Diagnostic Accuracy of Intraoperative Frozen Section in the Diagnosis of Ovarian Neoplasms in a Tertiary Training Hospital: A 10-Year Retrospective Report*

Jimmy A. Billod, MD, FPOGS, DSGOP, FPSCPC;
Efren J. Domingo, MD, PhD, FPOGS, FSGOP, FPSCPC and
Nelson T. Geraldino, MD, MPH, MBAH

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

Objective: This study aimed to determine the concordance between frozen section and final paraffin histopathologic diagnoses and the performance rates of frozen section in terms of accuracy, sensitivity and specificity in the diagnosis of ovarian neoplasm in a tertiary training government hospital.

Methodology: This is a retrospective validation study from 2004 -2013 involving 810 cases of ovarian neoplasms from gynecologic surgeries submitted for frozen section diagnosis. Records of all cases submitted for frozen section diagnosis pertaining to ovarian neoplasms were retrieved from the Surgical Pathology logbooks and computerized database. All histopathologic results of frozen and paraffin sections were retrieved and reviewed. In all the statistical tests, any associated p-values lesser than 0.05 alpha were considered significant.

Results: The frozen section results such as benign, borderline, and malignant were associated with the final histopath results ($p<0.001$) with 89.09% agreement. The overall performance rates of frozen section for the 10-year period across the three categories were as follows, sensitivity of 81.8%, specificity of 99.2%, and overall accuracy rate of 92.9%. Size of the ovarian mass, gross character (cystic versus solid) , and epithelial histology particularly mucinous significantly lowered the accuracy rate ($p <0.01$).

Conclusion: Accuracy rates of frozen section has maintained a promising record over a period of years. But, despite the high degree of accuracy, several findings have shown its limitations. For ovarian tumors with challenging features, increasing the number of section for frozen analysis will improve accuracy rate. Correlation should be made with the clinical presentation, preoperative imaging, tumor markers and other intraoperative findings and communication with the pathologists is vital to arrive at the most accurate intraoperative diagnosis.

Key words: frozen section, paraffin histopathologic diagnosis, ovarian neoplasm, ovarian mass

* First place winner, SGOP First Luciano SJ Sotto Research Contest, 2015

Ovarian cancer is responsible for 4% of all cancers affecting women[1] and is the second most common cause of death from gynecologic cancers[2-4] and the fourth most common cause of death from all types of cancers affecting women.[3] The incidence rate of Philippine residents in 2002 was estimated at 11.5 per 100,000.[4]

Generally, malignant ovarian tumors are managed with debulking surgery and complete surgical staging.[5] However, to improve survival, comprehensive surgical staging with lymphadenectomy is recommended even for early-stage ovarian cancer. Fertility-preserving surgery is an acceptable alternative to more extensive surgery in patients with well differentiated surgical stage I ovarian cancer. Hence, frozen sections (FS) for the intraoperative diagnosis of suspicious adnexal mass is recommended in settings in which availability and patients preference allow.[6]

Frozen sections (FS) are used in both gynecologic and general surgical practice mainly to aid in the differentiation of benign from malignant disease. Intraoperative evaluation of the specimen with frozen section is very important in determining the type and extent of surgery in gynecologic oncology.[7] Frozen section is referred to as intraoperative consultation, as its practice usually involves liaison between surgeon and pathologist, rather than the mere provision of histological diagnosis.[8]

Histopathology plays an integral role in the multidisciplinary approach of treating patients with cancers, the accuracy of which has important therapeutic and prognostic implications. Assessing the nature of tumors confined to the ovaries and uterus is even more problematic because benign and malignant neoplasms can have identical gross appearances. As the optimal management of benign, premalignant and malignant tumors differs, especially in patients who wish to retain fertility, intraoperative assessment frequently is used to provide a provisional pathological diagnosis and to guide the extent of surgery and/or the requirement for additional staging procedures.[9]

Various studies have reported high degree of accuracy of FS in determining the histologic status of ovarian tumors.[10-13] In the local setting, there were only 2 studies on the concordance rates of frozen section in gynecologic neoplasms.[14,15] There is no published study particularly on ovarian neoplasms. In addition, there are no studies that dealt on the impact of discordance in the surgical management of these patients. The result of this study will provide guidelines in the management of problematic gynecologic lesions in terms of intraoperative consultation and provide achievable solutions to improve accuracy of frozen section.

Objectives

General Objective:

1. To determine the concordance between frozen section and final paraffin histopathologic diagnoses of ovarian neoplasm in a government tertiary training hospital.

Specific Objectives:

1. To determine the utilization rate of frozen section in the practice of Gynecology in a government tertiary training hospital.

2. To determine the accuracy of frozen section, in terms of sensitivity, specificity, positive predictive value and negative predictive value in the diagnosis of various ovarian neoplasms.

3. To determine if the following affect concordance between the frozen section and final paraffin histopathologic diagnoses.
   a. age of patient
   b. laterality of ovarian neoplasm
   c. size of the ovarian mass
   d. nature of the ovarian neoplasm (cystic and solid)
   e. number of sections taken
   f. histologic types (epithelial versus non- epithelial)
   g. mucinous types
   h. borderline malignant or atypical proliferative tumors

4. To determine whether accuracy rates changed over the period of 10 years in the department and comparing it to the previous reported rates.

5. To review the impact of frozen section diagnosis in the decision of surgical management among those with discordant diagnoses.

Methodology

Study Design and Population

This is a retrospective validation study from January 2004 - December 2013 of ovarian tumors operated on by the Department of Obstetrics and Gynecology submitted for frozen section in a tertiary training hospital. This was approved by the Institution's Ethical Review Board.

In the study of Taskiran, et al.[16] on the the role of frozen section evaluation in the diagnosis of adnexal mass, the overall discordance rate was 5.3%. The accuracy reported was 97% sensitivity and 92% specificity wherein the prevalence of malignant was 45%. To achieve a precision of 0.06 for sensitivity and specificity, the total sample size needed for this study is 144. With this sample size, the precision will be at 0.042 (Figure 1, Appendix B).

All cases from gynecologic surgeries and/or procedures for ovarian neoplasms performed under the Department of Obstetrics and Gynecology submitted for histopathologic diagnosis were included in the study. Cases not operated on under the Department of Obstetrics and Gynecology and with incomplete records and/ or missing results were excluded from the study.

Study Description and Outcome Measures

Records of all cases submitted for frozen section diagnosis pertaining to ovarian neoplasms were retrieved from the Surgical Pathology logbooks and computerized database. All histopathologic results of frozen and paraffin sections were retrieved and reviewed. The following data were collected and recorded using the date extraction form (Appendix A). These include the following:

a. year of histopathologic result
b. demographic data (age, marital status, GP score)
c. size of the ovarian mass
d. number of sections taken for frozen and paraffin study
e. laterality
f. gross description of the ovarian mass (whether solid or cystic)
g. histology
h. surgical procedure performed prior to the frozen section diagnosis
i. final procedure performed after the release of the result

The collected data were encoded in a tally sheet.

The outcome of this study focused on discordance between frozen section and paraffin section diagnoses and to determine whether the enumerated factors influence such discordance.

a. age of patient
b. laterality of ovarian neoplasm
c. size of the ovarian mass
d. characteristic of the ovarian neoplasm (cystic and solid)
e. number of sections taken
f. histologic types (epithelial versus non-epithelial)
g. mucinous type
h. borderline malignant or atypical proliferative tumors

Accuracy rates were computed for each neoplasm category. Another expected outcome of this study is the impact of the discordance in the management of these patients.

Data Processing and Statistical Analysis

All retrieved data were encoded in MSEXCEL 2013. Categorical data were expressed using frequency and percentages while continuous data were indicated using mean and standard deviation. In testing associations among categorical variables for univariate analysis, Chi square test of independence and 2x2 Fisher exact test adjustment were employed. Meanwhile, in comparing average values among various groupings, Z test of mean differences and one way Analysis of Variance were used. Furthermore, to

identify factors, which would reveal significant predictors of the proponent's main outcome of interest, Logistic Regression was utilized. In all the statistical tests, any associated p-values lesser than 0.05 alpha were considered significant. To ensure accuracy of computation, SAS 9.1 and IBMSPSS version 21 were utilized as statistical software.

Results

Utilization Rate of Frozen Section

Between 2004 and 2013, the Department of Anatomic Pathology received an average of 14600 specimen per year for histopathologic diagnosis. A total of 6174 specimens were submitted for frozen section diagnosis giving a overall utilization rate of 4%. Of the total frozen section specimens, 15% were received from the Department of Obstetrics and Gynecology with an average of 93 specimens per year. Among all the specimens received from gynecologic surgeries, 87 % were from ovarian neoplasms, comprising 13 % of all frozen section specimens. The rest were from uterine lesions, tumor implants and lymph nodes. For the 10- year period, there were 810 specimens from ovarian neoplasms submitted for frozen section diagnosis.

Concordance and Accuracy Rates

The FS results such as benign, borderline, and malignant were associated with the final histopath results ($p<0.001$) with 89.09% agreement (Table 1). Thus, frozen section is a significant predictor of final histopathologic results, in detecting namely, benign, borderline, and malignant lesions. A total of 53 (6.5%) patients had benign diagnoses at frozen section evaluation but turned out to be borderline or malignant on final histopathologic result. Conversely, 4 patients had an initial borderline or malignant diagnoses but came out to be benign on paraffin evaluation. Three patients had deferred frozen section diagnosis. Deferred cases included two epithelial tumors (mucinous cystadenoma and serous cystadenocarcinoma) and one sex cord stromal tumor. The overall performance rates of FS for the 10-year period across the three categories were as follows, sensitivity of 81.8%, specificity of 99.2%, and overall accuracy rate of 92.9%.

Table 2 presents the performance of FS in the three categories of diagnosis. It shows that FS has the highest sensitivity on benign ovarian masses but with the lowest specificity and overall accuracy rate, 99.2%, 81.2% and 92.9% respectively. Specificity is equal between borderline and malignant ovarian lesions at 100%, but a higher sensitivity on malignant over borderline neoplasms, 86% and 72% respectively. Overall, FS has the highest accuracy on malignant lesions over borderline and benign, 97%, 94% and 92.9% respectively.

Clinical and Pathologic Variables

Analysis was done to further determine the potential factors that would affect the performance rates of frozen section.

Table 1. Concordance and discordance between frozen section and the final paraffin diagnoses.

	Paraffin/ Final Diagnosis			
FS Diagnosis	0-Benign	1-Borderline	2-Malignant	Total
Benign	511	33	19	563
Borderline	2	89	30	121
Malignant	2	1	120	123
Deferred	2	0	1	3
Total (%)	517 (0.64)	123 (0.15)	170 (0.21)	810

$x^2 = 954.29$, df = 6, $p<0.001$

Table 2. Performance of frozen section across the three classifications of diagnoses.

Performance rates	Categories		
	Benign	Borderline	Malignant
Sensitivity	99.2%	72.0%	86.0%
Specificity	81.8%	100.0%	100.0%
Predictive value positive	90.6%	98.0%	98.0%
Predictive value negative	98.4%	94.0%	96.0%
Overall accuracy**	92.9%	94.0%	97.0%

Age and Gravidity of Patients

Table 3 presents the baseline characteristics of patients and of the ovarian specimens. The mean age of patients who were subjected to frozen section was 34.50 +/- 14.90 years old (range of 5-78 years old). Age and gravidity of patients did not confound the agreement rates of frozen section and final paraffin diagnoses, p-value 0.064 and 0.392, respectively (Table 4).

Size of the Ovarian Mass and Number of Sections

The mean largest diameter of the ovarian masses subjected for frozen section was 17 cm (range 2- 43 cm) and the mean number of sections per ovarian mass was 4. Analysis showed that size of the specimen has an impact in the concordance of frozen section and the final histopathologic results. It has shown that an ovarian mass with more than 20 cm is associated

Table 3. Clinical and pathological characterisctics of patients and ovarian specimens.

Characteristics	n= 810 No. (%)
Age group	
< 10	4 (0.5)
10-19	140 (17)
20-29	222 (27.5)
30-39	175 (22)
40-49	113 (14)
>50	156 (19)
Gravidity	
G0	423 (52.2)
G1- G2	157 (19.4)
>G3	230 (28.4)
Laterality	
Unilateral	740 (91)
Bilateral	70 (9)
Ovarian size	
<10 cm	147 (18)
10-14.9 cm	95 (12)
15-20 cm	210 (26)
>20 cm	358 (44)
Gross Description	
cystic	515 (64)
cystic, with solid areas	186 (23)
solid	109 (13)
Histology	
Epithelial	589 (73)
Germ cell	140 (17)
Sex cord stromal	61 (8)
Infectious	11 (1)
Metastatic	9 (1)

Table 1. Age and gravidity and concordance of frozen section with final histopathologic diagnoses.

Patients' Characteristics	Concordant n=720		Discordant n=87		Deferred n=3		p-value
Age group							
< 10	3	0.4%	0	0%	1	33%	
10-19	128	18%	12	14%	0	0%	$x^2 = 14.8$, df = 8, p = 0.064
20-29	185	25.6%	37	43%	0	0%	
30-39	157	22%	17	20%	1	33%	
40-49	105	14%	7	8%	1	33%	
>50	142	20%	14	16%	0	0%	
Gravidity							
G0	370	51%	50	58%	3	100%	$x^2 = 4.10$,df = 4, p = 0.392
G1- G2	142	20%	15	17%	0	0%	
>G3	208	29%	22	25%	0	0%	

with discordance and deferrals in 67% of cases and those with size of 20 cm and below have higher rates of concordance (p 0.001). Correlation of the intraoperative size and the measurement of the pathologist with the number of sections taken during the processing conferred the same statistical significance, ($p < 0.0001$) (Table 5).

Table 1. Pathologic characteristics of ovarian mass and the concordance of frozen section with the final histopathologic diagnoses.

Patients' Characteristics	Concordant n=720		Discordant n=87		Deferred n=3		p-value
Intraop Size (largest diameter)							
<10 cm	141	20%	6	7%	0	0%	$x^2 = 23.2, df = 6, p = 0.001$
10-14.9 cm	90	13%	5	6%	0	0%	
15-20 cm	191	26%	18	21%	1	33%	
>20 cm	298	41%	58	67%	2	67%	
Laterality							
Unilateral (L/R)	656	92%	81	93%	3	100%	$x^2 = 0.268, df = 2, p = 0.874$
Bilateral	64	8%	6	7%	0	0%	
Gross Description							
cystic, unilocular	250	35%	7	8%	1	33%	$x^2 = 40.63$, df = 6, $p<0.01$
cystic, multiloculated	218	30%	38	44%	1	33%	
cystic with solid area	150	21%	36	41%	0	0%	
solid	102	14%	6	7%	1	33%	
Character And Contents							
Mucinous							
Mucinous	237	33%	39	45%	1	33%	$x^2 = 4.66, df = 4, p = 0.324$
Mucinous with excrescenses	20	3%	7	8%	0	0%	
Mucinous with focal thickness	58	8%	16	18%	0	0%	
Serous							
Serous	79	11%	1	1%	1	33%	$x^2 = 5.27, df = 4, p = 0.261$
Serous, excrescences	42	6%	4	5%	0	0%	
Serous with thickened wall	5	1%	0	0%	0	0%	
Sebum / Hair	87	12%	9	10%	0	0%	$x^2 = 0.224, df = 1, p = 0.636$
Solid							
Solid	44	6%	3	3%	0	0%	$x^2 = 0.808, df = 2, p = 0.668$
Solid with necrosis	81	11%	8	9%	1	33%	
Chocolate Fluid	55	8%	0	0%	0	0%	$x^2 = 7.38$, df = 2, $p = 0.025$
Abscess and pus materials	12	2%	0	0%	0	0%	$x^2 = 1.50, df = 2, p = 0.472$
Pathology Size (largest diameter)							
<10cm	173	24%	6	7%	0	0%	$x^2 = df = 6$, $p<0.0001$
10-14.99 cm	122	17%	6	7%	0	0%	
15-20 cm	229	32%	36	41%	1	33%	
>20 cm	196	27%	39	45%	2	67%	
Histology							
Epithelial							
Mucinous	323	45%	66	76%	1	33%	$x^2 = 21.4$, df = 4, $p<0.0001$
Serous	104	14%	4	5%	1	33%	
Others	86	12%	4	5%	0	0%	
Germ Cell	129	18%	11	13%	0	0%	$x^2 = 1.99, df = 2, p = 0.370$
Infectious	11	2%	0	0%	0	0%	$x^2 = 1.41$, df =2, $p = 0.494$
Metastatic	8	1%	1	1%	0	0%	$x^2 = 0.465, df = 2, p = 0.793$
Sex Cord Stromal	59	8%	1	1%	1	33%	$x^2 = 8.41, df = 2, p = 0.015$

Further analysis showed that the bigger the size of the mass, the more sections were taken for frozen section diagnosis ($p<0.0001$). Size and number sections processed have shown to influence the accuracy rates. Nevertheless, by utilizing the One Proportion Power Analysis, a 6-8 number of sections should be taken from the specimen to ensure a 99% accuracy rate.

Laterality and Gross Description of the Ovarian Neoplasm

Among the specimens submitted, 91% were unilateral and about 9 % has a concomitant contralateral ovarian pathology (Table 3). Laterality of the ovarian mass did not influence the concordance rate (p 0.874). Ovarian masses were described as follows, cystic and solid. Cystic masses were further classified into unilocular, multilocular or with solid areas (Table 3). Analysis showed that gross description or nature of the ovarian mass significantly affected the accuracy rate. Particularly, multiloculated cystic and cystic with solid areas resulted to discordant cases in 44% and 41%, respectively (p-value <0.01). Further analysis on the character of the mass and its contents showed no significant effect on the concordance between frozen section and final paraffin diagnoses (Table 5).

Histology

Epithelial tumors comprise 73% of the cases analyzed for frozen section diagnosis and almost 50% were of mucinous types (Table 3). When concordance of frozen section and final paraffin section was analyzed based on the major histologic categories of ovarian tumors, epithelial histology significantly influenced the performance of frozen section as compared to the other histologic classifications. Mucinous histology resulted to a highest discordant rate at 76% ($p< 0.0001$) (Table 5).

Since epithelial histology of ovarian tumors affected the agreement between frozen and final paraffin section diagnoses, a subanalysis test of accuracy was performed. Table 6 presented the performance rates of FS on epithelial histology. Mucinous category has a comparable accuracy rate between benign and borderline at 89 %, but significantly lower than the other types of epithelial tumors on the same category. FS on malignant epithelial tumors were consistently high regardless of histology but mucinous showed the lowest rate. This subanalysis revealed that FS on mucinous ovarian tumors has lower accuracy rates than their epithelial counterparts.

Accuracy Trends

For the 10 year- period of this study, the accuracy rates of frozen section in the diagnosis of ovarian tumors have been consistent to be approaching 90% as shown in Table 7. It was noted that year 2008 has the lowest accuracy rates for benign, borderline and malignant tumors with rates 84%, 89% and 90 %, respectively.

Table 6. Subanalysis frozen section performance rates of of epithelial types of ovarian tumors.

Category Histology	Sensitivity	Specificity	Pred value positive	Pred value negative	Overall accuracy**
Benign					
Epithelial, mucinous	99.5%	75.7%	84.2%	99.2%	89.2%
Epithelial, serous	98.8%	100.0%	100.0%	96.4%	99.1%
Epithelial, others	100.0%	96.3%	98.5%	100.0%	98.9%
Borderline					
Epithelial, mucinous	68.5%	99.5%	98.7%	86.6%	89.3%
Epithelial, serous	100.0%	98.8%	92.9%	100.0%	98.9%
Epithelial, others	100.0%	100.0%	100.0%	100.0%	100.0%
Malignant					
Epithelial, mucinous	80.6%	100.0%	100.0%	96.9%	97.3%
Epithelial, serous	100.0%	100.0%	100.0%	100.0%	100.0%
Epithelial, others	95.5%	100.0%	100.0%	98.5%	98.9%

Table 7. Table 7. 10- year period performance rates of frozen section.

Accuracy of Frozen Section	Year 2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Benign										
Sensitivity	100.00%	98.33%	100.00%	98%	100%	100%	100%	98%	97%	98%
Specificity	79.49%	84.85%	70.00%	89%	63%	74%	88%	93%	91%	82%
Overall accuracy**	92.23%	93.55%	91.30%	95%	84%	91%	97%	96%	95%	92%
Borderline										
Sensitivity	80.00%	78.60%	40.00%	79%	50%	63%	80%	91%	82%	69%
Specificity	100.00%	98.30%	100.00%	100%	100%	100%	100%	98%	100%	100%
Overall accuracy**	95.20%	94.60%	89.80%	96%	89%	93%	96%	97%	97%	94%
Malignant										
Sensitivity	76.50%	87.50%	100.00%	95%	65%	78%	100%	93%	93%	88%
Specificity	100.00%	100.00%	100.00%	100%	100%	100%	100%	100%	98%	98%
Overall accuracy**	95.10%	97.30%	100.00%	99%	90%	96%	100%	99%	97%	96%

Clinical Impact of Frozen Diagnosis of Surgical Management

Of the 52 cases that were signed out benign on FS but turned out borderline or malignant on the final PS (Table 8), 7 patients underwent complete surgical staging despite a benign FS diagnosis probably due to high suspicion of the surgeons that the ovarian masses were malignant. Other factors perhaps were considered (ie, preop UTZ, CA 125 levels). Forty five patients were incompletely staged/ "Under-treated" based on a benign FS diagnosis. This represents 15% (45/ 292) of women who should have obtained complete surgical staging by final histopathologic diagnosis. Of these under-treated patients, 80% percent (36/45) were of mucinous type and 87% (39/ 45) were ≥15 cm size. Furthermore, 4 patients with initial borderline or malignant FS diagnosis underwent complete surgical staging or classified as "Over-treated" (Table 8). However, this represents only 1% of all patients with benign diagnosis by final PS. Two cases were epithelial tumors (mucinous and serous) and 2 were germ cell tumors (teratoma). Grossly, there were noted focal thickness and excrescences on the 2 epithelial tumors and solid areas on the 2 germ cell tumors. This study showed a 15% chance of patients to be potentially under-treated based on the FS diagnosis.

Predictors of Borderline and Malignant Diagnosis

An exploratory analysis was executed to estimate the odds to predict the final diagnosis category of ovarian neoplasms. Using logistic regression, the equation model yielded significant predictors ($p = 0.0010$) in diagnosis of borderline or malignant findings. Under an equivocal frozen section result, the variables that are composite predictors of borderline neoplasms are bilaterality, unilocular and multilocular nature of the ovarian mass. The same way, the significant predictors for the diagnosis of malignant neoplasm are age of 20-39 years old, unilocular and multilocular nature of the ovarian mass, presence of solid areas, and a serous and mucinous epithelial histology. The presence of one these said variables increases the probability of the ovarian mass to be borderline and or malignant in the final histopathologic diagnosis.

