoic, and measured 0.26 cm. Both ovaries were not visualized. There was a large unilocular cystic mass in the pelvic cavity with a smooth outline measuring 11.7 x 10.6 x 9.0cm (Figure 1). There were fine internal calcifications noted within the cystic mass. An incomplete septum was noted in its anterior aspect. No color flow noted in the color doppler scan. There was also hyperechoic mass to the left of the cystic mass with lobulated border measuring 4.8 x 4.6 x 3.37 cm which may be colonic in origin. There was no fluid in the cul-de-sac. The impression on ultrasound was: unilocular cystic mass with morphologic features suggestive of a mature cystic teratoma (left), small anteverted uterus, thin and intact endometrium.

The patient was diagnosed preoperatively with ovarian new growth, probably benign, cannot totally rule out malignancy; Gravida 9 Para 9 (9009). She underwent exploratory laparotomy, peritoneal fluid cytology, total abdominal hysterectomy with bilateral salpingo-oophorectomy, bilateral lymph node dissection, para-aortic lymph node sampling, random peritoneal biopsy, and infracolic omentectomy under combined spinal and epidural anesthesia.

Intraoperative findings revealed that the left ovary was converted to a 15 x 15 cm cystic mass with a 5 x 5 cm solid mass on its capsule adherent to the posterior lower uterine segment (Figure 2). After performing left salpingo-oophorectomy, there was a 6 x 6 cm mass noted on the posterior lower uterine segment involving the cervix fixed to the cul de sac. The liver, gall bladder, stomach, small intestine, peritoneal surfaces, and omentum were smooth. On cut section of the left ovary, there was egress of sebum and hair. There were teeth, cartilage and bone noted. There was also an 8 x 7 cm friable

