Tumor Ploidy in Epithelial Ovarian Tumors: A Preliminary Report*

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Ovarian cancer is the second most common gynecologic malignancy of the female genital tract. It is the tenth leading cancer site for both sexes combined and the fifth among women in the Philippines. Survival is poor and usually predicted by the extent of the disease at the time of diagnosis. Established prognostic factors have significant limitations due to their subjectivity and lack of reproducibility. The search for additional prognostic factors that can be more objectively measured has intensified. DNA ploidy is a frequently investigated independent prognostic factor for epithelial ovarian cancer. The aim of this study was to determine the ploidy characteristics of epithelial ovarian cancers and correlate it with different clinicopathologic variables.

Methods: One hundred ninety four patients with a final histopathologic result of epithelial ovarian cancers were included. DNA ploidy was determined using flow cytometry of paraffin embedded blocks at another institution.

Results: In the 194 paraffin-embedded blocks of the epithelial ovarian tumors included in the study, DNA ploidy was obtained. Aneuploidy was established in 14 (7.22%) epithelial ovarian tumors. The average age of patients with aneuploid pattern was 48.64. Most of the patients were nulligravid (71.43%). The largest tumor size was 40 cm in its widest diameter and the smallest was 8 cm. Aneuploidy was not significantly associated with histopathologic type. Most of the patients with aneuploidy had an intraoperative and final stage of I (50%), followed by II (21.43%), III (14.29%), and IV (14.29%).

Conclusion: Results showed that aneuploidy is found in older age and that most patients were nulligravid. There was no correlation between aneuploidy and the rest of the clinicopathologic variables identified such as tumor size, histopathologic type and stage. In view of the small numbers of epithelial ovarian cancer with aneuploid profiles, these findings cannot be definitely analyzed until the completion of the sample size is attained.

Key words: Epithelial ovarian cancer, tumor ploidy, flow cytometry

* First Place, 2011 SGOP Fellows' and Residents' Research Contest.

Ovarian cancer is the second most common gynecologic malignancy of the female genital tract.[1] It is the tenth leading cancer site for both sexes combined and the fifth among women in the Philippines. It is one of the most frequent causes of cancer deaths among women and its mortality rate is higher than the combined mortality rates of cervical and endometrial cancers.[2] Two thirds of the ovarian neoplasms are epithelial tumors and in general, its incidence varies from 9 to 17 out of 100,000.[1,3] The initial symptoms are usually non-specific and most patients present with advanced disease.[4] Survival is poor and usually predicted by the extent of the disease at the time of diagnosis.[5] The International Federation of Gynecology and Obstetrics (FIGO) stages I and II account for 20% to 40% of all cases of epithelial ovarian cancer. The five year survival rates range from 60% to 95% for stage I and from 35% to 70% for stage II.[6] The main prognostic factors in early ovarian cancer mostly identified were FIGO stage, histologic type, histologic grade, amount of residual tumor, age and performance status. Most of these have significant limitations due to their subjectivity and lack of reproducibility.[7,8] As a result, the search for additional prognostic factors that can be more objectively measured has intensified.

One of the most frequently investigated independent prognostic factors for epithelial ovarian cancer is the determination of DNA ploidy.[9] Klemi, et al. in their study on the clinical significance of abnormal nuclear DNA content in serous ovarian tumors concluded that DNA ploidy can be a highly valuable and objective prognostic parameter.[10] Similarly, previous studies have shown that DNA ploidy adds independent prognostic information to the established prognostic factors such as FIGO stage and grade.[9]

Ploidy is usually assessed by flow cytometry, which can also measure the number of S-phase of the mitotic cycle. It can also be assessed by less commonly used technique of static image cytometry in which the DNA content is measured via an image analysis system. Although there is a good correlation between ploidy results obtained from flow and static image cytometry, the static image technique allows for identification of small populations of aneuploid tumor cells that may be missed on flow cytometry. However, most reported studies on DNA ploidy among gynecologic malignancies utilized flow cytometry.

Flow cytometry is a simple and rapid technique of measuring cellular DNA content which can be used on both fresh and archival tissue. It allows for tumors to be classified in general terms, as either diploid or aneuploid. Either cells are dissociated from tumors by mechanical or enzymatic techniques or recovered from paraffin blocks, stained with a fluorochrome dye that binds specifically and stoichiometrically with nucleic acids and then passed through a flow cytometer in a liquid suspension medium as a laminar flow jet. Flow cytometers measure and record fluorescence and light scatter in the cells and the fluorescence of the stained cells is converted into a digital electronic signal: the results are shown as a histogram in which the number of stained cells is plotted as a function of intensity of the fluorescence. If the main peak of the DNA histogram center around the 2C region and the overall DNA distribution is comparable to that of normal somatic cells, the tumor is classified as diploid. Populations of cells with DNA content dissimilar to that of normal cells are classed as aneuploid and these may be hypodiploid, hyperdiploid or tetraploid. The DNA index (DI) is calculated by dividing the modal DNA content of the tumor cells in G0/G1 phases of the mitotic cycle: diploid cells having a DI of 1 while aneuploid having a DI of less than 1, more than 1, or of tetraploid.[11,12,13] This technique can detect aneuploidy only if a significant proportion of the tumor cells have lost or duplicated several chromosomes. Other variables that should be taken into consideration when utilizing this technique are the method of extraction and staining of the nuclei, delays in tissue fixation, intra and interlaboratory variability, the minimum number and proportion of tumor cells analyzed, the choice of the reference cell population, the program for debris correction and more importantly, tumor heterogeneity.[13]

In order to demonstrate the significance of the determination of DNA ploidy among epithelial ovarian tumors, this study performed a flow cytometric DNA analysis among these tumors and compared aneuploidy with other established clinicopathologic variables such as age, tumor size, histopathologic type and age.