Discussion

Intraoperative consultation is primarily performed to confirm the presence and histologic type of malignancy, as well as to determine the adequacy of resection by examining the surgical margins. Other factors that affect surgery include the status of the

Table 8. Discordant cases and final operation performed

#	FS Diagnosis	PS Diagnosis	Final Procedure
		"Under- treated"	
1	Mucinous cystadenoma	Mucinous tumor, LMP	THBSO
2	Mucinous cystadenoma	Mucinous tumor, LMP	LSO
3	Mucinous cystadenoma	Mucinous tumor, LMP	THBSO
4	Mucinous cystadenoma	Mucinous tumor, LMP	RSO
5	Mucinous cystadenoma	Mucinous tumor, LMP	THBSO
6	Mucinous cystadenoma	Mucinous tumor, LMP	LSO
7	Mucinous cystadenoma	Mucinous tumor, LMP	LSO
8	Mucinous cystadenoma	Mucinous tumor, LMP	RSO
9	Mucinous cystadenoma	Mucinous tumor, LMP	LSO
10	Mucinous cystadenoma	Mucinous tumor, LMP	THBSO
11	Mucinous cystadenoma	Mucinous tumor, LMP	THBSO
12	Mucinous cystadenoma	Mucinous tumor, LMP	USO
13	Mucinous cystadenoma	Mucinous tumor of LMP	USO
14	Mucinous cystadenoma	Mucinous tumor of LMP	THBSO
15	Mucinous cystadenoma	Mucinous tumor of LMP	THBSO
16	Mucinous cystadenoma	Mucinous tumor of LMP	USO
17	Mucinous cystadenoma	Mucinous tumor of LMP	LSO, right cystectomy
18	Mucinous cystadenoma	Mucinous tumor of LMP	LSO
19	Mucinous cystadenoma	Mucinous cystadenocarcinoma, LMP	THBSO
20	Mucinous cystadenoma	Mucinous cystadenocarcinoma, LMP	LSO
21	Mucinous cystadenoma	Mucinous cystadenocarcinoma, LMP	RSO
22	Mucinous cystadenoma	Mucinous cystadenocarcinoma, LMP	THBSO
23	Mucinous cystadenoma	Atypical Proliferative Tumor	USO
24	Mucinous cystadenoma	Atypical proliferative mucinous tumor	RSO
25	Mucinous cystadenoma	Atypical proliferative mucinous tumor	USO
26	Mucinous cystadenoma	Borderline mucinous tumor	LSO
27	Mucinous cystadenoma	Borderline mucinous tumor	LSO
28	Mucinous cystadenoma	Borderline mucinous tumor	THBSO
29	Benign mucinous tumor	Borderline mucinous tumor	RSO
30	Mucinous cystadenoma	Borderline mucinous tumor	USO
31	Mucinous cystadenoma	Borderline mucinous tumor	THBSO
32	Favor mucinous cystadenoma	Borderline mucinous tumor	LSO
33	Mucinous cystadenoma	Mucinous tumor of borderline malignancy	USO
34	Mucinous cystadenoma	Mucinous cystadenocarcinoma, well differentiated	LSO
35	Mucinous cystadenoma	Mucinous cystadenocarcinoma	THBSO
36	Mucinous cystadenoma	Mucinous cystadenocarcinoma, grade 1	USO
37	Mature cystic teratoma, both	SCCA arising from MCT(L); MCT®	BSO
38	Mature teratoma elements	Immature teratoma, grade 2	LSO
39	Mature cystic teratoma	Immature teratoma, grade 1	LSO
40	Mature cystic teratoma	Immature teratoma, grade 3	RSO
41	Mature cystic teratoma	Immature teratoma, grade 2	RSO
42	Fibrothecoma	Yolk sac tumor	RSO
43	Fibroma versus Adenofibroma	Granulosa cell tumor	LSO
44	Fibroma	Krukenberg tumor	THBSO
45	Ovarian neoplasm probably benign	Poorly differentiated adenocarcinoma	LSO
		Completely-staged despite benign FS	
46	Mucinous cystadenoma	Mucinous cystadenocarcinoma, well differentiated	RSO, BLND, PALS, IO, RPB, appendectomy
47	Mucinous cystadenoma	Mucinous cystadenocarcinoma, well differentiated	THBSO, BLND, PALS, IO, RPB, appendectomy
48	Mucinous cystadenoma	Mucinous cystadenocarcinoma	THBSO, BLND, PALS, IO, RPB, appendectomy
49	Mucinous tumor probably benign	Papillary mucinous cystadenocarcinoma, well differentiated	RSO, BLND, PALS, IO, RPB, appendectomy

50	Mature cystic teratoma	Immature cystic teratoma, grade 1	RSO, BLND, PALS, RPB
51	Mature cystic teratoma	Immature teratoma, grade 2	RSO, BLND, PALS, IO, RPB
52	Mature cystic teratoma	Immature cystic teratoma, grade 1	LSO, IO, RPB, BLND
		"Over-treated"	
53	Borderline mucinous tumor	Mucinous cystadenoma	THLSO, BLND, PALS, IO, RPB, appendectomy
54	Serous papillary tumor, borderline	Serous cystadenoma	LSO, BLND, PALS, RPB
55	Adenocarcinoma	Mature cystic teratoma	THBSO, BLND, PALS, IO, RPB
56	Teratomatous neoplasm with areas suspicious for malignancy	Mature cystic teratoma	LSO, BLND, PALS, IO, RPB

RSO- right salphingooophorectomy; LSO- left salphingooophorectomy; THBSO- total hysterectomy with bilateral salphingooophorectomy; BLND- bilateral lymph node dissection; PALS- paraortic lymph node sampling; IO- infracolic omentectomy; RPB- random peritoneal biopsy

pelvic lymph nodes, the presence of peritoneal spread, and the differentiation of primary from metastatic malignant neoplasms.[1] Frozen section provides real-time evaluation usually within 20 minutes. This process utilizes rapid methods for tissue sampling, preparing slides, staining, performing microscopic examination and ultimately making an accurate diagnosis.[17]

Among the gynecologic cancers wherein intraoperative frozen sections are mostly requested are ovarian and endometrial tumors, but are feasible to use in all female genital cancers.[1,10] The primary management of these malignant entities requires more extensive surgery, which involves total hysterectomy, bilateral salpingo-oophorectomy with additional systematic lymphadenectomy.[5] In addition, the benign counterparts and early stage disease may be managed conservatively.[5,11,18] Frozen section is therefore carried out to ensure that proper surgical staging is carried out and to ascertain diagnosis prior to performing definitive surgery to prevent over-treatment or under-treatment of these patients.[11] Also, such morbidities related to unnecessary extensive operation can be avoided.

The recommended utilization ratio of frozen section in general surgical practice is between 5% and 15% and about 7.4% to 47% on ovarian lesions.[19] The utilization proportion (4%) of frozen section by the surgical department in our institution as shown by this present study is close to the reported figures. Frozen section rate for ovarian neoplams was 13%.

This present study reported a 93% overall accuracy of frozen section which is within the reported figures of the overall accuracy in general surgical practice from 89-99% in all tissue types.[1,8,10,20] It is as well similar to the rates on ovarian neoplasm alone which ranges from 86 % to 97%.[13,19] Sensitivity rates revealed from this study are not far from the results in a systematic review that included 14 studies on ovarian tumors which revealed a pooled sensitivity rates for benign and malignant ovarian tumors which were 99% and 94%, respectively.[3] This present study however showed a lower sensitivity at 86% on malignant neoplasms. The pooled sensitivity for borderline ovarian tumors was slightly higher that the reported rate at 66% in the review. Moreover, a metaanalysis[21] including 18 studies revealed that the pooled specificities and sensitivities varied between 65% and 100% which is similar to the results of this study.

Despite very promising accuracy rates, several factors were noted to affect the accuracy rates of frozen section in ovarian neoplasms. Several studies tried to elucidate factors from sampling technical and examination errors and factors innate from the tumor itself.[10,11,13,19] Some authors mentioned that the experience of the pathologist is of crucial importance of frozen section diagnosis.[12,19] Gross sampling error, misinterpretation, microscopic sampling and technical problems were the most frequent problems for low diagnosis rate.[12] Major problems include decreased histopathologic details compared with the standard permanent paraffin sections, and errors and difficulties in sampling. The freezing process itself may also damage the tissue and can lead to errors in the interpretation as well. Moreover, due to the need for

rapid interpretation, time constraints may be another factor that can adversely affect the accuracy rate. There may be inadequate processing time and tumor sampling as compared to a paraffin section for interpretation. Therefore, extensive samplings should be performed in suspicious cases to reduce probability of false results.

This present study attempted to look on the factors that can affect the accuracy rates beyond the technical and the mechanical aspects of frozen section. These factors are native to patients and distinct in the ovarian tumors. Few studies analysed the possible effect of clinical and pathological characteristics of patients. Consistent with the previous reports,[16,22] age, gravidity and laterality of ovarian disease did not influence the performance rates of frozen section.

Size of the ovarian mass is one of the pathological characteristics that was consistently reported to affect the accuracy rates of frozen section which was also shown in this present study. Taskiran, et al.[16] found out that the discordance rate was 3.1% in patients having adnexal mass smaller than 15 cm, while it was 14.3% if the size greater than 15 cm. Geominia, et al.[23] observed a false negative diagnosis in case with a tumor size greater or equal to 10 cms. Similar to the reports of Houck, et al.[24] and Tangjitgamol, et al.[25], there was an increase in the misdiagnosis in tumors greater than 20 cm, and no inaccurate diagnosis in tumors with less than 10 cm. This current study revealed that tumor size of more than 20 cm causes around 70% of misdiagnosis and deferrals. If a cutoff size was lowered to 15 cm, it produces around 90% of discordant and 100% of deferred cases. It is very evident that for larger ovarian tumors, more sections should be taken for frozen section evaluation.

There were no robust data on the impact of the nature and the characteristic of the mass and its content on the performance of frozen section. Gultekin, et al.[26] detected low rates of underdiagnosis in a frozen section of solid or semisolid masses than pure cystic masses. This statistical significant analysis has not been addressed in other studies. This present study presented and analysed these variables comprehensively. Nature of the ovarian mass whether cystic or solid statistically affects the the correctness of frozen section. Specifically, multiloculated ovarian masses and cysts with solid areas tend to cause almost half of the errors in the frozen section diagnoses. Unilocular and solid masses have a very low tendency of misdiagnoses. Analysis did not show significance on the effect of the character of the contents of the ovarian mass to the result of the frozen section.

Histology of the ovarian mass can cause significant confusion on frozen section diagnosis. Commonly, the diagnostic values of frozen section were slightly compromised among epithelial cell tumors compared to germ cell and other cell types.[13] Maybe because mucinous and borderline tumors are under epithelial subtypes, and germ cell tumors comprise only ~20% of ovarian tumors.[27] This report was confirmed in our study which accords with other previous reports. Almost 1/3 of the ovarian specimens examined for frozen section were epithelial type and mucinous subtypes caused 76% of misdiagnosis.

Consistent with the result of the subanalysis in our present study, mucinous[13] and borderline histology[2,28] or combination of both[29] imposes a higher discrepancy rate and relatively low sensitivity of frozen section diagnosis. This may be due to the larger mucinous tumor dimensions and more heterogenous components resulting in possible malignant areas to be overlooked.[3,12,13,25] Moreover, these mucinous ovarian tumors may sometimes contain benign, borderline and malignant components in contrast with serous tumors.[3,30,31] Storm, et al.[31,23] reviewed 73 cases of ovarian mucinous tumors and showed a 34% discordance rate between frozen section and final diagnosis as compared to serous tumor. Therefore, diagnoses cannot be made with a high level of certainty and further testing may be indicated.[3]

In the recent reports on borderline ovarian tumors, tumor diameter was the only independent predictor for underdiagnosis by frozen section in a multivariate analysis.[26,32] According to Wang, et al.[10], frozen section diagnosis of mucinous borderline tumors had a lower sensitivity than that of non-mucinous subtypes. The compatibility increases with the number of sections taken per whole of the tumor. Since the amount of tissue selected from the tumor influence the precision of diagnosis, it is recommended that one histologic section for each centimeter of the greatest tumor diameter be taken to improve sensitivity. This however is limited with the capability of sampling in terms of

frozen section, which affords only 2-4 sections per ovarian mass.

A retrospective review[32] of 4 studies on borderline tumors of the ovary revealed an overall sensitivity and a PPV of 71.1% and 84.3%, respectively. Overdiagnosis and underdiagnosis were identified in 6.6% and 30.6% of cases, respectively. In this study, tumor diameter was the only independent predictor of underdiagnosis of borderline tumors during frozen section analysis.

Our study performed a statistical analysis to come up with an achievable solution to improve accuracy of frozen section diagnosis especially on tumors with challenging features and can possibly overcome technical limitations of sampling. A section of 6-8 samples should be taken and processed to arrive at accuracy of around 99%. In our Logistic regression analysis, we presented predictors of borderline and malignant dagnosis. So for the same group of ovarian tumors, with equivocal or deferred histologic frozen diagnosis, these prognosticators maybe considered in the decision making.

For ovarian tumors, it is imperative to know the status of malignancy and histology of the these masses before or during the surgery to guide the surgical staging to be performed, which is important for further management and prognostication of patients.[2] Imaging studies and tumor markers may help in the preooperative assessment of adnexal masses whether benign or malignant.[3,6,7,33-36] Consequently, patients are advised with the possible extent of surgeries. The final decision regarding the extent of surgery will be based on the intraoperative findings and frozen section evaluation. This present study reported a higher incidence (15% chance) of under-staging of patients due to false negative FS diagnosis. So far, only two studies reported on this subject in the literature. First was that of Taskiran, et al.[16], accounted a 9% chance of incomplete surgery due to false negative FS diagnosis. These mentioned 8 patients underwent restaging laparotomy. In the more recent study of Cross, et al.[37] 4.3% of patients were under-staged at the first surgery, and potentially required a second procedure. Only 1.2% of patients were over-staged based on the FS report, which is similar to the result of our study that is 1%. Overall, of the 807 FS reported in our study, 94% of patients had a correct operative procedure at the time of initial operation based on FS diagnosis, which is comparable to the 94.5% report of Cross, et al.

Another problem in frozen section diagnosis are the deferred- histologic diagnoses. Although, it is very negligible in our study (< 0.5%), the reported rates varied from 0.4 -6% in various reports.[16,22,25,37] These authors suggested that radical surgery should be postponed at initial surgery for this group of patients to prevent unnecessary procedures.

Summary and Conclusion

Accuracy rates of frozen section over a period of years has maintained a promising record. FS evaluation of ovarian mass should be requested whenever there is doubt in the nature of the neoplasm. But despite the high degree of accuracy, several findings have shown the limitations of frozen section, such as frozen artifacts can produce inferior slides for microscopic examination and sampling errors can result from the heterogeneity of tumors. Hence, they are more difficult and challenging to interpret than paraffin-embedded sections.

Histopathologic characteristics of the tumor mass such as size of more than 20 cm, multiloculated mass, cystic mass with solid areas, mucinous and borderline tumors produces discordance between frozen section and final paraffin histopathologic diagnoses, and eventually lowers the accuracy rate. Due to these misdiagnoses, more patients would be "undertreated" more than "overtreated" surgically.

In an attempt to maximize the clinical utility of intraoperative frozen section on ovarian neoplams, to provide an appropriate surgical management to patients, subsequently improving survival and decreasing morbidities, especially those with tumors that possess characteristics that lowers the accuracy rate and causes deferrals, increasing the sections for frozen analysis is suggested. Predictors of borderline and malignant findings maybe considered in the decision making. A prospective study should be undertaken to assess the validity of these findings.

For ovarian tumors with challenging features, correlation should be made with the clinical

presentation, preoperative imaging, tumor markers and other intraoperative findings and communication with the pathologists is vital to arrive at the most accurate intraoperative diagnosis. Likewise, a discussion with a gynecologic oncologist is recommended for doubtful lesions.

Limitations and Recommendations

The limitation of this research is inherent of it being a retrospective study. So far, there were 7 studies in the literature that dealt on the diagnostic accuracy of frozen section on ovarian neoplams encompassing a period of 10 years or more. This present study being the latest, had the second most number of subjects analyzed. Unlike the previous reports, our study comprehensively examined the clinical and histopathologic characteristics of ovarian tumors that may affect performance rates. Additionally, we explored on measures how to overcome these sources of errors and discovered potential predictors that may help in the intraoperative decision-making. This study added to the limited knowledge on the clinical impacts of FS misdiagnosis on the surgical management of patients.

A prospective study on correlation of the frozen section diagnsosis with other clinical variables like tumor marker levels may be conducted. A follow up study may be done to determine the impact on prognosis of patients who were undertreated surgically due to misdiagnosis by frozen section.

References

1. Coffey D, Kaplan A, Ramzy I. Intraoperative consultation in gynecologic pathology. Arch Pathol Lab Med 2005; 129: 1544-57.
2. Malipatil R, Crasta J. How accurate is intraoperative frozen section in the diagnosis of ovarian tumors? J Obstet Gynaecol Res 2013; 39(3): 710-3.
3. Medeiros LR, Rosa DD, Edleweiss MI, et al. Accuracy of frozen-section analysis in the diagnosis of ovarian tumors: a systematic quantitative review. Int J Gynecol Cancer 2005; 15: 192-202.
4. Redaniel MT Laudico A, Lumague MR, et al. Ovarian cancer survival population differences: a "high resolution study" comparing Philippine residents, and Filipino-Americans and Caucasians living in the US. BMC Cancer 2009; 9:340
5. Domingo E, et al. Society of Gynecologic Oncologist of the Philippines Clinical Practice Guidelines 2012, 6th edition.
6. Dodge J, Covens A, Lacchetti C, et al. Management of a suspicious adnexal mass: a clinical practice guideline. Curr Oncol 2012; 19(4): e244-257.
7. Turan T, Oguz E, Unlubligin E, et al. Accuracy of frozen-section examination for myometrial invasion and grade in endometrial cancer. Eur J Obstet Gynecol Reprod Biol 2013; 167: 90-5.
8. Ghaemmaghami F, Behnamfar F, Ensani F. Inraoperative Frozen Section for the Assessment of Female Cancers. Asian Pacific J Cancer Prev 2008; 8:635-9.
9. Stewart C, Brennan B, Koay E, et al. Value of cytology in the intraoperative assessment of ovarian tumors. Cancer Cytopathol 2010; 118: 127-36.
10. Wang KG, Chen TC, Wang TY, et al. Accuracy of frozen diagnosis in Gynecology. Gynecol Oncol 1998; 70: 105-10.
11. Wasinghon P, Suthippintawong C, Tuipae S. The accuracy of intraoperative frozen sections in the diagnosis of ovarian tumors. J Med Assoc Thai 2008; 91(21): 1791-5.
12. Gol M, Baloglu A, Yigit S, et al. Accuracy of frozen section diagnosis in ovarian tumors: Is there a change in the course of time? Int J Gynecol Cancer 2003; 13: 593-7.
13. Boriboonhirunsarn D, Sermboon A. Accuracy of frozen section in the diagnosis of malignant ovarian tumor. J Obstet Gynaecol Res 2004; 30(5): 394-9.
14. Velasquez M, Banta E. Correlation of frozen and histopathologic diagnosis of borderline ovarian tumors in a tertiary hospital: A retrospective study. Phil J Gynecol Oncol 2010; 7(1): 7-11.
15. Macasaet P, Diwa M. Concordance of frozen section and final histopathologic diagnosis of mucinous ovarian tumors at the Philippine General Hospital. Unpublished
16. Taskiran C, Erdemi O, Onan A, et al. The role of frozen section evaluation in the diagnosis of adnexal mass. Int J Gynecol Cancer 2008; 18: 235-40.
17. Bui M, Smith P, Agresta S, et al. Practical issues of intraopertaive frozen section diagnosis of bone and soft tissue lesions. Cancer Control 2008; 15(1).
18. The writing committee on behalf of the ASTEC study group. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009; 373: 125-36.
19. Ilvan S, Ramazanoglu R, Akyildiz E, et al. The accuracy of frozen section (intraoperative consultation) in the diagnosis of ovarian masses. Gynecol Oncol 2005; 97: 395-9.
20. Wang X, Zhang H, Di W, et al. Clinical factors affecting the diagnostic accuracy of assessing dilatation and curettage vs frozen section specimens for histologic grade and depth of myometrial invasion in endometrial carcinoma. Am J Obstet Gynecol 2009; 201: 194. E1-10.
21. Geomini P, Bremer G, Kruitwagen R, et al. Diagnostic accuracy of frozen section diagnosis of the adnexal mass: a metaanalysis. Gynecol Oncol 2005; 96: 1-9.
22. Storm A, Sukumvanich P, Monaco S, et al. Mucinous tumors of the ovary: Diagnostic challenges at frozen section and clinical implications. Gynecol Oncol 2012; 125: 75-9.
23. Geominia P, Zuurendonkc L, Bremera G, et al. The impact of size of the adnexal mass on the accuracy of frozen section diagnosis. Gynecol Oncol 2005; 99: 362-6.

24. Houck K, Nikrui N, Duska L, et al. Borderline tumors of the ovary: correlation of frozen and permanent histopathologic diagnosis. Obstet Gynecol 2000; 95: 839-43.
25. Tangjitgamol S, Jesadapatrakul S, Manusirivithaya S, et al. Accuracy of frozen section in diagnosis of ovarian mass. Int J Gynecol Cancer 2004; 14: 212-9.
26. Gultekin E, Gultekin OE, Cingillioglu B, et al. The value of frozen section evaluation in the management of borderline ovarian tumors. J Cancer Res Ther 2011; 7(4): 416-20.
27. Di Saia P, Creasman W, et al. Clinical Gynecologic Oncology, 8th edition. Philadelphia, Elsevier-Saunders, 2012. 330.
28. du Bois A, Riegler NE, de Gregorio K, et al. Borderline tumours of the ovary: A cohort study of the Arbeitsmeinschaft Gynakologische Onkologie (AGO) Study Group. Eur J Cancer 2013; 49: 1905-14.
29. Maheshwari A, Gupta S, Kane S, et al. Accuracy of intraoperative frozens ection in the diagnosis of ovarian neoplasms. Experience at a tertiary oncology center. World J Surg Oncol 2006; 4(12): 1-4.
30. Rose PG, Rubin PB, Nelson BE, et al. Accuracy of frozen-section (intraoperative consultation) diagnosis of ovarian tumors. Am J Obstet Gynecol 1994; 171: 823-6.
31. Pinto PB, Andrade LA, Derchain SF. Accuracy of intraoperative frozen section diagnosis of ovarian tumors. Gynecol Oncol 2001; 81: 230-2.
32. Tempfer CB, Polterauer S, Bentz EK, et al. Accuracy of intraoperative frozen section analysis in borderline tumors of the ovary: a retrospective analysis of 96 cases and review of the literature. Gynecol Oncol 2007; 107: 248-52.
33. Bell D, Pannu H. Radiological Assessment of Gynecologic Malignancies. Obstet Gynecol Clin N Am 2011; 38: 45-68.
34. Medeiros LR, Rosa D, da Rosa M, et al. Accuracy of CA 125 in the diagnosis of ovarian tumors: A quantitative systematic review. Eur J Obstet Gynecol Reprod Biol 2009; 142: 99-105.
35. Kaijser J, Bourne T, Valentin L, et al. Improving strategies for diagnosing ovarian cancer: a summary of the International Ovarian Tumor Analysis (IOTA) studies. Ultrasound Obstet Gynecol 2013; 41: 9-20.
36. Molina R, Escudero J, Augé J, et al. HE4 a novel tumour marker for ovarian cancer: comparison with CA 125 and ROMA algorithm in patients with gynaecological diseases. Tumor Biol 2011; 32: 1087-95.
37. Cross PA, NAik R, Nayar A, et al. Intra-opertaive frozen section analysis for suspected early-stage ovarian cancer: 11 years of Gateshead Cancer Centre Experience. BJOG 2012; 119: 194-201.