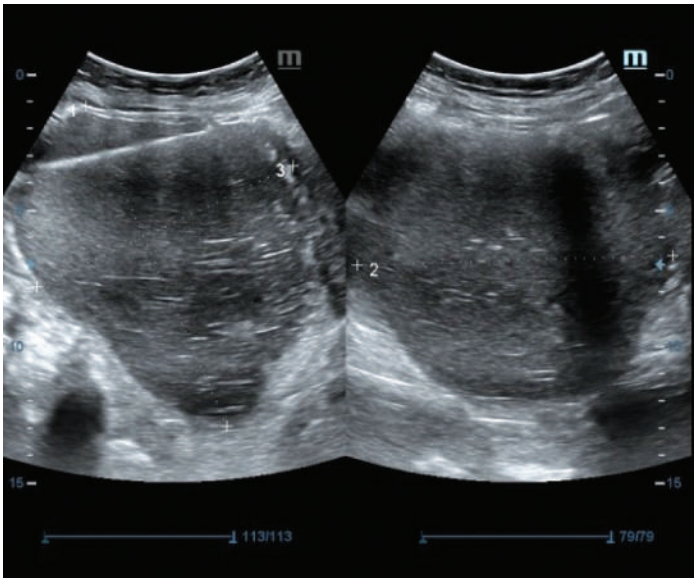

Figure 1. TVS: Large unilocular cystic mass, pelvis with echogenic stippling

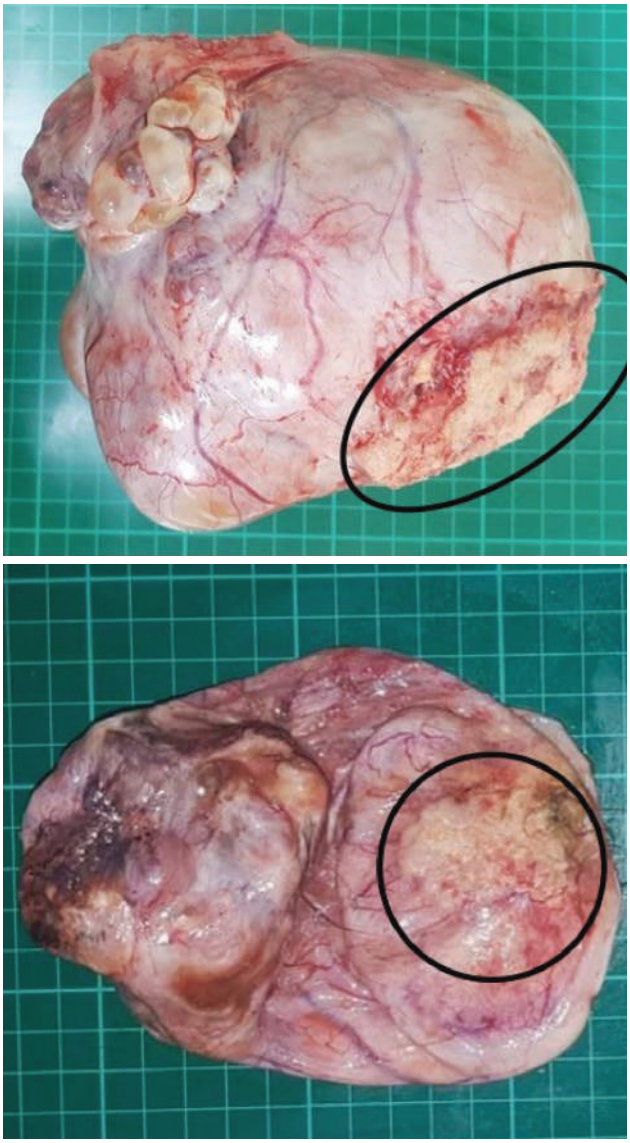

Figure 2. Gross, top ovary, 15x15 cm cystic mass with 5x5x solid mass on the capsule (circles).

mass on the lower uterine segment and the cervix (Figure 3). Other findings were unremarkable. Microscopic examination of the left ovary showed parts of mature cystic teratoma with an invasion of neoplastic cells similar to those of the cervical area (Figure 4). Sections of the mature cystic teratoma revealed stratified squamous epithelium, hair follicle, and fat. The microscopic examination of the cervix showed a cervical tumor consisting of diffuse sheets of neoplastic cells (Figure 5) characterized by pleomorphic enlarged nuclei with prominent nucleoli set in an eosinophilic cytoplasm. Several scattered mitotic figures were noted. The histopathologic report revealed squamous cell carcinoma, moderately differentiated involving the cervix, lower uterine segment, and left ovary. The right parametrium was positive for tumor. The omentum, cul de sac mass, cul de sac, and serosal implants were also positive for tumor metastasis. The peritoneal fluid was positive for atypical cells, giving a high suspicion for malignancy. Lymph nodes were negative for metastasis. Other findings include mature cystic teratoma with struma ovarii, left; atrophic right ovary; cystic atrophy, endometrium, and unremarkable fallopian tubes.

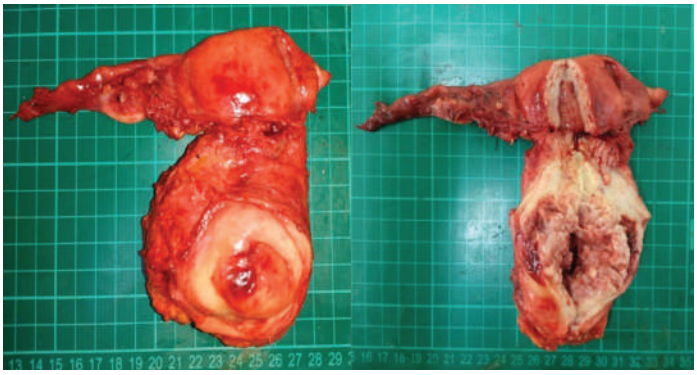

Figure 3. Gross: exocervix, smooth; endocervix, 8 x 7cm mass with extension to the lower uterine segment

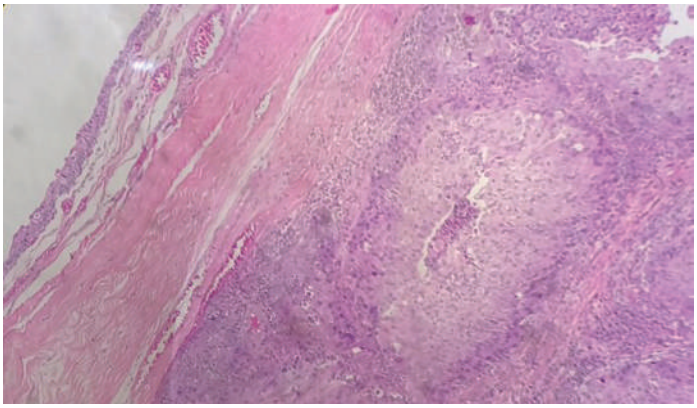

Figure 4. SCCA, ovary (infiltration of keratinized neoplastic cells similar to those of the cervical area)