Overall Survival and Disease-Free Survival in Endometrial Cancer: A Single Institution Review*

Dinah Marion A. Brazal, MD and Ricalynn B. Rivera, MD

Section of Gynecologic Oncology, Department of Obstetrics and Gynecology, Jose Reyes Memorial Medical Center

Objective: The aim of the study was to assess the disease free survival and overall survival of endometrial cancer patients at a single institution and to determine the factors affecting prognosis.

Methodology: This was a retrospective study at a single institution, with histologically confirmed endometrial cancer patients, who underwent extrafascial or radical hysterectomy with bilateral salpingooophorectomy and with bilateral lymph node dissection. Overall survival and disease free survival were analyzed using Kaplan Meier Analysis. Cox Regression Analysis was used to assess the prognostic significance of different variables.

Results: A total of 121 subjects were included. Eighty five percent of the subjects had no evidence of the disease (NED) while mortality was noted in 9 (7.4%). The disease free 5-year survival was 83.7% and the over-all 5 year survival was 91.3%. For disease free survival, the stage, histologic type, tumor grade, myometrial invasion, involvement of other organs, lymph node involvement and LVSI were significantly associated (p-values <0.05), except for age and tumor diameter. For overall survival, almost all of the variables were significantly associated (p-values <0.05) except for age, myometrial invasion and tumor diameter.

Conclusion: This single institution review of the clinical and surgicopathologic prognostic factors of endometrial cancer confirms that factors associated with poor prognosis, lower disease free survival and decreased overall survival include advanced stages, non-endometrioid type of endometrial cancer, poorly differentiated tumors, >50% myometrial invasion, extrauterine involvement, lymphovascular space invasion, and lymph node metastasis. No association with survival was seen with age and tumor diameter.

Key words: endometrical cancer

* Second place winner, SGOP Luciano SJ Sotto Research Contest, 2015

Endometrial cancer is the 13th most common cancer in both sexes, comprising 2% of the total cancers in the Philippines. It is the 7th leading cancer site in women, with 4% incidence. There were 1,760 new cases diagnosed in 2010. It is the third most common female genital malignancy, next to cervix and ovary. The estimated national standardized mortality rate was 2.2/100,000.[1]

In developed countries, it is the most common gynecologic malignancy, with an estimated 54,870 new cases expected to be diagnosed in 2015 in the United States. There is an increasing trend of new cases of 2.4% per year.[2]

Most cases are diagnosed at an early stage. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program that Stage I was found in 73% of patients, and 10% had Stage II disease.[3] Because of this early presentation of disease, endometrial cancer has been considered a "good cancer" and carries a good prognosis.[4] The standard approach to management of endometrial cancer is extrafascial hysterectomy with bilateral salpingo-oophorectomy, with peritoneal fluid cytology and lymph node dissection. Adjuvant therapy with radiation and chemotherapy may also be given if indicated.

SEER data showed that patients with early stage disease have a 96% 5-year survival.[3] According to American Cancer Society, the 5-year relative survival of all stages of endometrial cancer is 82%.[2] However, despite the relatively good prognosis of endometrial cancer compared to other gynecologic malignancies, there are many factors that may affect survival and prognosis of the patients. These factors include histologic type, FIGO stage, tumor grade, tumor size, depth of myometrial invasion, lymphovascular space invasion, peritoneal cytology, extrauterine metastasis, lymph node involvement, and age at diagnosis.[5]

Objectives

General Objective:

To determine the survival rates of patients with endometrial cancer at a single institution.

Specific Objectives:

1. To determine the demographic characteristics of patients with endometrial cancer
2. To determine the prognostic factors present in endometrial cancer patients
3. To determine the overall survival and disease-free survival of patients with endometrial cancer
4. To determine the association of the different prognostic factors with survival and disease-free survival

Methodology

The study was a retrospective study. Medical records of patients with endometrial cancer who underwent surgery at a single institution from January 2006 to December 2014 were reviewed. Demographic data were collected. Clinicopathologic reports were gathered as to: tumor grade, histologic type, depth of myometrial and lymphovascular space invasion, tumor stage, involvement of other organs and lymph node involvement. Overall survival time and disease-free survival time were evaluated using data from subsequent follow up of patients at the outpatient department of the institution. The patients who were lost to follow up were contacted thru phone calls and home visits.

Starting time or point of entry of the subjects in this study was the date of initial treatment, which was their surgery. The observed follow-up time is the time from the starting point to the time of recurrence or death or the end of the study. The end of the study was specified as July 2015. The status of the subjects were classified as follows: died, alive with ongoing treatment, alive with persistent disease, alive with recurrence, and alive with no evidence of disease.

Disease-free survival was the length of time between the initial treatment and the diagnosis of disease recurrence or death. Overall survival was the length of time measured from the time of initial treatment to the time of death or up to the end of study.

Study Subjects

a. Inclusion Criteria

Patients diagnosed with endometrial cancer who underwent surgery as primary treatment at a single institution from January 2006 to December 2014 were included in the study. The surgery done was either extrafascial or radical hysterectomy with bilateral salpingooophorectomy and with bilateral lymph node dissection.

b. Exclusion Criteria

Exclusion criteria are the following:

1. patients with endometrial cancer who underwent surgery at other institutions;
2. patients whose histology revealed uterine sarcomas;
3. patients with primary malignancies other than endometrial cancer;
4. patients with previous chemotherapy or radiotherapy prior to surgery.

Statistical / Data Analysis Plan

A. Sample Size Computation

The number of samples collected was computed using a 95% level of confidence. With an estimated prevalence of endometrial cancer at 4%, at least 59 subjects is needed at 5% error.

$$n = \frac{(z\alpha)^2 pq}{e^2}$$

Where:
n = is the number of subjects needed
p = estimated prevalence of endometrial cancer = 4%=0.04
q = 1 - p = 1 - 0.04 = 0.96
Zα = 95% confidence level = 1.
e = acceptable sampling error (5%)

B. Data Processing and Analysis

Data were encoded and tallied in SPSS version 10 for windows. Descriptive statistics were generated for all variables. For nominal data frequencies and percentages were computed. For numerical data, mean ± SD were generated. Analysis of the different variables was done using the following test statistics:

T-test - used to compare two groups with numerical data.

Chi-square test - used to compare/associate nominal (categorical) data

Fisher Exact test - a modification of chi-square used for 2x2 table when there are expected frequencies <5.

Kaplan Meier Analysis - used for survival analysis

Cox Regression Analysis - used for predicting tumor recurrence and overall mortality

Results

A total of 121 subjects were included in the study. Table 1 shows the distribution of subjects with endometrial tumor according to the different characteristics.

Table 2 shows the distribution of subjects with endometrial tumor according to outcome. Eighty five percent of the subjects had no evidence of the disease (NED) while mortality was noted in 9 (7.4%) subjects and recurrence in 5 (4.1%) subjects.

The disease-free survival was 83.7% and the overall survival was 91.3% (Figures 1 & 2). The estimated median follow-up was 38 months for disease-free survival and 37 months for overall survival.

Table 3 shows the disease-free and overall survival for the different variables analyzed. For disease-free survival, almost all of the variables listed were significantly associated as proven by all p-values <0.05 except for age and tumor size as shown by the p-value of 0.24 and 0.60 respectively. For overall survival, almost all of the variables listed were significantly

Table 1. Characteristics of endometrial tumor of the subjects.

	Frequency (n=121)	Percentage
Histological Type		
Endometrioid	116	95.9
Non-endometrioid	5	4.1
Tumor Grade		
1	69	57.0
2	38	31.4
3	14	11.6
FIGO Stage		
IA	58	47.9
IB	25	20.7
II	14	11.6
IIIA	3	2.5
IIIB	4	3.3
IIIC	12	9.9
IVA	2	1.7
IVB	3	2.5
Myometrial Invasion		
>50%	49	40.5
<50%	72	59.5
Cervical Involvement	25	20.7
Adnexae/serosa involvement	11	9.1
Vagina/parametrial involvement	9	7.4
Pelvic node involvement	14	11.6
LVSI	32	26.4

Table 2. Distribution of subjects with endometrial tumor according to outcome.

	Frequency (n=121)	Percentage
Outcome		
Died	9	7.4
Ongoing treatment	3	2.5
Persistent	1	0.8
Recurrence	5	4.1
NED	103	85.1

associated as proven by all p-values <0.05 except for age, myometrial invasion and tumor size as shown by the p-value of 0.70, 0.48 and 1.00 respectively.

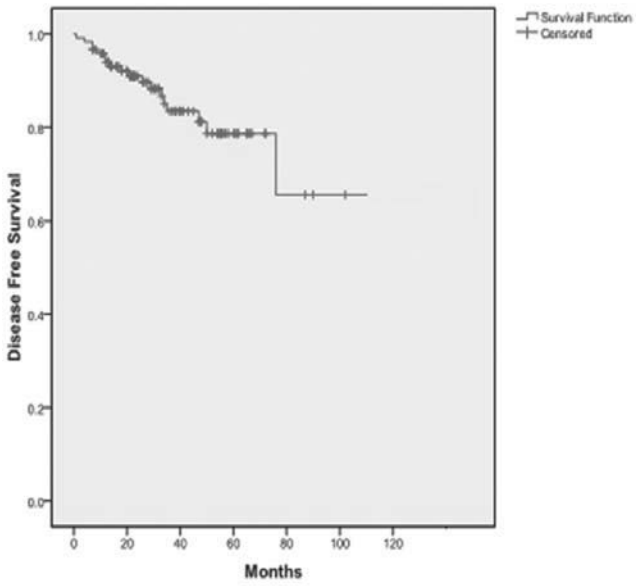

Figure 1. Disease-Free survival in the study population.

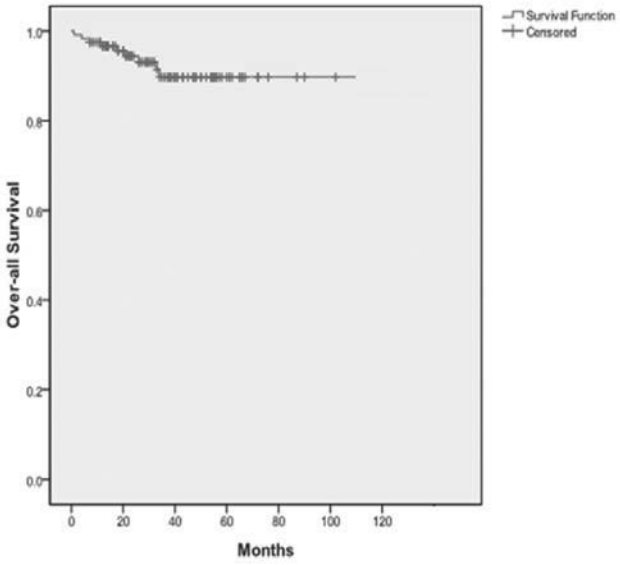

Figure 2. Overall Survival in the study population.

Table 4 shows the differences in disease-free and overall survival according to FIGO stage. There were significant associations noted both for disease-free and overall survival as shown by the p-values of <0.001 and 0.004 respectively. Disease-free and overall survival was significantly higher among those with lower FIGO stage (stage I) than those with stage II to IV.

Table 3. Disease-Free and overall survival for the different variables analyzed.

	n	Disease Free Survival		Over-all Survival	
		Percentage	p-value*	Percentage	p-value*
Age (in years)					
<50	34	91.2	Ref	91.2	Ref
≥50	87	82.8	0.24	93.1	0.70
FIGO Stage					
Local (Stage I)	83	94.0	Ref	97.6	Ref
Advance (Stage I-IV)	38	65.8	<0.0001	81.6	<0.01
Histological Type					
Endometrioid	116	87.9	Ref	94.8	Ref
Non-endometrioid	5	20.0	0.001	40.0	<0.01
Tumor Grade					
1	69	92.8	Ref	100	Ref
2	38	76.3	0.01	84.2	<0.01
3	14	71.4	0.03	78.6	<0.01
Myometrial Invasion					
<50%	72	93.1	Ref	94.4	Ref
>50%	49	73.5	<0.01	89.8	0.48
Cervical Involvement					
No	96	92.7	Ref	96.9	Ref
Yes	25	56.0	<0.0001	76.0	<0.01
Adnexae/serosa involvement					
No	110	90.9	Ref	95.5	Ref
Yes	11	27.3	<0.0001	63.6	<0.01
Vagina/parametrial involvement					
No	112	88.4	Ref	94.6	Ref
Yes	9	44.4	<0.01	66.7	0.01
Pelvic node involvement					
No	107	91.6	Ref	95.3	Ref
Yes	14	35.7	<0.0001	71.4	0.01
LVSI					
(-)	86	93.0	Ref	97.7	Ref
(+)	32	68.8	0.001	81.3	<0.01
Not Determined	3	33.3	0.02	66.7	0.10
Tumor >2cm					
No	7	100	Ref	100	Ref
Yes	114	84.2	0.60	92.1	1.00

* p-values >0.05- Not significant; p-values ≤0.05-Significant

Log Rank Statistics

Table 4. Differences in disease-free survival and overall survival according to International Federation of Gynecology and Obstetrics (FIGO) stage.

FIGO stage	n (Percentage)	Total	p-value*
Disease-free survival			
Local (stage I)	78 (94.0)	83	<0.001
Advanced (stage II-IV)	25 (65.8)	38	
Overall survival			
Local (stage I)	81 (97.6)	83	0.004
Advanced (stage II-IV)	31 (81.6)	38	

* p-values >0.05- Not significant; p-values ≤0.05-Significant

Table 5 shows the differences in disease-free and overall survival according to tumor grade. There was a significant associations noted both for disease-free and overall survival as shown by all p values <0.05. Disease-free and overall survival decreases with increasing tumor grade.

Table 5. Differences in disease-free survival and overall survival according to tumor grade.

Tumor Grade	n (Percentage)	Total	p-value*
Disease-free survival			
Grade 1	64 (92.8)	69	Ref
Grade 2	29 (76.3)	38	0.01
Grade 3	10 (71.4)	14	0.03
Overall survival			
Grade 1	69 (100)	69	Ref
Grade 2	32 (84.2)	38	0.001
Grade 3	11 (78.6)	14	0.003

* p-values >0.05- Not significant; p-values ≤0.05-Significant

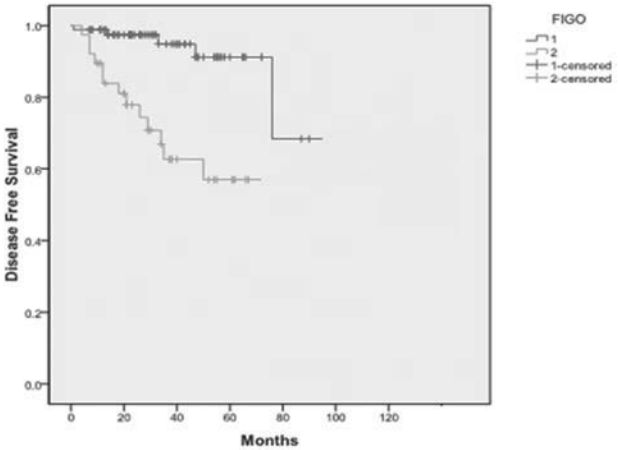

Figure 3. Differences in disease-free survival according to International Federation of Gynecology and Obstetrics (FIGO) stage.

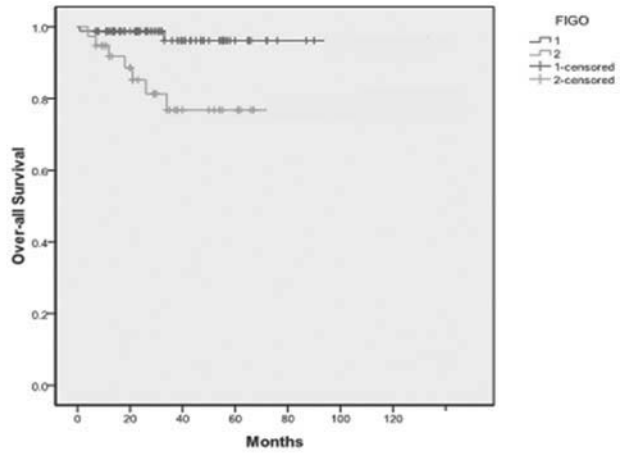

Figure 4. Differences in overall according to International Federation of Gynecology and Obstetrics (FIGO) stage.

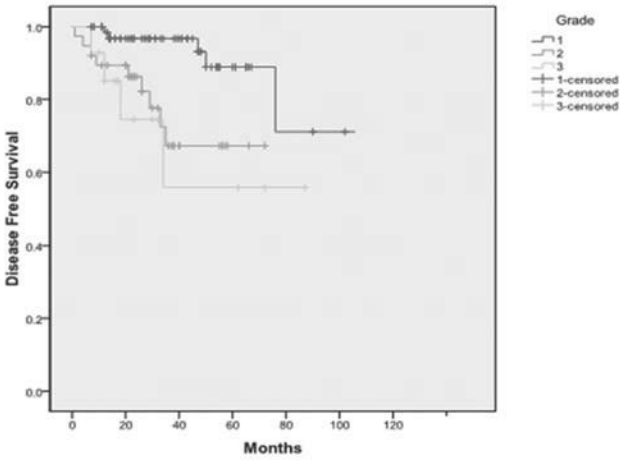

Figure 5. Differences in disease-free survival according to tumor grade.

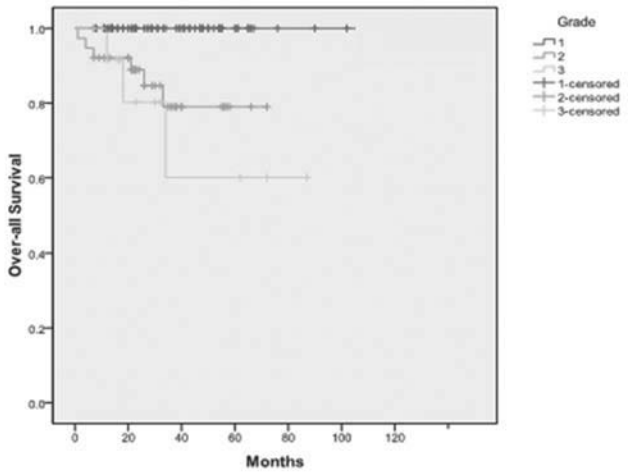

Figure 6. Differences in overall survival according to tumor grade.

Discussion

Endometrial cancer is the 7th most common cancer in women in the Philippines, comprising 4% of all malignancies. Being the 3rd most common female genital tract malignancy, there is an increasing trend of endometrial cancer cases.[1]

Most cases are diagnosed at an early stage. Stage I was found in 73% of endometrial cancer cases according to SEER program.[3] This datum is comparable to our study, wherein 68.6% of the patients were diagnosed with stage I disease. Most common histology noted in our study was endometrioid type, comprising 95.9% of all the endometrial cancers. This result on histopathologic type was higher than those reported by Prat, with endometrioid adenocarcinomas comprising 80% only of all endometrial tumors.[6]

In our study, no evidence of disease was noted in 85% of the patients, while mortality was noted in 7.4%. As shown in Figures 1 and 2, the disease-free survival is 83.7% and overall 5-year survival was 91.3%. This data is similar with other studies. Garcia et al reported 82.3% disease-free survival and 81% overall survival.[5] Another study by Hirai showed that recurrence-free 5-year survival was 81%.7 Li, et al. also reported an 83.3% 5-year recurrence-free survival rate, and 84.3% 5-year overall survival.[8]

There are factors which may affect prognosis and survival of patients with endometrial cancer. Clinical factors include age. Pathologic factors include FIGO stage, histologic type, histologic grade, extrauterine spread and lymphovascular space invasion.

Age is considered as unfavorable factor for survival and recurrence. Overall, older women have a worse prognosis and a lower 5-year survival than younger women. It is important to evaluate whether this difference is purely based on age or other poor prognostic features and co-morbidities associated with age. A study reported that women older than 40 years were less likely to have stage I disease and grade I tumors but more likely to have uterine papillary serous histology than women aged 40 years and younger. Older women faced an intrinsic poorer survival whether or not they underwent lymphadenectomy, and, unexpectedly, irrespective of the presence of nodal metastasis.[9] In our study, the overall survival of patients with <50 years old was higher with 91%, compared with 82% for ≥ 50 years old. However, it was not statistically significant. This is consistent with a study by Binesh et al, where they were able to show a longer survival with younger patients,but there was no significant relationship noted with age at diagnosis and overall survival.[10]

Stage is the most important prognostic factor in endometrial cancer. In our study, it is significantly associated with recurrence and death, as shown by Table 4. Stage I endometrial cancer has a disease-free survival and overall survival of 94% and 97.6%, respectively. As compared to advanced stages, comprising stage II-IV wherein there is extrauterine spread, the disease-free survival is only 65.8% and the overall survival is 81.6%. These results are consistent with other studies. Garcia et al reported disease-free survival of 91% for stage I and 52% for stages II, III or IV. It was also reported that the probability of tumor recurrence was 7.5 times higher in late stages than with stage I disease.[5] In another study by Kosary, the overall survival rate at 5 years was 90.2% for stage I and for advanced stages, it was only 48.8%.[12] In our study, table 3 shows significant associations with cervical involvement, adnexae/serosal involvement, vagina/parametrial involvement with disease-free and overall survival rates. This shows that extrauterine involvement, therefore advanced stages, has a significantly lower survival rates. Furthermore, it has been shown in Table 6 that the probability of death from advanced stages of endometrial cancer is 7.6 times higher than that of stage I.

Histologic classification of endometrial cancers is important in predicting biologic behavior of the tumor and probability of survival.[4] Endometrioid adenocarcinoma is the most common histologic type, comprising approximately 80% of all endometrial cancers.[6] This is associated with better prognosis as compared to non-endometrioid types. The non-endometrioid types include serous, clear cell and undifferentiated tumors, carrying a poorer prognosis. In our study, patients with endometrioid tumors have 87.9% disease-free survival and 94.8% overall survival. In contrast with those non-endometrioid tumors, with disease-free survival and overall survival of 20% and 40%, respectively. This supports other studies that the

Table 6. Results of univariate Cox proportional hazards analysis: risk of tumor recurrence and overall mortality associated with the variables analyzed.

	Tumor Recurrence		Over-all Mortality	
	Hazard Ratio (95% CI)	p-value*	Hazard Ratio (95% CI)	p-value*
Age (in years)	1.05 (0.94 - 1.17)	0.38	0.98 (0.91 - 1.07)	0.78
Histological Type				
Endometrioid	1.00	Ref	1.00	Ref
Non endometrioid	0.32 (0.03 - 8.22)	0.33	12.12 (2.47 - 59.42)	0.002
FIGO Stage				
Local (Stage I)	1.00	Ref	1.00	Ref
Advanced (Stage II-IV)	1.48 (0.24 - 8.88)	0.67	7.62 (1.58 - 36.72)	0.01
Tumor Grade				
1	1.00	Ref	1.00	Ref
2	1.22 (0.15 - 9.59)	1.00	14.85 (1.71 - 334)	<0.01
3	---	---	23.33 (2.11 - 600)	<0.01
Myometrial Invasion				
<50%	1.00	Ref	1.00	Ref
>50%	8.08 (1.05 - 76.91)	0.05	1.79 (0.48 - 6.67)	0.38
Cervical Involvement				
No	1.00	Ref	1.00	Ref
Yes	6.41 (1.08 - 59.15)	0.05	7.77 (1.94 - 31.12)	0.004
Adnexae/serosa involvement				
No	1.00	Ref	1.00	Ref
Yes	7.60 (0.75 - 76.70)	0.06	11.48 (3.01 - 43.84)	<0.0001
Vagina/parametrial involvement				
No	1.00	Ref	1.00	Ref
Yes	1.65 (0.16 - 16.68)	0.67	6.12 (1.53 - 24.52)	0.01
Pelvic node involvement				
No	1.00	Ref	1.00	Ref
Yes	18.15 (2.39 - 137.64)	0.005	8.30 (2.19 - 31.42)	0.002
LVSI				
(-)	1.00	Ref	1.00	Ref
(+)	2.80 (0.27 - 29.49)	0.29	9.78 (1.96 - 48.67)	0.005
Tumor >2cm				
No	1.00	Ref	1.00	Ref
Yes	0.44 (0.04 - 10.79)	0.41	0.75 (0.08 - 17.7)	0.58

* p-values >0.05- Not significant; p-values ≤0.05-Significant

5-year survival for serous and clear cell histology was significantly lower than that of endometrioid histology.[4,6,13] Most of the serous, clear cell and undifferentiated tumors were associated with deep myometrial invasion, extrauterine spread, and lymph node metastases. Furthermore, in our study, it was shown that for these poor histologic subtypes, the probability of mortality is 12-fold higher than those of the endometrioid histology, although no significant difference was noted between the 2 histologic types as to risk of tumor recurrence.

Tumor grade or degree of histologic differentiation of endometrial cancer is another prognostic factor for recurrence and survival. As the grade becomes less differentiated, there is a tendency for more aggressive tumors, with deeper myometrial invasion, lymph node metastasis, thereby giving a poorer prognosis.[4] In our study, the higher the grade, the lower the survival rate. As shown in Table 5, disease-free survival and overall all survival were 92.8% and 100% for Grade 1 tumors, but only 71.4% and 78.6% for Grade 3 tumors. These results are consistent with the study of Garcia, with decreasing disease free survival of 96.3% in Grade 1 endometrial carcinoma, to 80.8% in Grade 2 and 66.7% in Grade 3. There was also a decreasing trend in overall survival in the

same study.[5] However, it is difficult to assess the impact of tumor grade as an independent factor because of the relationship with other factors. Poorly differentiated tumors have higher risk of myometrial invasion, and lymph node metastases.[14] In a study by Bagadiong, it was reported that Grade 3 tumors have higher probability to have lymph node metastasis.[15]

The importance of depth of myometrial invasion has been consistently recognized as an important prognostic factor. It is an indication of tumor virulence, with higher probability of extrauterine tumor spread and recurrence, and decreased survival. In a study by Morrow, et al. 5-year relative survival was 94% for patients with tumors confined to the endometrium, 91% for inner 1/3 involvement, and 84% for middle 1/3 invasion, and only 59% if outer 1/3 of the myometrium is involved.[16] In our study, the myometrium was divided into inner ½ and outer ½. Those with less than 50% myometrial invasion have a significantly higher disease free survival with 93.1%, compared with more than 50% involvement of only 73.5%. However, there was no significant difference noted in overall survival.

Lymph node involvement in endometrial cancer is associated with multiple prognostic factors. The presence of metastases in lymph nodes is usually associated with poorly differentiated tumors, aggressive histologic types, deeper myometrial invasion, adnexal metastasis, and lymphovascular space invasion.[4] In our study, pelvic node involvement shows significantly lower disease-free survival and overall survival, with 35.7% and 71.4% only, compared with no lymph node metastasis, with 91.6 and 95.3% respectively. Furthermore, in univariate analysis, there is higher risk for tumor recurrence and overall mortality in patients with lymph node metastasis, with hazards ratio of 18 and 8, respectively.

Lymphovascular space invasion has been consistently reported as a strong predictor of recurrence and death, independent of myometrial invasion or tumor grade.[4] The presence of malignant cells in capillary-like spaces has 6-fold increased risk of lymph nodes metastasis.[13] In our study, it was shown that among those with positive LVSI, there is 68.8% of disease-free survival as compared to 93% to those without LVSI. Overall survival was also significantly lower with 81.3% to those with positive LVSI, than those negative LVSI with 97.7%. The risk of recurrence of patients with positive LVSI was 2.8 higher than those without LVSI. This result is consistent with the study by Guntupalli et al, wherein it was noted that the relative risk of recurrence for patients with LVSI compared to without was 2.4.[17] In another recent study evaluating early stage tumors, it was shown that LVSI was the only consistent prognostic factor affecting recurrence and survival.[18]

In a study by Ivanov, tumor size was noted to be an independent prognostic factor. According to this study, in tumor diameter of less than 2 cm, there is 3% risk of lymph node metastasis, compared with tumor size of more than 2 cm with 18% risk of lymph node involvement. In the same study, it was noted that if the tumor volume occupies the entire endometrial cavity and with deep myometrial invasion, risk for lymph node metastasis increased to 40%.[19] Our study, however, was not able to show significance in survival rates of patients with endometrial cancers as to tumor diameter. This is consistent with the study by Bagadiong, et al. in which there was no association with tumor size and lymph node involvement.

Several studies have demonstrated the prognostic importance of different factors, including age, stage of disease, tumor grade, histologic type, depth of myometrial invasion, lymphovascular space invasion and lymph node involvement.[5-8,10,12,19,20] The result of our study is consistent with other previous studies. Factors associated with poor prognosis, lower disease-free survival and decreased overall survival include advanced stages, non-endometrioid types of endometrial cancer, poorly differentiated tumors, >50% myometrial invasion, extrauterine involvement, lymphovascular space invasion, and lymph node metastasis. No association with survival was seen with age and tumor diameter.

Limitations of the study include small sample size, lost charts, and need for longer period for follow up of patients. The adjuvant treatments done for the patients were also not considered in this survival analysis.

Recommendations for further studies include larger sample size and longer follow up of patients included in the study. Associations of adjuvant treatments, such

as radiation therapy and chemotherapy, with survival can also be evaluated.

Conclusion

This single institution review of the clinical and surgicopathologic prognostic factors of endometrial cancer confirms that factors associated with poor prognosis, lower disease-free survival and decreased overall survival include advanced stages, non-endometrioid types of endometrial cancer, poorly differentiated tumors, >50% myometrial invasion, extrauterine involvement, lymphovascular space invasion, and lymph node metastasis. No association with survival was seen with age and tumor diameter.

References

1. Laudico A, et al. 2010 Philippine Cancer Facts and Estimates. Manila: Philippine Cancer Society: 2010
2. American Cancer Society. Cancer Facts and Figures 2015. Atlanta: American Cancer Society; 2015.
3. Hollander N, No one AM, Neiman N, et al. Surveillance, epidemiology, and end results (SEER) cancer statistics review, 1975-2008. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2008.
4. Barakat R, et al. Principles and Practice of Gynecologic Oncology, 6th edition. Wolters Kluwer: 2013.
5. Tejerizo-Garcia, et al. Overall survival and disease-free survival in endometrial cancer: Prognostic factors in 276 patients. Onco Targets and Therapy 2013; 6: 1305-13.
6. Prat J. Prognostic parameters of endometrial carcinoma. Hum Pathol 2004; 35 (6): 649-62.
7. Hirai M, Hirono M, Oosaki T, Hayashi Y, Yoshihara T, Matsuzaki O. Prognostic factors relating to survival in uterine endometrioid carcinoma. Int J Gynaecol Obstet 1999; 66(2): 155-62.
8. Li B, Wu LY, Li SM, Zhang WH, Zhang R, Ma SK. Multivariate analysis of prognostic factors in endometrial carcinoma Ai Zheng. 2004; 23(9): 1085-8.
9. Benedetti Panici P, Basile S, Salerno MG, et al. Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma. Am J Obstet Gynecol 2014; 210: 363.e1-10
10. Binesh F, et al. Endometrial adenocarcinoma: clinicopatologic and survival characteristics in Yazd, Iran. Asian Pacific J Cancer Prev 2014: 15: 2797-801.
11. von Gruenigen VE, Tian C, Frasure H, Waggoner S, Keys H, Barakat RR.Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma : a Gynecologic Oncology Group study. Cancer 2006; 107(12): 2786-91.
12. Kosary CL. FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973-87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. Semin Surg Oncol 1994; 10(1): 31-46.
13. Binder PS1, Mutch DG. Update on prognostic markers for endometrial cancer. Womens Health (Lond Engl) 2014; 10(3):277-88. http://doi: 10.2217/whe.14.13
14. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz AP, Ngan HY, Pecorelli S. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 2006; 95 Suppl 1:S105-43.
15. Bagadiong J, Tagayuna I. Tumor size, depth of myometrial invasion, and preoperative histologic grade as prognostic factors of lymph node involvement in endometrial cancer: analysis of data. Phil J Gynecol Oncol 2015; 12 (1): 1-7.
16. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecology Oncology Group Study. Gynecol Oncol 1991; 40: 55-65.
17. Guntupalli SR, Zighelboim I, Kizer NT, et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. Gynecol Oncol 2012; 124(1): 31-5.
18. Weinberg LE, Kunos CA, Zanotti KM. Lymphovascular Space Invasion (LVSI) is an isolated poor prognostic factor for recurrence and survival among women with intermediate-to high-risk early-stage endometrioid endometrial cancer. Int J Gynecol Cancer 2013; 23(8): 1438-45.
19. Ivanov I. Survival, prognostic factors and modern tendencies in adjuvant treatment of diagnosed endometrial cancer patients with or without lymph node dissection. Akush Ginekol (Sofiia). 2009; 48 Suppl 1:3-11.
20. Uharcek P. Prognostic factors in endometrial carcinoma. J Obstet Gynaecol Res 2008; 34 (5): 776-83.

Survival Outcome of Patients with Early Stage and Locally Advanced Cervical Cancer Who Underwent Radical Hysterectomy With or Without Lymph Node Dissection in a Tertiary Training Cancer Center A 10-year Retrospective Cohort Study*

Jimmy A. Billod, MD, FPOGS, DSGOP, FPSCPC and Maria Lilibeth L. Sia Su, MD, FPOGS, FSGOP, FPSCPC

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

Objectives: This study aims to determine the outcome of patients with early stage and locally advanced cervical cancer managed with radical hysterectomy with or without lymphadenectomy in a tertiary training cancer center. It aims to review the prognostic factors thats affects survival and recurrence.

Methodology: This was a retrospective cohort study of patients with early stage and locally advanced cervical who underwent radical hysterectomy with or without lymph node dissection, either as a primary treatment or after a neoadjuvant therapy from 2004-2013. Data collected were encoded using MSEXCEL 2013. For all the tests' statistics, any associated p-values lesser than 0.05 alpha were considered statistically significant. Also, the sample size of the study was tested at 80% power.

Results: A total of 171 patients were included in the recurrence and survival analysis The 1-, 3- and 5- year survival rates of early stage and locally advanced cervical cancer managed with radical hysterectomy with or without lymphadenectomy were 97.3%, 99.1%, and 98.2 %, respectively. The median survival of these group of patients was 3 years. Patients aged 35-64 years old have slightly higher median survival of 4 years as compared with those <35 years old and >65 years old. Patients with SCCA have slightly higher median survival of 4 years as compared to the ADC and adenosquamous. However, the difference is not statistically significant. Moreover, the difference in the median survival is not statisticaly significant in relation to stage, risk stratification, institution of neoadjuvant therapy and adjuvant therapy post surgery.

Conclusion: Patients with early stage and locally advanced cervical cancer who underwent RHBSO with or without lymphadenectomy have excellent prognosis and survival. Such procedures are safe under skilled gynecologic oncologists. Neoadjuvant and adjuvant treatment may improve survival of these group of patients.

Key words. Cervical cancer, radical hysterectomy, lymphadenectomy, adjuvant therapy, neoadjuvant therapy

* Third place winner, SGOP First Luciano SJ Sotto Research Contest, 2015

Cervical cancer is the second most common cancer among women, the third most common cause of cancer-related death, and the most common cause of mortality from gynecologic malignancy worldwide.[1] In the Philippines, it is the second most common site of cancer and is the second leading cause of cancer-related deaths among women. About 6,000 new cases and 4,349 deaths are expected to occur each year due to cervical cancer.[2] According to the Philippine Cancer Facts and Estimates, the incidence of cervical cancer remained stable form 1980 to 2005. The overall 5-year survival rate worldwide was 44% and mortality rate was 1 per 10,000 women.[3]

Based on the latest combined local data of 2 Cancer Training Centers in the Philippines, there were 3304 new cases of cervical cancer for the last 5 years and almost 50 % were diagnosed with Stage IIIB and only 10 % with early operable stages. Consistent with the universal statistics, squamous cell carcinoma (70-80%) and adenocarcinoma (15-20%) were the most common histologic types. Most studies suggest no difference in survival between adenocarcinoma, squamous carcinomas and adenosquamous based on stage.[4, 5]

The guidelines of the Society of Gynecologic Society of the Philippines recommend radical hysterectomy with lymph node dissection for stage IA2, IB1, IIA1 cervical cancer who are good surgical risk patients and concurrent chemotherapy and pelvic external beam radiotherapy EBRT plus brachytherapy for patients with poor surgical risk factors.[6] For early stage with tumor size greater than 4 cm, radical hysterectomy can still be performed in two occasions.[1] Radical hysterectomy with lymph node dissection and paraaortic sampling after a concurrent chemotherapy and pelvic EBRT and neoadjuvant chemotherapy.[2] Primary radical hysterectomy with lymph node dissection which usually needs to be followed with adjuvant chemoradiation, the type of radiotherapy will be dependent on the surgico-pathologic factors.[6,7]

This present study aims to determine the outcome of patients with early stage and locally advanced cervical cancer managed with radical hysterectomy with or without lymphadenectomy in a training institution. This would provide important information if survival rates of our patients improved over time with updates in the management guidelines. Also, it aims to review on the prognostic factors that affect recurrence and survival. All these will be significant in the formulation and updating of new guidelines and recommendations.

Objectives

General Objective:

To determine the survival outcome of patients with early stage and locally advanced cervical cancer who underwent radical hysterectomy with or without lymph node dissection in a tertiary training cancer center.

Specific Objectives:

- To determine the survival rate of patients with cervical cancer based on the following:
  a. stage
  b. risk stratification (GOG 92)
  c. neoadjuvant treatment prior to radical surgery
  d. adjuvant treatment post operation

- To determine morbidities related to the treatment
  a. radical hysterectomy with or without lymph node dissection
  b. with neoadjuvant treatment
  c. with adjuvant treatment

- To determine the relationship of the following clinical and histopathologic factors with recurrence.
  a. stage
  b. tumor size
  c. positive LVSI
  d. more than 1/3 stromal invasion
  e. positive margins
  f. histology
  g. tumor grade
  h. positive extracervical and extrauterine spread
  i. nodal metastasis

- To determine the rate , onset and site of recurrence based on the following;
  a. stage
  b. performance of lymph node dissection

c. neoadjuvant treatment prior to radical surgery
d. adjuvant treatment post operation

5. To identify the treatment modalities given to patients with persistence or recurrence.

Methodology

Study Design and Population

This was a retrospective cohort study involving all cervical cancer patients who underwent radical hysterectomy with or without lymph node dissection from 2004-2013 at a tertiary training cancer hospital. This study was approved by the Institution's Ethical Review Board.

The computation of sample size focused on survival rate which is the main emphasis of analysis. Five- year survival rates of patients with early cervical cancers treated with radical hysterectomy with lymph node dissection showed a rate from 50%- 87%. Hoskins et al showed a projected survival rate in excess of 70% in patients with microscopic disease in the pelvic lymph nodes treated by postoperative radiation. This study would need a minimum of 145 cases wherein the analysis has 95% power at 95% - 99% level of confidence. Number of study subjects may be limited by the availability of medical charts.

All patients with early stage and locally advanced cervical cancer who underwent radical hysterectomy with or without lymph node dissection, either as a primary treatment or after a neoadjuvant therapy. Patients who were referred to the section not operated in the same institution; those who had operations less than a radical hysterectomy and patients with incomplete records were excluded from the study

Study Description and Outcome Measures

A review of all patients who underwent radical hysterectomy with or without lymph node dissection either as primary treatment or after a neaodjuvant therapy for an early stage cervical cancer at a tertiary training hospital from 2004 to December 2013 was performed. Patients' medical records were retrieved and the following data were collected and recorded using the data extraction form.

1. demographic data (age, marital status, GP score)
2. year of diagnosis and surgery
3. stage of disease
4. cervix size (preoperative size)
5. tumor size (based on the histopathologic report)
6. histologic type of tumor
7. grade of tumor
8. depth of cervical invasion (DCI)
9. status of lymphovascular invasion (LVSI)
10. parametrial extension
11. positivity of vaginal margins
12. presence of extracervical/ uterine/ adnexal metastases
13. use and type of neoadjuvant therapy prior to surgery
14. use and type of adjuvant therapy post surgery
15. reported morbidities from the surgery and adjuvant therapy

Follow up records were reviewed. The following information were extracted and recorded.

1. onset and site of recurrence
2. treatment given for the recurrence and or persistence
3. present status of disease during the last follow up

The collected data were then be encoded in MS EXCEL format.

Date Processing and Statistical Analysis

Data collected were encoded using MSEXCEL 2013. In describing all categorical variables, frequency and percentage were used while all continuous data were expressed in median and ranges. In testing associations among categorical variables, Chi square test with adjustment of Fisher's Exact test among those with 2x2 matrices' association. Moreover, in performing survival analysis, Kaplan-Meier test was used wherein the differences of survival curves (various stratification) were tested using Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon), and Warone-Ware tests' statistics to reflect on the

consistency of inferences. For all the tests' statistics, any associated p-values lesser than 0.05alpha were considered statistically significant. Also, the sample size of the study was tested at 90% power. To ensure accuracy of computation, coding, data cleaning, and processing were aided by IBMSPSS ver 21, NCSSPASS 2000, and MyStat statistical softwares.

Results

Demographic and Clinical Characteristics

Between 2004 to 2013, a total of 224 patients underwent radical hysterectomy with or without lymphadenectomy for early stage and locally advanced cervical cancer. This showed an average of 22 patients per year. The clinical characteristics of the patients are displayed in Table 1. The age distribution of early stage and locally advanced cervical cancer is almost equal between reproductive and non-reproductive women with a median age of 46.5 years (average age of 48 years). Eleven percent of the reproductive women were less than 35 years old. The average gravidity and parity of the cohort was 4. Sixty five percent were gravida 4 or more and 55% were parity 4 or more. Most of the patients who underwent radical hysterectomy were at stage IB1 and IIA1 at 76% and 15% respectively.

Table 1. Clinical characteristics of patients who underwent radical hysterectomy.

Variables	n = 224 number (%)
Age at Diagnosis	
</= 35	24 (10.7)
36-64	190 (84.8)
=/> 65	10 (4.5)
Gravidity	
</= G3	79 (35.3)
G4 -G6	111 (49.6)
=/> G7	34 (15.1)
Parity	
</= P3	104 (46.4)
P4 - 6	98 (43.8)
=/> P7	22 (9.8)
Marital status	
Married	160 (71.4)
Single	21 (9.4)
Unknown	43 (19.2)
Clinical Stage	
IA1	5 (2.2)
IB1	171 (76.3)
IB2	8 (3.6)
IIA1	34 (15.2)
IIA2	1 (0.4)
IIB	5 (2.2)

Histopathologic Characteristics

The pathologic characteristics of the patients are presented in Table 2. Majority of patients had a final histopathologic diagnosis of squamous cell carcinoma and adenocarcinoma at 68% and 29%, respectively. About 3% comprised the poor histologic types (neuroendocrine tumor and malignant melanoma). With regards to tumor size, 89% of patients had a tumor size of less than or equal to 4 cm, and 28% of these had tumor size of less than 2 cm. More than 1/3 cervical stromal invasion and positive lymphovascular invasion were seen in 70% and 26% of patients, respectively. Based on the GOG 92 risk stratification, 76% were intermediate to high risk requiring adjuvant treatment post surgery.

Treatment and Morbidity

Of the 224 patients, 95 % had pelvic lymphadenectomy with or without paraaortic lymph node sampling. The remaining had paraaortic palpation and or assessment. 18 patients (8%) had resultant morbidities from the surgery. The morbidities are displayed in Table 3. The intraoperative complications were primarily related to the pelvic anatomy.

A total of 12 patients received neoadjuvant treatment, 8 underwent concurrent chemoradiation and 4 were given systemic chemotherapy prior to the radical hysterectomy. There were no related morbidities associated with neoadjuvant treatment.

Almost half of the patients received adjuvant therapy in the form of concurrent chemoradiation with or without brachytherapy after the surgery. There were no reported morbidities. About 55% had their adjuvant therapy at the Philippine General Hospital.

Table 2. Histopathologic characteristics and Risk stratification of patients who underwent radical hysterectomy

Variables	n= 224 number (%)
Histopathologic Diagnosis	
Squamous cell carcinoma	152 (67.9)
Adenocarcinoma	65 (29.1)
Adenosquamous	3 (1.3)
Neuroendocrine carcinoma	3 (1.3)
Malignant melanona	1 (0.4)
Tumor size	
</= 2 cm	62 (27.7)
> 2 - 4 cm	137 (61.2)
> 4 - 6 cm	24 (10.7)
> 6 cm	1 (0.4)
Stromal invasion	
< 1/3	68 (30.4)
> 1/3 -<2/3	57 (25.4)
> 2/3	99 (44.2)
LVSI	
negative	166 (74.1)
positive	58 (25.9)
Metastases	
Vaginal margin	3 (1.3)
Parametria	3 (1.3)
Uterine	15 (6.7)
Fallopian tube	1 (0.4)
Ovary	0 (0)
Nodes	23 (10.3)
Risk Stratification (GOG 92)	
Low risk	44 (19.6)
Intermediate risk	127 (56.7)
High risk	53 (23.7)

Table 3. Morbidities related to radical hysterectomy with or without lymphadenectomy.