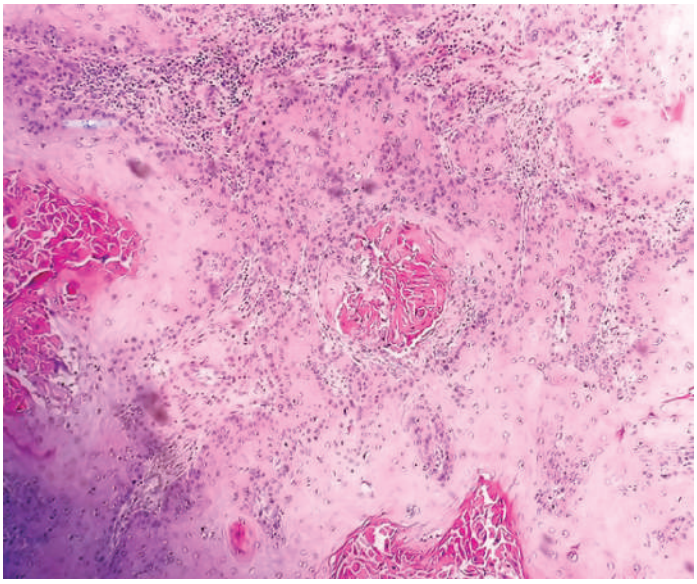

Figure 5. SCCA, cervix (neoplastic cells)

The postoperative diagnosis was Squamous Cell Carcinoma arising from a mature cystic teratoma, ovary stage III-C versus Squamous Cell Carcinoma, Moderately Differentiated, Cervix stage IVB. The patient was advised systemic chemotherapy of carboplatin-paclitaxel every 21 days for 6 cycles, and underwent 1 cycle but then decided to undergo palliative care. On follow up at the Outpatient Department, there was a 6x5 cm palpable mass on the hypogastric area with associated on and off pain. She was advised on nutritional build-up and continuation of chemotherapy. The patient was, however, lost to follow up.

CASE DISCUSSION

Cervical cancer usually starts as a locally infiltrating cancer. The manner of spread is from the cervix to the vagina and adjacent paracervical and parametrial areas. The tumors may appear ulcerated with or without an exophytic growth pattern, similar to the appearance of a cauliflower coming out of the cervix. On the other hand, they may be endophytic. Cases like these are usually asymptomatic, predominantly during the early stages. They also have a tendency to be already deeply invasive at the time of diagnosis. These often originate from the endocervix and progress to saturate the cervix and lower uterine segment, causing a barrel-shaped cervix.[5] This endophytic type of cervical cancer is rarely encountered which may contribute to the non-diagnosis as in the patient's case.

Cervical carcinoma was not detected nor considered during the patient's outpatient consults due to the absence of the usual symptoms of cervical cancer as well as abnormal physical examination and ultrasound findings related to the cervix. Intraoperatively, there were findings of an endophytic type of cervical tumor up to the lower uterine segment partly attached to the cul de sac. This type of tumor is often more advanced than the exophytic variety mainly because of the late diagnosis. On top of the nodal spread, this carcinoma spreads hematogenously to the lung, liver, and bone[5]. Other areas of metastatic spread are rare.

Mature teratomas are generally a benign tumor with cystic, solid, or mixed component.[5] The patient was preoperatively diagnosed with an MCT. However, intraoperatively, in addition to the ovarian mass, the cervix and lower uterine segment consisted of necrotic, brain-like

tissue which pointed to a malignancy. This posed a dilemma in the diagnosis of either a primary cervical carcinoma with ovarian metastasis or a primary ovarian carcinoma with cervical metastasis.

Ovarian cancer rarely has metastasis to the cervix, vagina, or vulva. A review conducted by Guidozzi, F, et al showed that only 7 out of 148 patients with FIGO stage III or IV ovarian cancer had metastatic deposits to the cervix which showed the presence of adenocarcinoma rather than SCC. Other associated findings in these patients were malignant ascites, retroperitoneal lymph node involvement, and significant peritoneal carcinomatosis[6] which was not evident in the presented case. This suggests a shift in the diagnosis away from a primary ovarian cancer and leading more towards a cervical origin.

Early stages of ovarian cancer is often an incidental finding during physical examination or a postoperative finding. Meanwhile, a palpable mass, early satiety or bloating and painful abdomen are usual complaints of patients in advanced stages. In the presented case, there was a one-year history of palpable pelvoabdominal mass and abdominal pain. The risk of malignancy is relative to age such that it is significantly greater in postmenopausal women with the highest incidence in the fifth and sixth decades[3]. A study conducted by Wang, Yang, and Pan stated that the associated complications with cystic teratoma cases include malignant degeneration but only in 2% of the cases. Other complications observed were torsion, rupture and infection.[8]

Ovarian SCC rarely metastasizes to the cervix with only a very few reported cases and mostly are adenocarcinomas. This tumor is usually in its advanced stage already as well.

Total hysterectomy with surgical staging and chemotherapy are the usual treatment for this type of ovarian tumor.[3] Early detection and removal of the entire tumor, guided by the oncosurgical treatment principles, together with complete cytoreduction is vital in further improvement of the outcomes in these patients.[3]

Serum tumor markers and imaging are two essential components in the differentiation of malignant from benign ovarian tumors. Metastatic workups were done in the presented case. Tumor markers such as CA-125 and alpha fetoprotein and transvaginal ultrasound were also done which gave the picture of a benign tumor more than a malignant one. The patient's case, however, intraoperatively, showed gross malignancy on the cervix, lower uterine segment, ovary, and cul de sac. There were no workups for cervical cancer done, like cervical punch biopsy, which could have changed the approach of treatment and management of the patient's condition.

A possible approach to this case involves the molecular aspect of the said diseases. Newer research and studies discussed that the protein p16INK4a (or p16) is a cellular protein involved in cell cycle regulation which is expressed at a very low level in normal cells making it barely detectable by immunohistochemistry. It may be regarded as a surrogate marker for the activated oncogene expression of HR-HPV in dysplastic cervical cells[9].

A study by Narges, et al, (2012) showed that the expression of p16 is elevated in invasive squamous carcinoma of the cervix highlighting that it could be a valuable marker for predicting the risk of development of cervical cancer.[9] In correlation to the case, expression of p16 in the ovarian mass points to a primary cervical cancer rather than ovarian cancer. But the absence of the said protein does not rule out primary ovarian cancer entirely.

Hall, et al, (2008) conducted a study in a cohort of patients with histologically proven epithelial dysplasia which concluded that p16 promoter methylation can be a reliable predictor of malignant transformation.[10]

For the present case, this immunochemistry staining using p16 is recommended to increase the certainty of the SCC of the cervix as the primary tumor. Platinum-based chemotherapy, nutritional build-up, and regular follow up could have been beneficial to the patient. However, due to the poor prognosis of this case, there is no certainty of increasing the chances of survival and improving the quality of life even with the recommended treatments.

SUMMARY

To conclude, the detection of cervical carcinoma in a setting of a pelvoabdominal mass with normal preoperative cervical findings poses a difficulty. Routine Pap smear is highly recommended to screen for cervical cancer. This, however, is not accurate 100% of the time.

SCC of the cervix rarely metastasize to the ovaries and the endophytic type usually presents with a barrel-shaped cervix. Because of its unusual presentation, it is often diagnosed late and is already in its advanced stage. It is therefore fitting to be vigilant in doing routine gynecologic examinations to recognize the slightest abnormalities which will assist in pointing to the right diagnosis. Concurrent chemotherapy and radiotherapy is the cornerstone treatment for this cancer.

The rarity of cervical metastasis of an ovarian SCC also does not aid in the proper diagnosis. Collection of sufficient samples is fundamental in these ovarian cancers to establish their teratomatous origin histologically and to avoid errors in diagnosis.

With the advancement of science and technology, the expression of p16 in the cervix can help in predicting the risk of cervical cancer even in women with normal pap smear results.

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