Morbidities	Type	n= 18 (8%) number
Bladder injury	Intraoperative	2
Ureteral injury	complications	3
Bowel injury		1
Inferior vena cava injury		1
Total		7 (39%)
Surgical site infection	Post operative	5
Lymphedema	complications	1
Voiding dysfunction		3
Incisional hernia		2
Total		11 (61%)

Tumor Recurrence

Rate and Onset

There were 51 patients (23%) who did not follow up after the surgery and postsurgery treatment. These were excluded from the recurrence and survival analysis. Of the 173 patients who had adequate follow up, 17 patients had recurrence. In general, the recurrence rate of patients with early stage and locally advanced carcinoma who underwent radical hysterectomy with or without lymphadenectomy regardless of histology is 9.8 %, with a average onset of 20 months (median: 12 months). Table 4 shows the rate, onset and sites of recurrences for each histologic diagnosis.

Table 4. Association of histologic diagnosis and recurrence.

Variables	Squamous cell Carcinoma	Adenocarcinoma	Neuroendocrine	Adenosquamous
Recurrences $x^2 = 11.8$, df = 3, p = 0.008	11/ 110 (10%)	4/59 (7%)	2/2 (100%)	0/2
Median age of patients with recurrence	44.5 years	40 years	35.5 years	-
Onset of recurrence (median)	15.5 months	12 months	12 months	-
Site of recurrence	Lungs= 4 Vagina= 3 Pelvic LN= 2 Bone= 2	Pelvic LN= 4	Pelvic LN= 2	-
Treatment	Cisplatin-Topotecan Cisplatin-Paclitaxel Carboplatin-Paclitaxel	Oxaliplatin-Docetaxel		

Recurrence rates for SCCA, ADC and neuroendocrine tumors were 10%, 7% and 100%, respectively. Analysis showed that histopathologic diagnosis is statistically associated with recurrence ($p < 0.05$) with neuroendocrine carcinoma showing the most significant trend to recurrence (Table 4). Hence, patients with neuroendocrine tumor histology were excluded from further recurrence and survival analysis.

Clinical and Histopathologic Variables in Relation to Recurrence

A total of 171 patients with histology of SCCA, ADC and adenosquamous were included in the subsequent analysis. Analysis revealed that tumor size and differentiation were statistically associated with recurrence. Patients with a tumor size > 4 cm showed significant tendency to recurrence ($p < 0.05$). Tumor grade, particularly moderate and poorly differentiated adenocarcinoma is associated with recurrence ($p < 0.01$). Although not statistically significant, clinical stage IIA1 and IIB, > 1/3 cervical stromal invasion, positive LVSI and positive nodes showed an affirmative trend towards recurrence. These associations are presented in Table 5.

More recurrences were observed in the group of patients who required adjuvant therapy than those who did not . However, among these patients, the difference

Table 5. Association between clinical and pathological variables and recurrence.

Factors	Recurrence (-) n=156		Recurrence (+) n=15		Total n=171	p-value
Stage						
IA1	5	3%	0	0%	5	0.330
IB1	118	76%	11	73%	129	
IB2	6	4%	0	0%	6	
IIA1	24	15%	3	20%	27	
IIA2	1	1%	0	0%	1	
IIB	2	1%	1	7%	3	
Tumor size						
</= 2 cm	44	28%	2	13%	46	0.008
> 2 - 4 cm	97	62%	10	67%	107	
> 4 - 6 cm	14	9%	2	13%	16	
> 6 cm	1	1%	1	7%	2	
Stromal invasion						
< 1/3	45	29%	1	7%	46	0.115
> 1/3 -<2/3	42	27%	6	40%	48	
> 2/3	69	44%	8	53%	77	
LVSI						
negative	118	76%	10	67%	128	0.538
positive	38	24%	5	33%	43	
Parametria mets						
negative	154	99%	14	93%	168	0.168
positive	2	1%	1	7%	3	
Uterine mets						
negative	146	94%	15	100%	161	0.603
positive	10	6%	0	0%	10	
FT mets						
negative	155	99%	15	100%	170	0.912
positive	1	1%	0	0%	1	
Pelvic node mets						
negative	144	92%	13	87%	157	0.353
positive	12	8%	2	13%	14	
Aortic node mets						
negative	155	99%	15	100%	170	0.912
positive	1	1%	0	0%	1	

in recurrence rate is not statistically significant. There is no significant difference in the recurrence rates between high risk patients who received or did not receive adjuvant treatment. With regards to neoadjuvant therapy and lymphadenectomy, recurrence rates did not show significant difference (p>0.05alpha).

Recurrence and Treatment

Systemic chemotherapy was contemplated after the diagnosis of recurrence. The chemotherapeutic regimens used were Cisplatin-Topotecan, Cisplatin-Paclitaxel, Carboplatin-Paclitaxel, Oxaliplatin-Docetaxel. The rest were lost to follow up after being diagnosed with recurrence.

Survival Rate

Patients with early stage and locally advanced cancer who underwent radical hysterectomy with or without lymphadenectomy had a median survival of 3 years (CI 95% 2.19-3.82). The 1-, 3- and 5- year survival rates were 97.6%, 99.1%, and 98.2 %, respectively. When grouped based on histologic diagnosis, SCCA patients have a slightly higher median survival of 4 years (CI at 95% 2.87- 5.12) as compared to the ADC (median 3 years, CI 95% 1.68-4.35) and adenosquamous (median 2 years). However, the difference of this median survival for the three histologic types was not statistically significant (p>0.05alpha).

In the survival analysis, 3 analytical models were utilized to test the equality of survival distributions for the different variables. Those within 35-64 years old have slightly higher median survival of 4 years (CI 95% 2.58-5.42) as compared with those </35 years old (median = 3 CI at 95% 0.57-5.43) and 65 years old and above (median= 3, CI 95% 1.44-4.56). However, the difference of median survival time across the three-age group stratification was not statistically significant (p>0.05alpha).

Table 6 shows the median survival of patients based on stage, risk stratification, neoadjuvant therapy and adjuvant therapy. The group of patients in this study did show significant difference in the median survival when analyzed per clinical stage (p>0.05alpha). Patients who were given neoadjuvant and adjuvant compared to those who were not have a higher median survival but the difference was not statistically significant (p >0.5alpha). Patients who required but did not receive adjuvant treatment had comparable survival with those who received adjuvant treatment postsurgery. The computed 5- year survival was 98%. Figures 2-4 present the Kaplan-Meier plot of the survival of patients based on these variables. A subanalyis was done on patients who received neodjuvant therapy prior to surgery. The 1- 3- and 5-year survival rates were 100%, 93% and 100%, respectively.

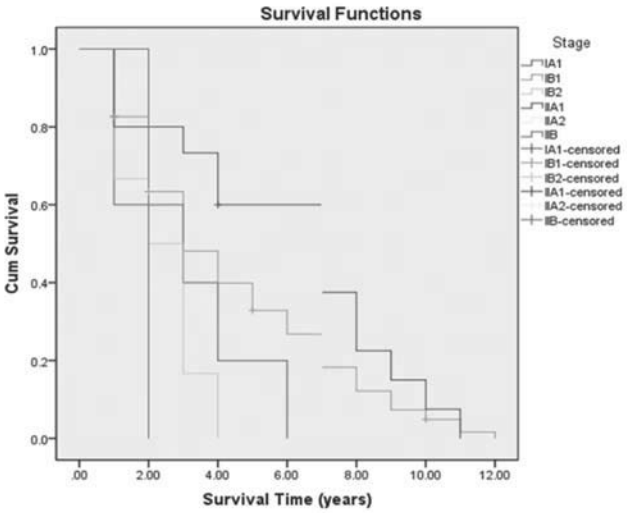

Figure 2. Stage and survival.

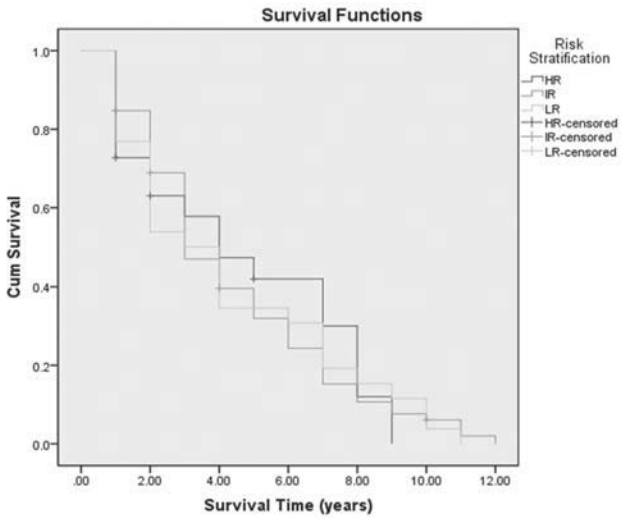

Figure 3. Risk stratification and survival.

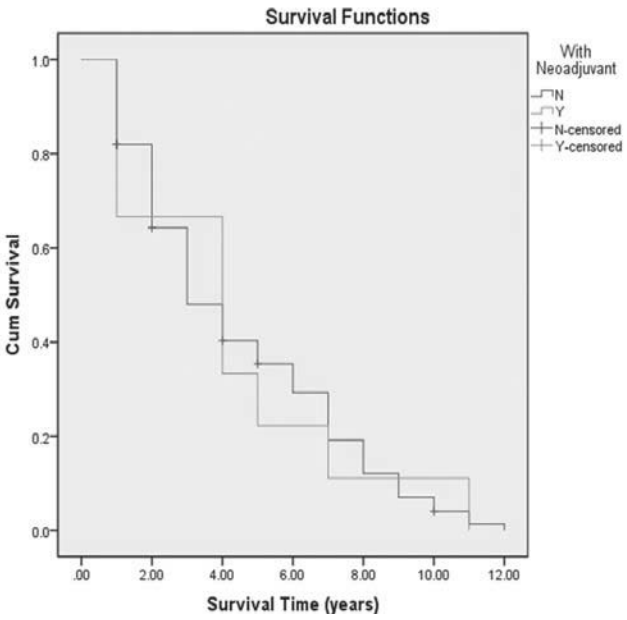

Figure 4. Neoadjuvant therapy and survival.

Patients with tumor recurrence had a lower median survival of 2 years (95% CI 1.21- 2.78) as compared to those without recurrence at 4 years (95% CI 3.28-4.75). The difference of this median survival is statistically significant ($p < 0.05$alpha). Figure 6 presented the Kaplan-Meier plot of survival in relation to tumor recurrence.

Discussion

Radical hysterectomy continues to be the treatment of choice for stage IA2, IB1 and IIA cervical cancer. Over the past 3 decades, patient selection and identification of prognostic factors for recurrence and survival have allowed primary and adjuvant treatment to be tailored to the individual patient. This philosophy has resulted in an approximately 90% cure rate associated with surgery for stages IA2, IB1 and IIA

Table 6. Survival analysis models of factors associated with Overall Survival for early stage and locally advanced cancer who underwent radical hysterectomy with or without lymphadenectomy.

	Median (years)			
			95% Confidence Interval	
Survival Factors	Estimate	Std. Error	Lower Bound	Upper Bound
Stage				
IA1	3.00	2.19	0.00	7.29
IB1	3.00	0.46	2.11	3.89
IB2	2.00	0.82	0.40	3.60
IIA1	7.00	1.73	3.61	10.39
IIA2	7.00	.	.	.
IIB	2.00	.	.	.
Risk Stratification				
Low	4.00	1.41	1.24	6.76
Intermediate	3.00	0.41	2.20	3.80
High	3.00	0.70	1.64	4.36
With Neoadjuvant therapy				
no	3.00	0.40	2.21	3.79
yes	4.00	1.41	1.23	6.77
With Adjuvant Treatment				
Those who required and were given adjuvant tx.	4.00	0.88	2.28	5.72
Those who needed no adjuvant post surgery bec they are low risk	4.00	0.96	2.13	5.87
Those that required adjuvant but did not receive	3.00	0.40	2.22	3.78

cervical cancers, while the proportion of patients receiving dual modality therapy for their malignancy has decreased. However, despite significant medical advances in perioperative care over this time period, the high cure rate associated with surgically managed stage I cervical cancer has not appreciably improved.[8]

There has been a progressive increase in the utilization of surgical management for Stage IB and IIA carcinoma of the cervix in many medical centers. Proponents of this method of management have pointed out the following advantages: 1) Many young women are seen with early invasive disease in whom preservation of ovarian function, sexual function, and avoidance of late radiation therapy complications is important; 2) clinical staging can be confirmed by surgical exploration at the time of surgery; 3) the overall treatment period is shorter; 4) the primary tumor is removed; 5) survival and complication rates are at least comparable with radiotherapeutic management of similar lesions; and 6) young pelvic surgeons are taught the anatomy of the pelvis and the techniques of pelvic surgery.[9]

Benefits of surgical treatment include preservation of ovarian function and the chance of simultaneous assessment of the lymph node status (which is an important variable associated with survival)[10,11] and improved coital function.[12,13] Assessment of node status may also dictate type of adjuvant therapy. On the other hand, radiation is easy to deliver, which is particularly important for poor surgical risk patients such as the elderly and obese patients and in patient with multiple medical morbidities or contraindications to surgery.[6,10] According to Landoni, et al.[14], although radiotherapy is feasible and effective in patients with early and locally advanced stages, radical surgery affords opportunity to study pathological findings, so that groups at risk may benefit from adjuvant treatment. Pelvic relapses after surgery can be successfully cured by radiotherapy, whereas salvage surgery after primary irradiation carries high rate of failures and severe morbidity.

Radical Hysterectomy and Survival

Several studies have reported on similar outcomes of radical hysterectomy and primary radiation for patients with early-stage cervical cancer.[14-16] In the recent SEER data report of Bansal, et al.[10], radical hysterectomy is superior to primary radiation in women with cervical cancer lesions of less than 6 cm. There was a 69% improvement in the survival rate for tumor size less than 4 cm and 49% survival rate improvement for tumor size 4-5 cm.

The cure rate of early stage cancer (IA2 to IIA) is high. They can be treated by radical hysterectomy (RH) or primary radiotherapy (RT) with similar outcomes with overall survival rates that exceed 80%.[11,14,17] The choice of therapeutic modality is based on patient comorbidities, patient or physician preference and the availability of radiation facilities.

The reported 5 year survival rates of early cervical cancer treated with radical hysterectomy is from 81-87% which is a little bit higher than radiotherapy (74-83%) but not statistically significant.[9-10, 4-15,18] All these studies are limited by small sample sizes, which may not have detected a survival difference. In other studies, the reported 5- year survival rate of stage IB is 84.5% and 71.1% in stage II.[4] Hoskins, et al.[9] showed a projected survival rate in excess of 70% in patients with microscopic disease in the pelvic lymph nodes treated by postoperative radiation.

This present study reported that the 1-, 3- and 5-year survival rates of early stage and locally advanced cervical cancer managed with radical hysterectomy with or without lymphadenectomy were 97.6%, 99.1%, and 98.2 %, respectively. The median survival of these group of patients was 3 years. Patients aged 35-64 years old have slightly higher median survival of 4 years as compared with those <35 years old and >65 years old. However, the difference of median survival time across the three-age group stratification was not statistically significant. Patients with SCCA have slightly higher median survival of 4 years as compared to the ADC and adenosquamous. However, the difference for the three histologic types was not statistically significant.

Moreover, the difference in the median survival is not statisticaly significant in relation to stage, risk stratification, institution of neoadjuvant therapy and adjuvant therapy post surgery. Administration of neoadjuvant and adjuvant therapy may improve median survival but the difference in survival is not significant.

Tumor Recurrence and Survival

Tumor recurrence alone has been shown to significantly affect survival in these group of patients. The median survival of patients with recurrence is 2 years compared to patients with no recurrence which is 4 years. The recurrence rate of patients with early stage and locally advanced carcinoma who underwent radical hysterectomy with or without lymphadenectomy regardless of histology is 9.8 %, with a average onset of 20 months (median: 12 months). Recurrence rates for SCCA, ADC and neuroendocrine tumors were 10%, 7% and 100%, respectively.

Tumor size and grade is statistically associated with recurrence. Patients with a tumor size > 4 cm and moderate to poorly differentation showed significant tendency of recurrence. Clinical stage IIA1 and IIB, > 1/3 cervical stromal invasion, positive LVSI and pelvic nodes showed an affirmative trend towards recurrence, but the difference is not statistically significant.

Several studies reported on the factors that affect recurrence and survival. An analysis of data on 575 women enrolled in a Gynecologic Oncology Group (GOG) study of clinical and pathologic predictors of surgically treated stage IB carcinoma of the cervix with more than or equal to 3 mm invasion confirmed the roles of large tumor diameter (TD), deep stromal invasion (DSI), and capillary lymphatic spaces (CLS)/ LVSI as risk factors, increasing the probability of cancer recurrence at 3 years from 2 to 31%.[19]

Similarly, Tsai, et al.[20] in their multivariate analysis identified only three risk factors in relation to 5- year disease-free survival: pathological nodal involvement, bulky tumor size, and parametrial invasion. Lymph node status was found to be the most important prognostic factor. The survival rate for patients with positive pelvic lymph node is 71% vs 87% for those with negative node. Those with multiple pelvic lymph nodal metastases have worse survival rate than those with one pelvic node. Sedlis et al reported that pelvic lymph node metastases decrease the 5-year survival from 82-90% to 38-61%. Large tumor diameter, deep stromal invasion, and lymphovascular involvement (LVSI) were also proven as independent risk factors because of their frequent association with increased cancer recurrence and mortality.[17]

The most powerful predictor of survival among patients treated for locally advanced cervical cancer is the extent of disease expressed as FIGO stage.[21] A study by Finan, et al.[5] showed that patients with stage IB2 disease have a significantly worse 5-year survival (72.8%) when compared with stage IB1 (90.0%) (p=0.0265). Stage, however, is not an independent predictor of poor survival. Stage appears to impact survival through nodal status. Those patients with stage IB2 tumors but with negative nodes had a significantly better survival than patients with stage IB1 with positive nodes. They concluded that patients with stage IB2 cervical cancer could safely undergo radical hysterectomy with similar morbidity as patients with stage IB1 disease. Patients undergoing paraaortic lymphadenectomy have a higher complication rate than patients not undergoing para-aortic node dissection. Tumor diameter and histology did not have an impact on the morbidity and survival. A retrospective study of Kamelle, et al.[22], displayed the role of tumor size and cervical stromal invasion. He suggested that lymphovascular invasion (LVSI) is an important independent predictor of recurrence. Nodal and parametrial metastases were surrogates for LVSI.

A local study of Pagkatipunan, et al.[23] reported that tumor diameter (TD) and nodal metastasis were significantly related to recurrence after a radical hysterectomy and lymph node dissection. Patients with tumor diameter of 4 cm and above had a 4-8-fold risk of developing recurrence. There was no recurrence in TD of <2 cm. The mean survival time is 68, 54, 51, 28 and 25 months for TD of <2 cm, 2-2.9 cm, 3-3.9cm, 4-4.9 cm and ≥ 5cm, respectively. Histologic type, vaginal invasion and postoperative adjuvant radiotherapy did not influence the incidence of recurrence. Similarly, in the retrospective study of Al-Kalbani, et al.[24], their data suggested an extremely low risk of parametrial and lymph node involvement with tumors 2 cm or smaller. None of the 74 patients had recurrence nor developed metastatic disease (median follow up of 35-36 months). Moreover, survival rate is more than 90% for patients with less than 4 cm tumor size[25] and when the lesion diameter was greater

than 6 cm, the 5- year survival was 43% similar with the stage IIIB cases at 48%.[26]

Havrilesky, et al.[27] showed an overall 5-year survival of 72 % for patients with stage IB2 who underwent radical hysterectomy with lymph node dissection. 5-year survival was 100% in low-risk group, 80% in the intermediate-risk group, and 47% in the high risk-group. In a multivariate analysis, younger age, non-Caucasian race, outer 1/3 cervical wall invasion, and lymph vascular invasion were significantly associated with lower overall survival. In the same study, twenty-three patients had disease recurrence. Sites of recurrences were in the pelvis (65%), nodes (9%), distant (22%) and multiple sites (4%). Salvage therapies included radiotherapy (22%), chemotherapy (13%), and combination chemotherapy and radiation. Another report of Kinney, et al.[28] confirmed the decrease in local recurrence after pelvic irradiation and the corresponding increase in short-term survival, however the overall 5-year recurrence rates were not different. Median time to recurrence was 1.85 years for all patients, 1.4 years (range, 0.3-7.0 years) in the surgery only group, and 2.1 years (range, 0.4-11.8 years) in the adjuvant irradiation group. Median time to recurrence was 0.9 year for those patients who had recurrence in pelvic and distant sites, 1.5 years for pelvic recurrence alone, and 3.0 years for distant recurrence alone.

In the study of Rutledge, et al.[29], clinicopathologic factors that predicted nodal involvement in patients with stage IB1 and IB2 included LVSI, >2/3 depth of invasion, and parametrial invasion. LVSI and parametrial involvement were identified as independent predictors of nodal disease in multivariate analysis. These 2 factors influenced the disease-free survival irrespective of the stage and nodal metastasis. Neoadjuvant chemotherapy, age, BMI, grade, stage, tumor size and histology did not significantly influence disease-free-survival.

Treatment and Related Morbidities

A study of Covens, et al. (2000)[8] quantified changes in demographics, perioperative care, and recurrence-free survival of stages of early stage cervical cancer undergoing radical surgery as a definitive management over the past 16 years, and found out that surgery related morbidities decreased significantly although with no significant change in survival rates. Our study arrived at a low incidence (9%) of morbidity from radical hysterectomy with lymphadenectomy in our training hospital. Majority of the morbidities were anatomic and infectious in nature and not related to stage, tumor size, performance of lymphadenectomy and administration of neoadjuvant therapy. This justifies that such procedures should be performed by skilled gynecologic oncologists. Patient preoperative preparation and postoperative care should also be emphasized.

Some authors argue against surgery in patients with larger tumor size (>4 cm) due to the increased morbidity. But recent reports did not show significant difference in morbidity and complication rates between stage IB1 and IB2.[19,29] Overall rate of severe complications from radical hysterectomy is 11.1% and 13.9% if followed by radiation therapy. In the GOG 92 study, the rates of grades 3-4 gastrointestinal and genitourinary toxicity noted among patients treated with RH followed by pelvic RT is 2-3%, similar to the 3-5% rate of toxicity found among patients treated with primary radiotherapy on GOG 123.[27] In the series of Yessaian, et al.[30] major complications of surgical treatment were seen in 5 of the 58 patients with bulky tumors, including vesicovaginal fistulas, non-fatal pulmonary embolism, blood loss necessitating blood transfusion. There were no treatment- related deaths. The presence of positive pelvic lymph nodes was significantly associated with risk of major complications. However, the overall complication rate was not significantly associated with postsurgical radiation or paraaortic lymph node dissection.

In an earlier series of Sartori, et al. (1995)[31], the major complication rate was significantly lower in patients treated with class II than in those who underwent class III radical hysterectomy. The complication rate was increased with the addition of radiotherapy in both types of radical hysterectomy. There was no treatment death in the whole series. In a earlier local study[32], the reported post operative morbidity rate of radical hysterectomy was 8% and 4% for non-nerve sparing and nerve sparing radical hysterectomy, respectively. Most of the complications were non-specific and infectious in nature. However,

they did not correlate these morbidities with the presence nor absence of poor prognostic factors.

Adjuvant Therapy

After radical hysterectomy with lymph node dissection, some patients will require postoperative adjuvant radiation therapy due to several clinical and histopathologic factors which may increase risk of treatment failure and recurrence. These include tumor size > 2 cm, greater than 1/3 stromal invasion, positive lines of resection, nodal metastasis and positive lymphovascular space invasion.[6, 20]

The effect of postoperative radiotherapy on improving local control in early stage cervical cancer after radical hysterectomy has been demonstrated. Adjunctive radiation also delays the clinical development of recurrence.[33,34] Clinical and pathologic factors such as LVSI, resection margins or the invasion depth of invasion of the cervical wall were not observed among patients who received postoperative radiotherapy.[20] Studies in the early 1990s on adjunctive therapy showed no major improvement in the overall survival rates of patients treated with postoperative radiotherapy[35] but these studies have small sample size. In the analysis of Lai, et al.[36] involving 370 patients with stages IB and IIA cervical carcinoma, there was a trend towards improved survival rate among patients who received postoperative radiotherapy compared to the no-adjuvant group. The 5- year recurrence- free survival rate was 50% in radiotherapy group and 58.3% in no-adjuvant group (p= <0.5). Addition of concurrent cisplatin- based chemotherapy to radiotherapy significantly improves progression-free and overall survival for high-risk, early-stage patients who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix.[37]

Neoadjuvant Therapy

The use of preoperative adjuvant chemotherapy as part of multimodality treatment is known to offer some theoretical advantages in the treatment of bulky and locally advanced cervical cancer. Recent reports have focused on the use of neoadjuvant chemotherapy (NACT) to improve the outcome of patients with bulky cervical tumors. Such modality showed excellent short-term response rates, improved operability and surgical downstaging of patients, hence a radical surgery may be employed.[38] Serur, et al.[25] in their 6- year period study found out that neoadjuvant chemotherapy reduced the mean cervical surface area by an average of 77%. The time interval between the last course of neoadjuvant chemotherapy and surgery was a median 21.5 days. A significant reduction in high-risk pathologic variables, such as nodal involvement, vascular space involvement and depth of invasion was noted among the patients in the NACT group. However this approach did not translate into a statistically significant 5- year survival rate with an 80% compared to the primary surgery group of 68.7% (p= 0.162). The pelvic failure rates were 15% in NACT group and 31.3% in primary surgery group, however was not statistically significant because of the small sample size. In both groups, the best predictor of recurrence was depth of stromal invasion.

A comparative study by Namkoong, et al.[39] on patients with locally advanced stage I and II cervical cancer treated by radical surgery with or without preoperative adjuvant chemotherapy showed that overall recurrence rates, time to recurrence and lymph node metastases were significantly higher in patients without preoperative chemotherapy. The 4-year tumor free survival of locally advanced cervical cancer patients who were treated with preoperative adjuvant chemotherapy (87%) was significantly longer than those treated with radical surgery without NACT (77.8%) (p=0.0067). Other studies confirmed the high rate of response after NACT with a platinum-based regimen in cervical cancer stage IB-IIB.[26,40]

A retrospective review of Behtash, et al.[41] reported that neoadjuvant chemotherapy (NACT) did not improve long-term overall survival of patients with bulky early stage cervical cancer compared to primary radical surgery. During the 9-year follow up, recurrence rates were 47.1 % for those who received NACT and 30.2% for those treated with primary surgery.

Local studies explored on the outcomes of multimodality treatment in early bulky stage cancer and locally advanced cervical cancer. A study of Arias and

Toral, et al.[42] compared 4 modalities on the management of cervical cancer FIGO stage IB2 and bulky IIA. The 2-year disease free rate was 34% for patients who had external pelvic beam radiotherapy and intracavitary radiation concomitant with single agent Cisplatin, 84% for patients who had external pelvic beam radiation and intracavitary radiation concomitant with single agent cisplatin followed by extrafascial hysterectomy and bilateral salpingooophorectomy, 88% for those who had external pelvic beam radiation followed by radical hysterectomy, bilateral salpingooophorectomy and pelvic lymph node dissection , and 80% for patients who had external pelvic beam radiation concomitant with Cisplatin followed by radical hysterectomy, bilateral salpingooophorectomy and pelvic lymph node assessment. Another local study[43] involving 16 patients who received neoadjuvant chemoradiation followed by radical hysterectomy for large tumor cervical cancer demonstrated the best survival rates at 97% and 85% in 1-and 5- years, respectively. This present study showed that administration of neoadjuvant and adjuvant therapy may improve survival but the difference is not statistically significant.

Summary and Conclusion

Patients with early stage and locally advanced cervical cancer who underwent RHBSO with or without lymphadenectomy, either as primary treatment or after neoadjuvant therapy have excellent prognosis and survival. Such procedures are safe under skilled gynecologic oncologists. The difference in survival rates between SCCA, ADC and ADS in early stage is not statistically significant. Younger (<35 years old) and elderly (>65 years old) patients may carry a poorer survival rate.

Radical hysterectomy for bulky tumors and cervical cancer with local metastasis who were given neoadjuvant therapy offered survival advantage. Likewise, adjuvant treatment may improve survival of patients with intemediate and high risk for recurrence. Tumor recurrence alone is significantly associated with survival of these group of patients.

Limitations and Recommendations

The limitation of this study is inherent of it being a retrospective study. Although, some patients were lost to follow up and were not included in the survival analysis, the computed sample size was attained to provide a significant power of results. So far, this study has the largest sample size with a considerably longest range of patients' follow up in the local setting.

Since this study showed a considerably excellent survival of patients with early stage and locally advanced cervical cancer managed with radical hysterectomy with or without lymphadenectomy, neoadjuvant and adjuvant therapy, primary surgery should be offerred as primary treatment for these group of patients with proper counseling.

A study may be conducted to compare survival rates of early stage patients treated with primary surgery and primary radiation therapy.

References

1. WHO/ICO Information Center on HPV and Cervical Cancer (HPV Information Center). Summary Report on HPV and cervical cancer statistics in the Philippines, 2007.
2. Domingo, E. Clinical Practice Guidelines for the Obstetrician-Gynecologist. Society of Gynecologic Oncologists of the Philippines (Foundation), Inc. 2nd Edition, November 2010.
3. Kurman R, Ellenson L, Ronnett B , Blaustein's Pathology of the Female Genital Tract (6th ed.), DOI 10.1007/978-1-4419-0489-8_6,
4. Di Saia P, Creasman W, et al. Clinical Gynecologic Oncology, 8th edition. Philadelphia, Elsevier-Saunders, 2012.
5. Finan M, Decesare S, Fiorica J, et al. Radical Hysterectomy for Stage IB1 vs IB2 Carcinoma of the Cervix: Does the New Staging System Predict Morbidity and Survival? Gynecologic Oncology 1996; 62: 139-47.
6. Domingo E, et al. Society of Gynecologic Oncologist of the Philippines Clinical Practice Guidelines 2012, 6th edition.
7. Domingo E, et al. Society of Gynecologic Oncologist of the Philippines Clinical Practice Guidelines 2008, 5th edition.
8. Covens A, Rosen B, Murphy J, et al. Changes in the Demographics and Perioperative Care of Stage IA2/IB1 Cervical Cancer over the Past 16 Years. Gynecol Oncol 2001; 81: 133-7.
9. Hoskins WJ, Ford JH Jr, Lutz MH, Averette HE: Radical hysterectomy and pelvic lymphadenectomy for the management of early invasive 1995 carcinoma of the cervix. Gynecol Oncol 1976; 4: 278-90.

10. Bansal N, Herzog T, Shaw R, et al. Primary therapy for early-stage cervical cancer: radical hysterectomy vs radiation. Am J Obstet Gynecol 2009; 201:485.e1-9.
11. Gray H, Seifert E, Sal V, et al. The Abandoned Radical Hysterectomy for Cervical Cancer: Clinical Predictors and Outcomes. Obstet Gynecol Int 2010; 1-6.
12. Vistad I, Fossa SD, Dahl AA. A critical review of patient-rated quality of life studies of long-term survivors of cervical cancer. Gynecol Oncol 2006; 102: 563-72.
13. Frumovitz M, Sun C, Schover L, et al. Quality of life and sexual functioning in cervical cancer survivors. J Clin Oncol 2005; 23: 7428-36.
14. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997; 350: 535-40.
15. Newton M. Radical hysterectomy or radiotherapy for stage I cervical cancer: a prospective comparison with 5 and 10 years follow-up. Am J Obstet Gynecol 1975; 123: 535-42.
16. Jewell E, Kulasingam S, Myers E et al. Primary surgery versus chemoradiation in the treatment of IB2 cervical carcinoma: A cost effectiveness analysis. Gynecol Oncol 2007; 107: 532-40.
17. Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. Gynecol Oncol 1999; 73: 177-83.
18. Morley GW, Seski JC. Radical pelvic surgery versus radiation therapy for stage I carcinoma of the cervix (exclusive of microinvasion). Am J Obstet Gynecol 1976; 126: 785-98.
19. Delgado G, Bundy BN, Fowler WC, et al. A prospective surgical pathological hysterectomy and pelvic lymphadenectomy for FIGO stage IB bulky. Gynecol Oncology Group Study. Gynecol Oncol 1989; 35: 314-20.
20. Tsai CS, Lai CH, Wang HC, et al. The prognostic factors for patients with early cervical cancer treated by radical hysterectomy and postoperative radiotherapy. Gynecol Oncol 1999; 75: 328-33.
21. Monk B, Tewari K, Koh W. Multimodality Therapy for locally Advanced Cervical Carcinoma: State of the Art and Future Directions. Journal of Clinical Oncology 2007; 25(20): 2952-65.
22. Kamelle S, Rutledge T, Tillmanns T, et al. Surgical-pathological predictors of disease-free survival and risk groupings for IB2 cervical cancer: do the traditional models still apply? Gynecol Oncol 2004; 94: 249-55.
23. Pagkatipunan MG, Limson G, Manalo A. Prognostic Factors in the Recurrence of Cervical Cancer After radical Hysterectomy with Bilateral Lymph Node Dissection. Acta Medica Philippina 1993; 29(1): 18-27.
24. Al-Kalbani M, McVeigh G, Nagar H, et al. Do FIGO stage IA and small (e2 cm) IB1 cervical adenocarcinomas have a good prognosis and warrant less radical surgery? Int J Gynecol Cancer 2012; 22: 291-5.
25. Serur E, Mathews R, Gates J, et al. Neoadjuvant chemotherapy in stage IB2 squamous cell carcinoma of the Cervix. Gynecol Oncol 1997; 65: 348-56.
26. Eddy GL, Manetta A, Alvarex RD, et al. Neoadjuvant chemotherapy with vincristine and cisplatin followed by radical staging of stage I squamous carcinoma of the cervix: a Gynecologic cervical cancer: a Gynecologic Oncology Group pilot study. Gynecol Oncol 1995; 57: 412-6.
27. Havrilesky L, Leath C, Huh W, et al. Radical hysterectomy and pelvic lymphadenectomy for stage IB2 cervical cancer. Gynecol Oncol 2004; 93: 429-34.
28. Kinney W, Alvarez R, Reid G, et al. Value of adjuvant whole-pelvis irradiation after wertheim hysterectomy for early-stage squamous carcinoma of the cervix with pelvic nodal metastasis: A matched-control' study. Gynecol Oncol 1989; 34: 258-62.
29. Rutledge T, Kamelle S, Tillmanns T, et al. A comparison of stage IB1 and IB2 cervical cancers treated with radical hysterectomy. Is size the real difference? Gynecol Oncol 2004; 95: 70-6.
30. Yessaian A, Magistris A, Burger R, Monk, B. Radical hysterectomy followed by tailored postoperative therapy in the treatment of stage IB2 cervical cancer: feasibility and indications for adjuvant therapy. Gynecol Oncol 2004; 94:61-6.
31. Sartori E, Fallo L, La Face B, et al. Extended radical hysterectomy in early-stage carcinoma of the uterine cervix: tailoring the radicality. Int J Gynecol Cancer 1995; 5: 143-7.
32. Strebel E, Luna JT, Domingo E. A comparison of the feasilbility and safety of nerve-sparing radical hysterectomy with the conventional radical hysterectomy. Phil J Gynecol Oncol 2008; 5(1): 1-13.
33. Hart K, Han I, Deppe G, Malviya V, et al. Postoperative radiation for cervical cancer with pathologic risk factors. Int J Radiat Oncol Biol Phys 1997; 37: 833-8.
34. Remy J, Di Maio T, Fruchter R, et al. Adjunctive radiation after radical hysterectomy in stage Ib squamous cell carcinoma of the cervix. Gynecol Oncol 1990; 38: 161-5.
35. Baltzer J, Zander J. Adjuvant radiotherapy in the surgical treatment of the carcinoma of the cervix. Biomed Pharmacorhe 1985; 39: 422-6.
36. Lai CH, Chang HC, Chang TC, et al. Prognostic factors and impacts of adjuvant therapy in early-stage cervical carcinoma with pelvic node metastases. Gynecol Oncol 1993; 51: 390-6.
37. Peters WA III, Liu PY, Barrett RJ Jr, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000; 18: 1606-13.
38. Sardi J, Giaroli A, Sananes C, et al. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: The final results. Gynecol Oncol 1997; 67: 61-9.
39. Namkoong SE, Park JS, Kim JW, et al. Comparative study of the patients with locally advanced stages I and II cervical cancer treated by radical surgery with and without preoperative adjuvant chemotherapy. Gynecol Oncol 1995; 59: 136-42.

40. Bolis G, Zainten-Przybysz IW, Scarfone G, et al. Determinants of response to a cisplatin-based regimen as neoadjuvant chemotherapy in stage Ib-IIb invasive cervical cancer. Gynecol Oncol 1996; 63: 62-5.
41. Behtash N, Nazari Z, Ayatollahi H, et al. Neoadjuvant chemotherapy and radical surgery compared to radical surgery alone in bulky stage IB-IIA cervical cancer. EJSO 2006; 32: 1226-30.
42. Arias C, Toral JA, Luna JT. Continuing treatment outcomes of cervical cancer stage IB2 and bulky IIA using four different multimodality protocols in a tertiary institution: A follow-up study. Phil J Gynecol Oncol 2007; 4(2): 65-79.
43. Pua S, Cuenca B, Santos R, et al. Radical hysterectomy following neo-adjuvant therapy in bulky stage I-IIA cervical cancer: A tertiary hospital experience. Phil J Gynecol Oncol 2009; 6(1): 6-15.

The Blackhole : A Case Report on Vaginal Melanoma*

Heysale G. Casalem MD and Grace Q. Madis, MD, FPOGS, FSGOP, FPSCPC

Section of Gynecologic Oncology, Department of Obstetrics and Gynecology, Southern Philippines Medical Center

Mucosal melanomas are melanomas located in the vagina. Considered as a rare tumor, mucosal melanoma is very aggressive owing to its location where a vast blood and lymphatic supply is available and early recognition is not possible.
This report discusses the case of a 69-year old widow complaining of unusual vaginal discharge. Gynecologic examination revealed a hyperpigmented lesion at the vaginal vault with the involvement of the distal urethra. Further workup showed that the biopsy of the lesion was consistent with malignant melanoma. Treatment was multidisciplinary involving Gynecologic Oncology, Urosurgery, Reconstructive Surgery and Internal Medicine. The patient underwent anterior pelvic exenteration with ileal conduit and total vaginectomy. Reconstruction of the vagina was done using gracilis flap.

Key words: Vaginal melanoma, pelvic exenteration

Primary Vaginal Melanoma is a rare gynaecologic malignancy which is confined to the epithelial mucosa for which the prognosis remains ominous and the optimal treatment not clearly defined. Population-based incidence of vaginal melanoma in Asian and Hispanic individuals is almost unknown. The annual age-adjusted incidence rates in Asians and Pacific Islanders is 1.03. In the Philippines, there has been no reported case of primary vaginal melanoma until the present time and with only a few reported cases published internationally. This is a case report of 69-year old woman who was diagnosed with primary vaginal melanoma through histopathology and was managed multidisciplinarily, through pelvic exenteration and vaginectomy.

The Case

This is a case of S.T., a 69-year old widow G4P3 (3013) from Bukidnon who was admitted last May 2014 with a chief complaint of vaginal discharge. The patient complained of an 8-month history of non-foul smelling vaginal discharge. No other associated signs and symptoms were noted. She consulted a private gynecologist who observed a hyperpigmented lesion at the vaginal vault. A biopsy of the said lesion revealed sheets of atypical melanocytes invading the surrounding fibrous stroma. Individual cells exhibited round to oval deeply basophilic nuclei and abundant clear to eosinophilic cytoplasm which was consistent with malignant melanoma. The patient was then referred to a gynecologic oncologist. CT scan of the whole abdomen with contrast revealed negative for lymph node involvement. The patient was then advised

* First Place, 2015 SGOP Interesting Case Contest

for adjuvant treatment but she was not able to comply. One month prior to admission, there was still persistence of the vaginal discharge along with scattered hyperpigmented lesions on the labia minora. She was again seen at the Outpatient Department. As she was advised to undergo definitive surgery, she was admitted in our institution.

The patient is a retired teacher. Her health history is unremarkable as she is a non-smoker, a non-alcoholic beverage drinker with no known co-morbidities. Also, there was no history of cancer in the family. She had her menarche at the age of 14 years old with regular intervals lasting for 3-4 days soaking 2-3 cloth pads per day with no associated dysmenorrhea. Coitarche was at the age of 26 with one sexual partner.

She is a G4P3 (3013). All the living children were delivered via normal spontaneous delivery without any complications. An abortion occurred last 1987, associated with the case of hydatidiform mole. She had undergone suction and sharp curettage and was given chemoprophylaxis prior to discharge in a hospital in Bukidnon. After the procedure, the patient was lost to follow-up thus proper monitoring of her β-hcG was not done. The patient is already menopausal for 14 years. She never underwent any gynecologic screening procedures in the past.

On admission, the evaluation of the patient was unremarkable as she has a thin built, afebrile with stable vital signs, no pallor, well hydrated, no cough, and no abdominal pain. She was conscious, coherent and was not in cardio-respiratory distress. Upon inspection of the external genitalia, there were hyperpigmented black elevated lesions with irregular borders occupying the labia minora extending to the urethral meatus. On speculum examination, same characteristic of the lesions were noted to occupy the entire length of the vagina, predominantly on the lower 1/3 of the vagina with majority on the anterior portion. The cervix was midline, pinkish with minimal mucoid whitish discharge. There were hyperpigmented lesions with irregular borders at the 11 o'clock and 7 o'clock positions approximately 1cm x 1cm in diameter. On bimanual examination, the entire length of the vagina was thickened by the lesions, the cervix was 2cm x 2cm and was smooth, corpus was small, no adnexal masses nor tenderness, the bilateral parametria were smooth and pliable.

Baseline laboratories were all normal except for the presence of hypoalbuminemia. Repeat CT scan of the pelvis was done which revealed a heterogeneously enhancing signal intensity changes noted in the diffusely thickened vaginal walls extending down to both labia minora without cervical involvement. There was preservation of the flat plane delineation between the vagina and adjacent viscera. No abnormally enlarged pelvic lymph nodes were demonstrated. Given these findings, the initial consideration was vaginal malignancy with involvement of the bilateral labia minora.

This rare case of a vaginal melanoma involved a multidisciplinary approach involving Gynecologic Oncology, Urosurgery, Reconstructive Surgery, Colorectal Surgery, Internal Medicine and Palliative Medicine. This case also emphasized the importance of a good clinical judgement and what surgical approach should be done to arrive with a correct diagnosis, adjuvant treatment and post-operative care which has an overall impact on the patient's quality of life and survival. Since there was already gross involvement of the distal urethra, (Figures 1 & 2) Urosurgery did preoperative cystoscopy to further evaluate the bladder for possible metastasis. The procedure showed spread of the lesion at the neck of the urinary bladder. Proctosigmoidoscopy was also performed to assess possible involvement of the distal colon. The scope was inserted 25cm from the anal verge with note of smooth mucosa. Neither masses nor polyps were noted. Pre-operative diagnosis was vaginal melanoma.

With the aforementioned findings and after obtaining clearance from on board services and departments, the patient underwent anterior pelvic exenteration with ileal conduit, total vaginectomy, wide vulvar excision, reconstructive gracilis flap, repair of rectal mucosa tear, colostomy, and jp drain insertion under general anesthesia.

Intraoperatively, no ascites were noted. The surfaces of the liver, gallbladder, kidneys, intestines, appendix were palpated and were smooth and grossly normal. The vulva measured 4 cm. Vaginal length was 7cm. The cervix measured 2.5cm x 2.5cm x 2cm. The corpus

measured 5cm x 4cm x 4cm. Both the ovaries were atrophic 1cm x 1cm x 0.5cm. Both the fallopian tubes were grossly normal measuring 5cm x 1cm. The bladder measured 5cm with smooth serosa. On cut section of the corpus, the endometrial cavity measured approximately 3 cm while the endocervical canal measured 2cm. The endometrium was thin while both the anterior and posterior myometrium measured 2cm. The cervix measured 2cm x 2cm. There were 2 nodular lesions located at the 11 o'clock and 7 o'clock positions measuring 0.5cm x 0.5cm and 1x 0.5cm respectively. On further sectioning of the bladder, a flat hyperpigmented lesion was noted at the base of the bladder neck approximately 3cm x 3cm. (Figure 3) On the vagina were black nodular lesions of various sizes ranging from 0.5cm to 2cm x 3cm with depth approximately 0.5cm. The lesions extended up to the labia minora and majora. The operation lasted for 10 hours wherein the patient had episodes of hypotension. Post-operative diagnosis is vaginal melanoma stage IVA since there was already involvement of the bladder neck and distal urethra. The specimen was sent for biopsy. Microscopy was consistent with malignant melanoma of the vaginal wall with positive tumor cells at bladder wall, cervix and labia majora. The endometrium was atrophic. There were no diagnostic abnormalities recognized on both the right and left parametria and adnexae. The final diagnosis for this case is malignant melanoma of the vagina stage IVA.

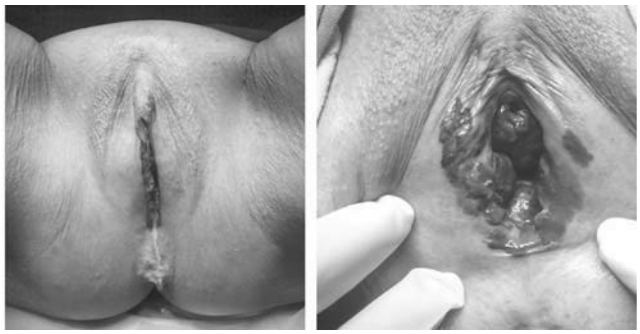

Figure 1. Gross appearance of the vulva with involvement of the distal urethra.

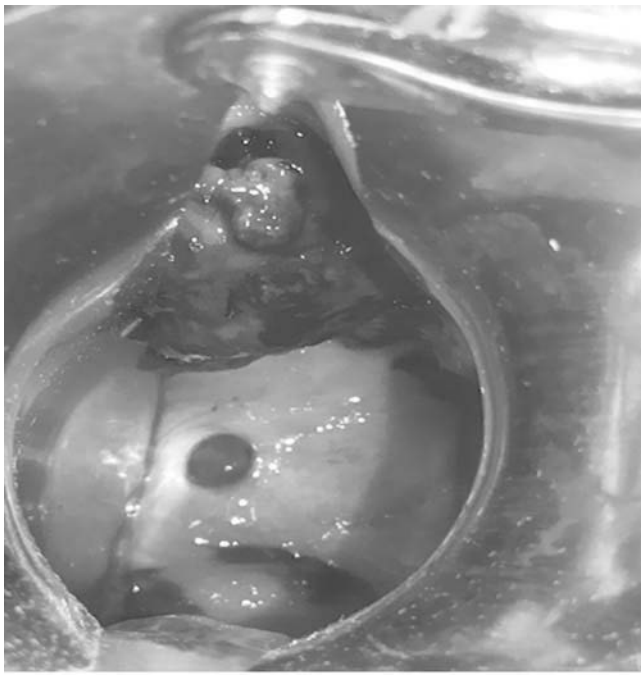

Figure 2. Gross involvement of the anterior lower vaginal wall and the cervix.

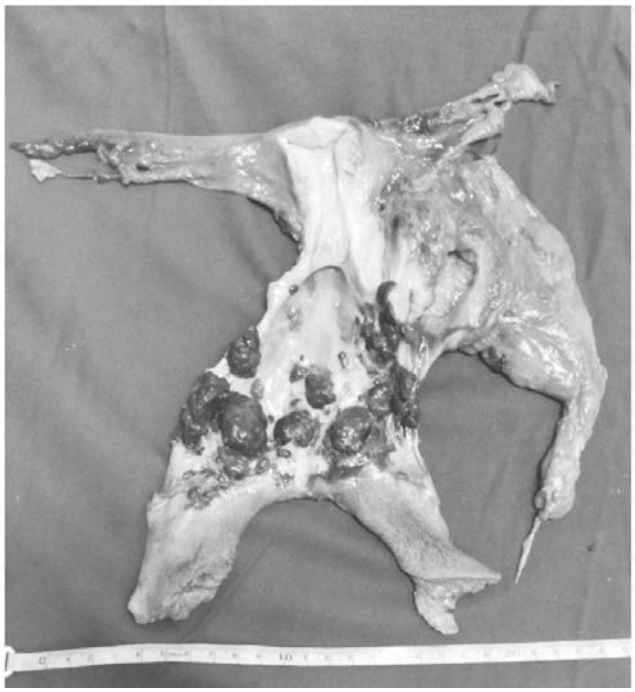

Figure 3. On cut section of the corpus, the endometrial cavity measured approximately 3cm while the endocervical canal measured 2cm. The endometrium is thin while both the anterior and posterior myometrium measure 2cm. The cervix measured 2cm x 2cm. There were 2 nodular lesions located at the 11 o'clock and 7 o'clock position measuring 0.5cm x 0.5cm and 1cm x 0.5cm respectively. On further sectioning of the bladder a flat hyperpigmented lesion was noted at the base of the bladder neck approximately 3cm x 3cm. On the vagina were black nodular lesions of various sizes ranging from 0.5cm to 2cm x 3cm with depth approximately 0.5cm.

Discussion

Melanoma is a type of skin cancer which is common in areas of the body with increased sun exposure. However, 1% of it may arise from the meninges[5], eyes[5], respiratory, alimentary and genitourinary tracts.[1] These are called mucosal melanomas.[2] Vaginal melanoma accounts for 0.3-0.8% of all melanomas in women and is approximately 2-3% of primary vaginal cancer.[1] It is the second most prevalent female genital tract melanoma[7] while an estimated 20% of mucosal melanomas are multifocal. Unfortunately, risk factors for its development have not been identified.[4]

The vagina is a strong muscular canal with the length of approximately 7.5cm long that extends from the uterus to the vestibule of the external genitalia, where it opens to the exterior. Anteriorly, the vagina is in close proximity to the bladder, ureters, and urethra. The posterior fornix is concealed by the peritoneum of the rectovaginal pouch, which may contain coils of intestine. Below the pouch, the vagina lies almost directly on the rectum, separated from it by a thin layer of areolar connective tissue. The vaginal branch of the uterine artery serves as the main blood supply. The lymphatic is segmented into a 1) superior group which terminates in the external iliac nodes or form anastomoses with the uterine plexus, 2) middle group of drains the greater part of the vagina, 3) inferior group anastomoses between the right and left sides and either courses upward to anastomose with the middle group or enters the vulva and drains to the inguinal nodes.[9]

Melanocytes arise from the neural crest which migrates from neural crest through embryonic mesenchyme along characteristic pathways to their final destination in the human body. They are pigment cells with the main function of pigmentation and UV protection in the skin and eye. However, the existence of these melanocytes in mucosal membranes, in which they are not required for sun protection, is not understood. But, there are evidences supporting that melanocytes also play roles in antimicrobial and immunological functions.[3]

Primary malignant melanoma of the vagina is defined as melanoma stemming from the vaginal wall without involving the vulva and/or the uterine cervix.[6] Apparently, it originates from melanocytes that are present in the vaginal mucosa. Its occurrence is very rare especially in Asian women,[7] evidenced by reports of only fewer than 300 patients to date.[2] Commonly, the tumor appears in the sixth and seventh decades of life, with the average age at 57 years old.[3] Compared to males, malignant melanoma occurs more commonly in females primarily due to the development of the disease in the genital tract. Although this disease is uncommon in Asian women, in this case, the age of the patient and her gender are her contributory risk factors.

Malignant melanoma more commonly occurs in the lower third of the vagina and mostly on the anterior vaginal wall.[2] In the case of the patient, there were already multiple lesions seen almost occupying the whole lower half of the vaginal vault and the vulva while small lesions were found at the cervix. However, a huge bulk of the lesion is at the anterior lower 1/3 of the vagina. It is an aggressive and exceptionally rare malignancy.[1] It has a critical prognosis caused by the delay in diagnosis because of its mucosal location, which then predisposes it to earlier metastasis via the bloodstream and lymphatics. The common sites of metastasis include the iliac and/or inguinal nodes, lungs, liver, brain, and bones.[3] In the aforementioned case, surprisingly, the physical examination and the CT scan revealed no abdominal lymphatic involvement despite the extent and size of the lesions.

The biological and histologic characteristics of vaginal melanoma tend to be similar with those of melanomas occurring elsewhere in the skin.[8] As with the case of the patient, the most observable presenting symptom is malodorous vaginal discharge.[2] Other than that, presenting symptoms may include vaginal bleeding, presence of mass lesion, and pain in less common instances. In general, melanoma is speculated once there is a newly-found hyperpigmented lesion. Vaginal melanoma appears as dark pigmented lesion although its color may vary from shades of black, brown, red, dark blue and gray.[5] Their borders are often irregular and notched, and they may be flat, polyoid, nodular or ulcerated. In the patient, majority of her lesions were nodular. Flat lesions with ill-defined

borders were found at the neck of the urinary bladder as well as at the lower 1/3 of the vagina.[2] Macroscopically, it presents like variably pigmented lesions, which are fragile and easily bleeds when touched.[4]

Microscopically, melanoma cells are often larger compared to normal melanocytes. They contain large nuclei with irregular contours, chromatin that is characteristically clumped at the periphery of the nuclear membrane and prominent eosinophilic nucleoli.[5] In 10-23% of cases, however, it could be amelanotic. Since it is initially confined to the epithelium, melanoma may resemble Pagets disease, both grossly and histologically. It can usually be differentiated by its uniform reactivity with antibodies to S100 protein, absence of reactivity to cytokeratin and the lack of mucopolysaccharides. HMB-45 positivity is specific for melanocytic lesions.[8]

There are lesions that may also involve the genitals and could be our differential diagnosis. One differential could be lentiginosis which is a benign localized hyperplasia of melanocytes often during infancy and childhood which consist of small (5-10 mm across), oval, tan-brown macules or patches. It is characterized by linear (non-nested) melanocytic hyperplasia restricted to the cell layer immediately above the basement membrane that produces a hyperpigmented basal cell layer. Another differential diagnosis is congenital nevus which is present at birth. It is common in deep dermal and sometimes subcutaneous growth around adnexa, neurovascular bundles, and blood vessel walls. Another differential is blue nevus which is highly dendritic black-blue, heavily pigmented nevus cells, non-nested dermal infiltration, often with associated fibrosis.[8]

The two types of melanoma are the cutaneous and mucosal melanoma. Both stem from the embryonic cells but they differ in the location in the body. Mucosal type may arise from meninges[5], eyes[5], respiratory, alimentary and genitourinary tracts.[1] Commonly, sun exposure is the most prevalent risk factor for cutaneous melanoma while it remains unknown for the mucosal type. In the given case, the patient had mucosal melanoma of the vagina.

Staging of the Carcinoma of the Vagina is according to the FIGO staging (Table 1) wherein Stage I is defined as tumor limited to the vaginal wall. Stage II, the tumor has involved the subvaginal tissue but has not extend to the pelvic wall. In stage III, the carcinoma has extended to the pelvic wall. And lastly Stage IV, which is defined as when there is involvement beyond the true pelvis and/or the mucosa of the bladder and/or rectum (IVA) or presence of distant metastasis such as the liver and lungs (IVB).[9]

As in our index patient, her surgicopathologic stage is that of Stage IVA wherein there was the involvement of the bladder neck as confirmed by histopath.

Regardless of therapy, prognosis of vaginal melanoma remains poor because of the high incidence of local recurrence and regional or distant metastasis. This may be attributed to the extensive lymphatic and vascular supply of the lamina propia of the vaginal mucus membranes.[6] However, a study by Takehara, et al. concluded that early detection and early treatment may improve prognosis. The reported five-year survival rate is 0-21%. Also, the size of tumor appears to be the most predictive for survival. Tumors which are less than 3cm in size have a median survival of 41 months. In comparison, tumors greater than or equal to 3 cm only have 12 months. In this case, the size of the patient's tumor is larger than 3 cm.[4]

On the other hand, tumor thickness reportedly does not significantly affect survival. Huang et al conducted a study which suggests that macroscopic tumor growth and treatment method are prognostic

Table 1. Carcinoma of the vagina: FIGO staging.

Stage 0	O Carcinoma in situ; intraepithelial neoplasia grade 3
State I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall.
Stage III	The carcinoma has extended to the pelvic wall
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. As such, bullous edema does not permit a case to be allotted to Stage IV
IVA	Tumor invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

factors. Cases with cauliflower-like vaginal melanomas had the worst prognosis in contrast to those with ulcerative type tumors which survived the longest.[7] Patients with positive lymph nodes have considerably lower median survival compared with patients with negative lymph nodes. Also, local recurrence is frequent, as it is experienced by about 40% of patients. The vagina, vulva and groin are often the sites of recurrence. For this case, the tumor was multiple with the largest size of 2cm x 3cm and already metastasized at the bladder. On palpation as well as on imaging studies, there was no involvement of the lymph nodes. Prognosis for this case is poor.

The most appropriate management for vaginal melanoma has been under debate.[6] While surgery has been widely accepted, some authors have found no significant difference in the overall five-year survival among conservative surgery, radical surgery, radiation, and chemotherapy. Despite this, surgery, compared to radiotherapy, seemed to play the most vital role in treatment since it provides local control of the tumor in a better way. In these cases, achieving negative margins can be challenging without pelvic exenteration, given the high occurrence of multifocality and anatomic constraints. Also, radical surgery does not show an advantage over conservative surgery. For many patients, wide local excision after radiotherapy is appropriate for many patients, but when impossible, exenteration is reasonable.[6] Similarly, the patient presented had a wide local excision of the tumor with anterior exenteration due to bladder involvement.

Pelvic exenteration describes a radical surgery involving the en bloc resection of the pelvic organs, including the internal reproductive organs, bladder, and rectosigmoid. There are three types of alternative procedures: 1) anterior pelvic exenteration wherein the bladder and internal reproductive organs are removed but spares the rectosigmoid, anus, and lower portion of the posterior vagina; 2) posterior pelvic exenteration wherein the internal reproductive organs and the rectosigmoid are removed but spares the anterior vagina, urinary bladder, and ureters and lastly 3) supralevator pelvic exenteration is indicated if the lesion does not involve the vulva or lower third of the vagina and an anorectal stump is left with a possibility for low rectal anastomosis. Patients who are the best candidates for exenteration are those with otherwise good medical health and could tolerate long surgical procedures with extensive fluid shifts and prolonged hospital stay. This is indicated not only in advanced primary or recurrent pelvic malignancies, most commonly centrally recurrent cervical carcinoma, but also other gynecologic, urologic and rectal cancers.[10]

The said patient underwent anterior pelvic exenteration, wherein the bladder and the internal reproductive organs were all removed. Since there was already involvement of the lower part of the posterior vaginal wall, an ileal conduit was then formed which would act as a pseudobladder. It is composed of an isolated segment of the distal ileum with its vasculature. The ureters were anastomosed directly to the ileum at one end, and the other end was brought to the skin as a stoma. A drainage bag was then attached to capture the urine. In this institution, this is the first time this type of procedure was done in a gynecologic case with a vaginal melanoma.

The incidence of perioperative complications is relatively high, ranging between 32% and 84%.[11] It is also associated with a significant rate of both major (40-50%) and minor (80%) complications. Forty-five percent of patients may require at least one readmission to the hospital, while only 32% required additional operative procedures.[11] Mortality rate is 1-16% commonly caused by sepsis, thromboembolic disease, and cardiopulmonary failure. Inevitable risks are also encountered due to the extensive nature of the surgery, blood loss, fluid shifts, and operative time. Infection is still the most common cause of morbidity reaching as high as 86% followed by urinary and wound infections. Also, anastomotic leaks and fistulae from either diverting system are frequent at 8-36%. Fortunately, most leaks can be handled conservatively with prolonged conduit drainage and, if needed, the urine stream may be diverted with percutaneous nephrostomy tubes.[11] Ileal conduit has been considered the "standard" urinary diversion method for most patients. It is the most clinically adequate, reliable, and cost-effective solution. In addition, small bowel and ureteral obstructions also occur in about 5-10% of patients. But in general, most of these complications

can be managed conservatively, although a significant number of patients require operative revisions.

Since a vital consideration in this procedure is the occurrence of complications, a study was done by Baiocchi et al in patients who underwent pelvic exenteration for gynecologic cases. The findings concluded that pelvic exenteration has a satisfactory morbidity and mortality and may be the only method that can offer long term survival in highly selected patients.[10] In the case previously presented, due to bladder involvement and high recurrence rate, pelvic exenteration should be done. Although the patient is already old, pelvic exenteration is a long procedure, complications are common, blood loss is extensive and a significant fluid shift may occur, these are greatly outweighed by the benefits of performing the procedure. Most importantly, the preoperative evaluation and discussion with the patient should be prioritized.

In conclusion, vaginal melanoma is a rare yet very aggressive type of cancer. Early identification and prompt aggressive treatment is beneficial to improve the prognosis of the patient. Although, there has been no consensus as to what is the ideal management of patients with primary vaginal melanoma, surgery (pelvic exenteration) or an extirpative approach remains to be the most favorable. However, this approach does not always guarantee success in management because of its inherent complications that maybe encountered intra and post-operatively, that is why proper preparation is crucial. Hence, primary vaginal melanomas should be managed individually according to the patient's medical status, institutional capabilities and tumor stage.

References

1. Takehara K, Nakamura H, Mizunoe T and Nogawa T. Primary malignant melanoma of the vagina with a survival of longer than 5 years after recurrence: Case report and review of the literature.
2. Katz VL, Lentz GM, Lobo RA, Gershenson DM, Katz: Comprehensive Gynecology, 5th ed.
3. Lin LT, Liu CB, Chen SN, Chiang AJ, Lioua WC, Yu KJ. Primary malignant melanoma of the vagina with repeated localrecurrence and brain metastasis. February 21, 2011
4. Mihajlovic M, Vlajkovic S, Jovanovic P, Stefanovic V. Primary mucosal melanomas: a comprehensive review. September 4, 2012.
5. Kumar V, Abbas AK, Fausto N and Aster J. Robbins & Cotran Pathologic Basis of Disease, 8th Edition
6. Takehara K, Nakamura H, Mizunoe T and Nogawa T. Primary malignant melanoma of the vagina with a survival of longerthan 5 years after recurrence: Case report and review of the literature.
7. Huang Q, Huang H, Wan T, Deng T, Liu J. Clinical outcome of 31 patients with primary malignant melanoma of the vagina.
8. Diver EJ, Rauh-Hain A and del Carmen MG. Total pelvic exenteration for gynecologic malignancies. Int J Surg Oncol 2012; (2012), Article ID 693535, 9 pageshttp://dx.doi.org/10.1155/2012/693535
9. Benedet JL, Ngan HYS , Hacker NF. Staging classifications and clinical practice guidelines of gynaecologic cancers.
10. Baiocchi G1, Guimaraes GC, Rosa Oliveira RA, Kumagai LY, Faloppa CC, Aguiar S, Begnami MD, Soares FA, Lopes A. Prognostic factors in pelvic exenteration for gynecological malignancies. Eur J Surg Oncol. 2012 Oct;38(10):948-54. doi: 10.1016/j.ejso.2012.07.002. Epub 2012 Jul 18.
11. Pawlik TM, Skibber JM and Rodriguez-Bigas MA. Pelvic exenteration for advanced pelvic malignancies. Educational review.

Ewing Sarcoma of the Vulva*

Charlene M. Flores, MD and Filomena S. San Juan, MD, PhD, FPOGS, FSGOP, FPSCPC

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

Ewing sarcoma is a very aggressive malignant neoplasm that often originates in the skeletal system. Primary extraskeletal Ewing sarcoma is uncommon and tumors arising from the vulva extremely rare with only 20 reported cases in literature to date. Reported here is another case of Ewing sarcoma that presented as a vulvar mass in a 24-year old multigravida. Characteristic histologic features of Ewing sarcoma were present, including a population of small round cells and positive immunohistochemical staining for CD99 and FLI-1. The patient underwent wide local excision with bilateral groin node dissection but refused adjuvant therapy. About 1 year and 3 months after surgery, she developed lung and bone metastases. Published literature regarding differential diagnoses, clinical presentation, management, and prognosis of vulvar Ewing sarcoma were also reviewed.

Key words: Ewing sarcoma, vulva

Ewing sarcoma (ES) is an aggressive malignant neoplasm described in 1921 by James Ewing as a primary tumor of bone in a 14-year old girl. It is composed of uniform small round cells that undergo neuroectodermal differentiation. ES most commonly arise in young patients and usually occur in the skeletal system, which is the classic ES. Extraskeletal sites are uncommon, with reports involving the soft tissues of lower extremities, paravertebral region, chest wall and pelvis. The female genital tract is an unusual site for ES. Cases involving the vulva are extremely rare, only 20 cases have been reported to date.

ES in an uncommon location can pose a diagnostic dilemma because they morphologically resemble other small round cell tumors. Immunohistochemical analysis is the most reliable aid in the differential diagnosis, and demonstration of characteristic chromosomal translocation thru molecular techniques is definitive for diagnosis. Presented here in is a case of a 24-year old diagnosed with Ewing sarcoma of the vulva.

The Case

A 24-year old, gravida 2 para 2, from Bicol with no significant medical history presented with a one-year history of an enlarging painless mass on the vulva. There were no abnormal findings in the systemic examination and no palpable inguinal lymph nodes. On pelvic examination, there was an 8cm x 6cm, soft-pink, solid mass arising from the right labium minus, involving the clitoris, and extending superiorly to the left labium minus up to the middle portion. (Figure 1) There was no involvement of the labia majora, urethra,

* Third place, 2015 SGOP Interesting Case Contest

perineum or vagina. The rest of the pelvic examination was unremarkable. Colposcopy revealed normal findings. Transvaginal sonography showed a 7.8cm x 5.8cm x 4.7cm irregular heterogenous solid mass arising from the right labium minus. Color flow mapping of the mass showed moderate central vascularity which on Doppler interrogation revealed low resistance indices. Chest radiograph and abdominal computed tomography did not reveal any tumor. An incisional biopsy was positive for atypical cells, malignancy considered. She was referred to a Gynecologic Oncologist, where repeat biopsy showed malignant small round cell tumor. Considerations were rhabdomyosarcoma, non-Hodgkin lymphoma and primitive neuroectodermal tumor, among other possibilities. She then underwent wide local excision and bilateral groin node dissection.

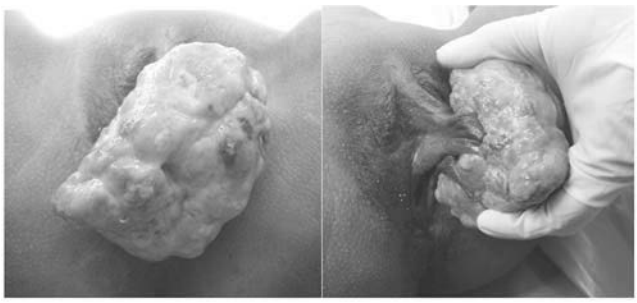

Figure 1. Gross appearance of ewing sarcoma of the vulva. The vulvar mass measured 8cm x 6cm, soft-pink, solid, arising from the right labia minora.

The excised tumor was solid and measured 8.5cm x 6.5cm x 6cm, which on cut section showed cream-white tissue with areas of hemorrhage and necrosis. (Figure 2) Hematoxylin and eosin-stained sections showed an infiltrating proliferation of small round blue cells with a sheet like growth pattern. Some variably sized areas of necrosis were noted. (Figure 3a) Higher power view showed monomorphic tumor cells with a high nuclear-cytoplasmic ratio and inconspicuous cytoplasm with a cellular size 1 to 1.5 times that of a small mature lymphocyte. (Figure 3b) No rosette formation was observed. The chromatin was coarse, the nucleoli were inconspicuous and no nuclear molding was observed. Mitotic figures were present. The tumor showed diffuse positive immunohistochemical staining with a membranous pattern for CD99 (Figure 4a) and positive staining with nuclear location for FLI-1. (Figure 4b) It was negative for leukocyte common antigen/LCA, cytokeratin, synaptophysin, chromogranin, desmin and muscle actin. Resection line was positive for tumor; all lymph nodes submitted were negative. Histopathologic diagnosis was consistent with Ewing sarcoma. Molecular confirmation was not performed because it was not available in the country.

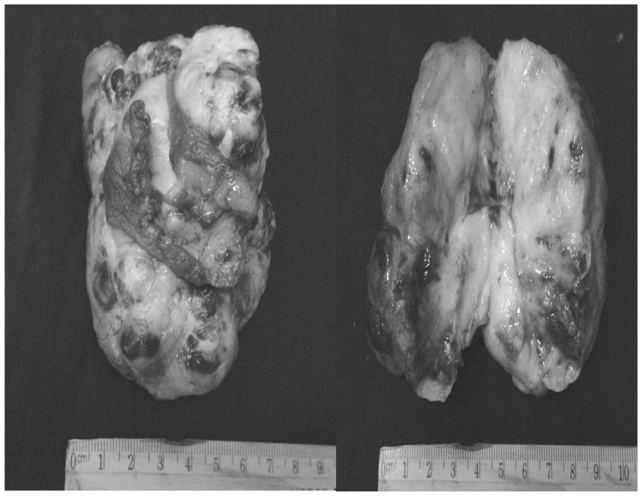

Figure 2. The excised tumor measured 8.5cm x 6.5cm x 6 cm, solid, with areas of hemorrhage and necrosis.

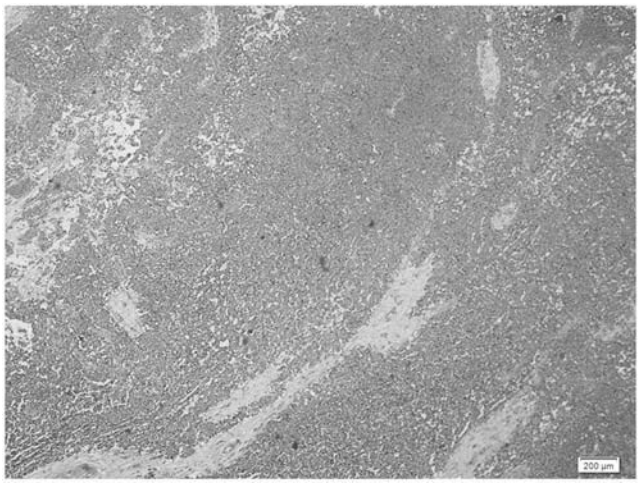

Figure 3a. Scanning view: Tumor shows an infiltrating proliferation of small round cells with a sheet like growth pattern and areas of necrosis.

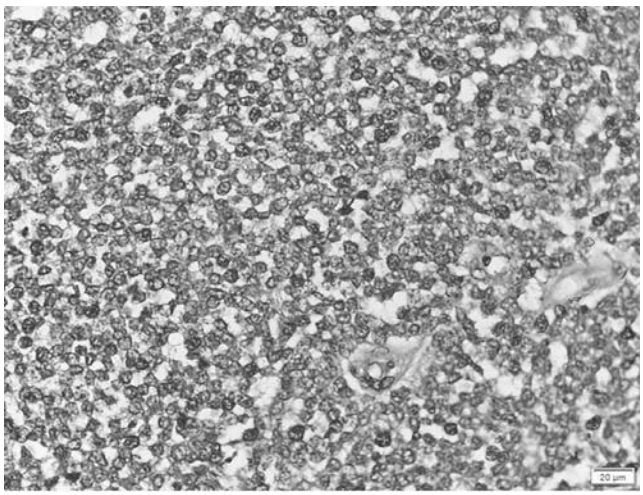

Figure 3b. High power view: Monomorphic small round cells with a high nuclear-cytoplasmic ratio, coarse chromatin and inconspicuous cytoplasm. No rosette formation observed.

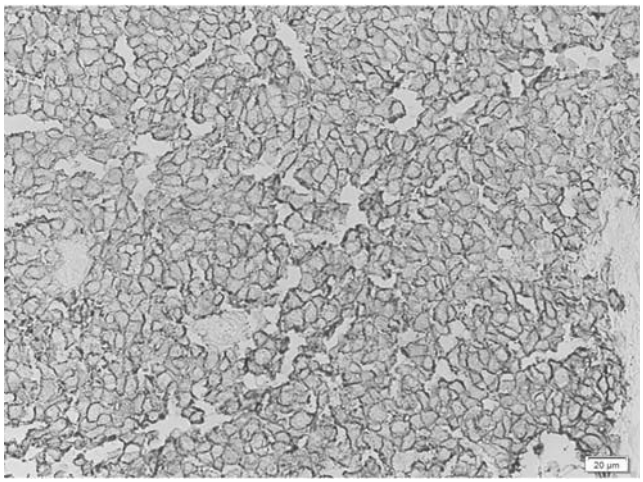

Figure 4a. Diffuse-positive membranous staining with CD99.

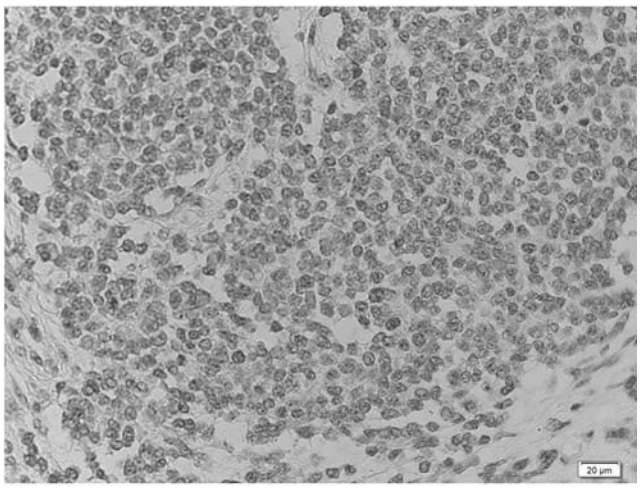

Figure 4b. Diffuse-positive nuclear staining with FLI-1.

The patient was diagnosed with Ewing sarcoma of the vulva, stage IB. Plan was for alternating courses of 1) vincristine, doxorubicin, cyclophosphamide, actinomycin and 2) etoposide, ifosfamide chemotherapy every 3 weeks, to be followed by radiation therapy. However, the patient refused to undergo further treatment due to geographic and financial constraints. Patient developed lung and bone metastases one year and 3 months after surgery. She is alive up to the present time and still refused treatment.

Discussion

Ewing sarcoma (ES) of the vulva is extremely rare. Literature search returns only 20 reported cases, more than half of which have not had molecular confirmation. The Section of Gynecologic Oncology in a tertiary government hospital in the Philippines had 76 cases of vulvar and vaginal cancer from 2010-2014.[1] None reported ES on histopathologic diagnosis making this case the first documented ES of the vulva in the country.

Historically, ES has been interchangeably referred to as primitive neuroectodermal tumor (PNET); both are now collectively referred to as Ewing sarcoma family of tumors (ESFT) because they share similar morphological features and chromosomal translocation.[2] The two differ primarily by the extent of neuroectodermal differentiation, ES is an undifferentiated tumor whereas PNET shows neuroectodermal differentiation.[3,4]

ES/PNET is typically diagnosed based on histologic features and immunohistochemical staining profile in addition to clinical symptoms. These neoplasms are composed of solid sheets of primitive small round blue cells, are uniform sized and have hyperchromatic nuclei and scant cytoplasms.[5] ES is characterized by the absence of Homer Wright rosettes, a specific marker for neuroectodermal differentiation.[6] On the other hand, PNETs exhibit neural differentiation by rosette formation.[5]

The diagnosis of ES/PNET in unusual sites is challenging because of overlapping clinical, histologic and immunophenotypic features with other small round cell tumors, which include neuroblastoma, rhabdomyosarcoma, lymphomas, and leukemias. In the

vulva, considerations should also be given to small cell neuroendocrine carcinoma, undifferentiated carcinoma, small cell non-keratinizing squamous carcinoma, malignant melanoma, and Merkel cell carcinoma.

ES/PNET neoplasms are usually diagnosed after exclusion of other small round cell tumors through judicious use of panel of tumor markers. The initial immunohistochemical panel for small round cell tumors usually includes: vimentin, keratin, desmin, synaptophysin, S-100, neuron-specific enolase (NSE), chromogranin, leukocyte common antigen (LCA), and CD99.[3] In recent years, CD99 and FLI-1 immunohistochemical analysis have emerged to be useful in diagnosing ES/PNET. CD99 is a cell surface glycoprotein, encoded by the MIC2 gene and expressed with a membranous staining distribution in almost all ES/PNET.[7,8] However, CD99 is not specific for ESFT and may be expressed in other malignancies, such as rhabdomyosarcoma, neuroblastoma, some lymphomas and leukemias, Merkel cell carcinoma, mesenchymal chondrosarcoma, small cell neuroendocrine carcinoma, and synovial sarcoma. FLI-1, meanwhile, is normally expressed in endothelial cells and hematopoietic cells including T lymphocytes.[9] It is a DNA-binding transcription factor involved in cellular proliferation, tumorigenesis, and endothelial differentiation. It is expressed as nuclear staining in majority of ESFT and lymphoblastic leukemia and is occasionally positive in Merkel cell carcinoma, neuroblastoma, synovial sarcoma, malignant peripheral nerve sheath tumor, and malignant melanoma.[7,10]

CD99 is a very sensitive marker but lacks specificity.[6,10] FLI-1 is less sensitive (71%) than CD99 but appears to be more specific (92%) for ESFT.[6,9] Thus, the combination of positive immunostaining for CD99 and FLI-1 improves specificity for diagnosis of ESFT.[9] ES may also stain with cytokeratins, which may result in an erroneous diagnosis of epithelial neoplasm especially in sites such as the vulva or vagina.[7] The lack of expression of cytokeratins, desmin, smooth muscle actin (SMA), S-100, synaptophysin and chromogranin are pertinent negative findings to exclude other small round blue cell tumors.[6]

Molecular confirmation of the characteristic translocation is regarded as the gold standard for diagnosis. More than 90% of ES/PNET neoplasms harbor the same t(11;22) (q24;q12) chromosomal translocation, leading to fusion of the EWS gene on chromosome 22 to the FLI-1 gene on chromosome 11.[7] This translocation is specific for ES/PNET and is not found in other small round cell tumors.[3] In less than 10% of cases, translocation is t(21;22)(q22;q12), where the EWS gene is fused with ERG gene. The EWS/FL1 and EWS/ERG fusion proteins can be demonstrated by RT-PCR from mRNA isolated from fresh or formalin-fixed paraffin-embedded tissue or by fluorescence in situ hybridization (FISH) analysis.[3] These fusion proteins are present in both ES and PNET, hence the designation of "Ewing sarcoma family of tumors.[6]

ESFTs with classic morphology and are positive for CD99 and FLI-1 immunostaining may be diagnosed without molecular confirmation, which is available only in specialist molecular pathology laboratories. The characteristic t(21;22)(q22;q12) translocation in ES/PNET leads to overexpression of FLI-1 protein; its detection may therefore be a valuable technique for identification of ES/PNET in cases when genetic evaluation is not feasible. However, molecular techniques are prudent in the diagnosis of neoplasms with unusual morphological features and in suspected cases at unusual sites.

ES in the female genital tract has rarely been described to occur in vulva, vagina, cervix, uterine corpus, ovary, broad ligament and rectovaginal septum.[2,11] In the uterus, some of these neoplasms include a component of an endometrial adenocarcinoma and may be viewed as carcinosarcoma, in which the sarcomatous element belongs to ES. In the ovary, a single case has been reported with immunohistochemical and molecular confirmation. Ovarian PNETs have also been described as part of a teratomatous neoplasm but these are generally CD99 negative and do not harbor the characteristic chromosomal translocations of ESFT. A single case of PNET in the broad ligament and several cases in the cervix with molecular confirmation have also been reported.[7]

Data on 21 reported cases of vulvar ES/PNET including the current case are shown in Appendix IV. Most cases were found in young women, ages ranging from 10 to 60 years and an average of 25 years. They

all presented with solid masses ranging from 0.9 to 20 cm in size. CD99 and FLI-1 were performed in 17 (81%) and 6 (29%) of cases, respectively. Negative staining of CD99 and FLI-1 were identified in only one case each, with CD99 virtually positive in all cases. Molecular confirmation (RT-PCR and/or FISH) was done in less than half of the cases (43%). Almost all of the patients underwent surgery, 15 (71%) of which received adjuvant therapy, consisting of either combined chemotherapy and radiotherapy or chemotherapy alone. Of the 18 patients with available follow-up, 10 (56%) had documented recurrence. Eight (38%) had distant metastasis, 88% of which were pulmonary and 25% with bone metastasis. Two (9.5%) had local recurrence of disease. Six (29%) patients were documented to have died in less than one year. Follow-up data was relatively short to determine outcome of vulvar ES compared to other tumors of ESFT.

Due to its rarity, no standard therapy exists for vulvar ES. Management of extraskeletal ES (i.e. lung, vulva) is usually in accordance with skeletal ES protocol. The recommended treatment includes complete surgical excision followed by aggressive chemotherapy and radiotherapy if indicated. Review has shown more favorable prognosis among patients who have undergone surgical resection.

The chemotherapy used in the treatment of vulvar ES is patterned to the high-risk protocol for skeletal ES. The intergroup Ewing's sarcoma study and Cooperative Ewing Sarcoma Study recommend using doxorubicin, cyclophosphamide, vincristine, actinomycin, alternating with ifosfamide and etoposide.[12] The introduction of chemotherapy for patients with localized tumors improved the survival rate of ES from 10% to 75%. Neoadjuvant chemotherapy is considered as a further therapy option. However, it is uncertain if this treatment approach results in a favorable outcome.[4]

ES originating in the bones (skeletal ES) shows an aggressive behavior with rapid metastasis and poor prognosis.[3] Approximately 25% of patients have detectable metastatic lesions commonly pulmonary at diagnosis. Literature suggests a relatively favorable outcome for extraskeletal ES or peripheral PNET arising in cutaneous and superficial sites, as this may be associated with smaller size, superficial location, early detection and complete surgical removal of the lesion.[13] Long-term survival is possible with complete resection of the tumor followed by combined adjuvant treatment. Review of older publications indicates an overall survival of only 30% for skeletal ES and 65-70% for extraskeletal ES.[9] Five-year survival rate for patients with recurrence at local sites was 31.4% (SD: 11.6) in the surgical group and 9.1% (SD: 6.1) in the non-surgical group. However, the rarity of cases and poor patient follow-up make it difficult to ascertain the prognosis and effect of therapy in vulvar ES.

Poor prognostic factors in ESFT include age at presentation >15 years, lesions in the body trunk, larger tumor volume (>200 mL or >8 cm), presence of distant metastasis, high levels of serum lactate dehydrogenase, poor response to chemotherapy and recurrence within two years.[5,9] Most unfavorable is the presence of distant metastasis with only 20% chance of long-term survival even with aggressive treatment.[5,9]

In the present case, differential diagnoses of a small round cell tumor include neuroblastoma, rhabdomyosarcoma, lymphoma, small cell neuroendocrine carcinoma, undifferentiated carcinoma, small cell non-keratinizing squamous carcinoma and Merkel cell carcinoma. Rhabdomyosarcoma and neuroblastoma are common in children and thus not highly considered given the age of our patient. Prudent use of panel of markers had helped us further exclude other small round cell tumors (see Appendix 2). Positive membranous staining for CD99 and nuclear staining for FLI-1 extremely favored Ewing sarcoma. Lymphoma was excluded, as the tumor was negative for LCA/CD45. Neuroblastoma was also excluded as the tumor stained positive for CD99 and negative for synaptophysin and rhabdomyosarcoma was disregarded due to the absence of desmin and muscle actin on staining. Neuroendocrine tumors and Merkel cell carcinoma were disregarded due to negative staining for synaptophysin and chromogranin. Molecular confirmation was not performed due to its unavailability in the country.

The characteristic histopathology, CD99 and FLI-1 positivity and negative staining with a wide range of other markers made the diagnosis of ES likely correct and excluded other differentials. Given the propensity

of the disease for pulmonary metastasis and the patient's high risk for local recurrence (positive resection margin), adjuvant chemotherapy followed by radiotherapy was advised. However, our patient was treated by surgery alone and did not consent to adjuvant therapy due to geographic and financial constraints. She developed lung and bone metastases one year and three months after surgery. She is still alive to date (1 year 7 months post surgery) but the occurrence of distant metastases seems to signify a grave prognosis, as evidenced in the cases reported elsewhere.

Conclusion

Ewing sarcoma/primitive neuroectodermal tumor of the vulva (ES/PNET) is a very rare aggressive small round cell neoplasm. An appropriate panel of

Appendix 1. Reported cases of ewing sarcoma/Pnet of the vulva

Authors	Age	Site/Size	Treatment	IHC	Molecular	Metastases	Follow-up
Habib et al, 1992	23	Vulva	None	None	None	NA	NA
Scherr et al, 1994	10	Left labium major, 6.5 cm	Surgery	CD99	None	NA	NA
Nirenberg et al, 1995	20	Right labium major, 12 cm	Surgery, chemotherapy, radiation	(-)CD99	None	NA	DOD, 10 months
Paredes et al, 1995	29	Left vulva, 5 cm	Surgery, chemotherapy, radiation	None*	None	None	NED, 8 months
Vang et al, 2000	28	Right labium minor, 0.9 cm	Surgery, chemotherapy	CD99	RT-PCR	None	NED, 18 months
Lazure et al, 2001	15	Vulva, 20 cm	Surgery, chemotherapy	CD99	RT-PCR	None	NED, 7 months
Takeshima et al, 2001	45	Right labium major, 3 cm	Surgery	CD99	None	Local recurrence	3 years (alive)
Moodley et al, 2005	26	Right labium major, 5 cm	Surgery, chemotherapy, radiation	None	None	Pulmonary	DOD within short period of time
McCluggage et al, 2007	40	Right labium minor, 3 cm	Surgery, chemotherapy	CD99, FLI-1	FISH	None	NED, 12 months
McCluggage et al, 2007	20	Right labium, 6.5 cm	Surgery	CD99, FLI-1	FISH	Pulmonary	DOD
McCluggage et al, 2007	19	Vulva, 4 cm	Surgery, chemotherapy	CD99, (-)FLI-1	RT-PCR (-)FISH	NA	NA
Fong et al, 2008	17	Left vulva	Excisional biopsy, chemotherapy	CD99, FLI-1	RT-PCR	None	NED, 2 years
Centiner et al, 2009	23	Left labium major, 6 cm	Surgery, chemotherapy, radiation	CD99	RT-PCR	None	NED, 7 years
Centiner et al, 2009	29	Left vulva, 1 cm	Surgery, chemotherapy	CD99	(-)RT-PCR	None	NED, 4 years
Dadhwal et al, 2009	20	Right labium major, 20 x 15 x 10 cm	Surgery	CD99	None	Pulmonary	DOD within 20 days after surgery
Halil et al, 2011	14	Left vulva	Surgery, chemotherapy, radiation	NA	NA	Pulmonary	DOD, 9 months
Kelling et al, 2011	18	Right labium major, 1.7 cm residual tumor	Surgery, chemotherapy, radiation	CD99	FISH	Pulmonary	3 months (alive)
Anastasiades et al, 2012	28	Left labium minor, 3 cm	Surgery, chemotherapy, radiation	CD99	None	Bone	DOD, 1 year
Shao-Min Che et al, 2013	37	Left vulva, 5 cm	Surgery, chemotherapy	CD99, FLI-1	None	Pulmonary	Stable disease, 7 months
Matsuda et al, 2014	60	Right vulva	Surgery, chemotherapy, radiation	CD99	None	Local recurrence	NED, 4 years
Present case, 2015	24	Right labium minor, 8.5 cm	Surgery	CD99, FLI-1	None	Bone and pulmonary	1 year and 7 months, alive

*Panel of markers done except for CD99 and/or FLI-1
RT-PCR – reverse transcriptase polymerase chain reaction
FISH – fluorescent in situ hybridization
NA – not available
NED – no evidence of disease
DOD – dead of disease

Appendix V. Immunohistochemistry results.

Tumor Marker	Small Round Cell Tumor Differentials	Case Result
CD99	Ewing sarcoma/PNET, lymphoma/leukemia, rhabdomyosarcoma, neuroblastoma, Merkel cell carcinoma	Positive
FLI-1	Ewing sarcoma/PNET, lymphoblastic leukemia	Positive
Leukocyte common antigen (LCA) / CD45	Lymphoma/leukemia	Negative
Cytokeratin	Small cell squamous carcinoma	Negative
Synaptophysin	Small cell neuroendocrine carcinoma, neuroblastoma, PNET, rhabdomyosarcoma, Merkel cell carcinoma	Negative
Chromogranin	Neuroendocrine carcinoma, PNET, Merkel cell carcinoma	Negative
Desmin	Rhabdomyosarcoma	Negative
Muscle actin	Rhabdomyosarcoma	Negative

immunohistochemical stains is crucial in excluding other small round cell tumors in the vulva and molecular confirmation, if necessary, should be performed for accurate diagnosis and appropriate management. Metastatic disease, mainly pulmonary, rather than local recurrence seems to be the main cause of mortality. Complete surgical resection and adjuvant therapy may prolong survival but it is difficult to draw any statistically significant conclusions regarding ideal treatment modality and prognosis given the small number of reported cases.

References

1. Section of Gynecologic Oncology. Department of Obstetrics and Gynecology. Philippine General Hospital. Annual Report 2010-14.
2. Fong YE, López-Terrada D, Zhai QJ. Primary Ewing sarcoma/peripheral primitive neuroectodermal tumor of the vulva. Human Pathology 2008; 39(10): 1535-9.
3. Cetiner H, Kir G, Gelmann EP, et al. Primary vulvar Ewing sarcoma/primitive neuroectodermal tumor: a report of 2 cases and review of the literature. Int J Gynecol Cancer 2009; 19(6): 1131-6.
4. Kelling K, Noack F, Altgassen C, et al. Primary metastasized extraskeletal Ewing sarcoma of the vulva: report of a case and review of the literature. Arch Gynecol Obstet 2012; 285(3): 785-9.
5. Matsuda M, Ichimura T, Kasai M, et al. Primitive neuroectodermal tumor originating in the vulva: a case report. Oncology Letters 2014; 8(1): 187-9.
6. Anastasiades EN, El Abiad SA, Chouairy CJ. Ewing sarcoma/primitive neuroectodermal tumor (PNET) of the vulva. Case report and review of the literature. The Lebanese Medical Journal 2012;60(2):113-6.
7. McCluggage WG, Sumathi VP, Nucci MR, et al. Ewing family of tumours involving the vulva and vagina: report of a series of four cases. J Clin Pathol 2007; 60: 674-80.
8. Che SM, Cao PL, Chan HW, et al. Primary Ewing's sarcoma of vulva: a case report and a review of the literature. J Obstet Gynaecol Res 2013; 39(3): 746-9.
9. Pinto A, Dickman P, Parham D. Pathobiologic markers of the Ewing sarcoma family of tumors: state of the art and prediction of behavior. Sarcoma 2011; Article ID 856190, 1-15.
10. Dadhwal V, Bahadur A, Gupta R, et al. Peripheral neuroectodermal tumor of the vulva: a case report. The Journal Lower Genital Tract Disease 2010;14(1):59-62.
11. Moodley M, Jordaan A. Ewing's sarcoma of the vulva - a case report. International Journal of Gynecological Cancer. 2005; 15(6): 1177-8.
12. Jain S, Kapoor G. Chemotherapy in Ewing's sarcoma. Indian J Orthop 2010; 44: 369-77.
13. Liao X, Xin A, Lü X. Primary Ewing's sarcoma-primitive neuroecto-dermal tumor of the vagina. Gynecol Oncol 2004; 94: 684-8.