General Objective

The general objective of the study was to determine the ploidy characteristics of epithelial ovarian cancers.

Specific Objectives

1. To determine the prevalence of epithelial ovarian cancers
2. To determine the clinical profile of patients with epithelial ovarian cancers
3. To determine the prevalence of aneuploidy of epithelial ovarian cancers
4. To determine the association of age and aneuploidy
5. To determine the association of tumor size and aneuploidy
6. To determine the association of histologic type and aneuploidy
7. To determine the association of stage and aneuploidy

Materials and Methods

Patient Population

The inclusion criteria of this study comprised of patients with a final histopathology of epithelial ovarian cancer who underwent exploratory laparotomy and were surgically-staged based on the FIGO classification. In addition, the paraffin blocks representative of the tumor should have been available for flow cytometry analysis. These patients should not have received prior treatment (surgery, chemotherapy, radiotherapy, hormonal therapy) for any malignancy. Patients with a concomitant malignancy and who received any treatment (surgery, chemotherapy, radiotherapy, hormonal therapy) for a previous or current malignancy were excluded from the study.

Methodology

Data Collection

The list and registry of epithelial ovarian cancer cases from 2004 to June 2011 were obtained and reviewed from the surgico-pathologic census and weekly ward reports of the Department of Obstetrics and Gynecology in a tertiary hospital. A total of 194 patients with a final histopathologic result of epithelial ovarian cancers were included with the following distribution: 49 mucinous cystadenocarcinoma, 49 mucinous tumors of low malignant potential, 44 serous cystadenocarcinoma, 4 serous tumors of low malignant potential, and 48 endometrioid adenocarcinoma. Epithelial ovarian cancer tumor type was documented according to the World Health Organization classification. Clinical data were obtained from the Medical Records Section, documents from the Cancer Institute and the Surgical Pathology Census of the Department of Obstetrics and Gynecology. Clinical data were retrospectively analyzed and recorded. The patient characteristics retrieved were age, gravidity, tumor size, intraoperative and final stage based on the International Federation of Gynecology and Obstetrics. Histopathologic reports, paraffin blocks and their corresponding slides were retrieved from the Surgical Pathology Section and were sent to the Histopathology/Immunology Section of another institution for review and tumor ploidy testing using flow cytometry.

DNA Ploidy by Flow Cytometry and Analysis

Briefly, a monodispersed cell suspension was prepared from physical and chemical disruption of 5 strips of 50 micron section from paraffin embedded tissue, previously microdissected for tumor cell enrichment. The resulting cell suspension was incubated simultaneously with RNAse to remove RNA and Propidium iodide for DNA staining. The tissue sections were deparaffinized using 3 cycles of xylene incubation and rehydrated with decreasing strengths of ethanol and final incubation in distilled water. The rehydrated sections were enzymetically digested with pepsin incubation at 37°C for 45 minutes after mechanical disaggregation with a glass pestle. The sample was resuspended in RPMI, filtered using a membrane filter and stained with Bauer's salt solution at 37°C for 20 minutes. Room temperature Bauer's salt solution was added and the sample was vortezed and stored at 4°C until flow cytometric analysis.

Flow cytometric analysis of the cell suspension was performed with an excitation wavelength of 342nm-514nm and the resultant emission was measured at 610 nm. DNA histograms were generated and analyzed for diploid and aneuploid peaks. Criteria for aneuploidy included the following:

1. Two or more distinct G0/G1 peaks with the second peak having a DNA index a 0.95 to 1.05.
2. Single G0/G1 peak with right-sided shoulder.
3. G2M peak over 10% of the total population.

Sample Size

The study required 323 patients based on the incidence of aneuploidy in epithelial ovarian cancers of 70%, margin of error of 0.05 and confidence level of 95%.

Statistical Analysis

Univariate analyses were performed to identify and describe the distribution of epithelial ovarian cancer and the clinical profile of the patients included in the study. Frequency distribution, mean, percentage and range were used to describe the clinicopathologic variables and the tumor ploidy characteristics of the patients. The Pearson-r correlation coefficient was employed to determine significant associations between aneuploidy and the clinicopathologic variables.

Results

From 2004 to 2011, 194 patients with primary epithelial ovarian cancer were included in the study. Paraffin blocks were obtained from these with the following distribution: 49 mucinous cystadenocarcinoma, 49 mucinous tumors of low malignant potential, 44 serous cystadenocarcinoma, 4 serous tumors of low malignant potential, and 48 endometrioid adenocarcinoma.

There were 49 patients with a final histopathologic result of mucinous cystadenocarcinoma. The mean age was 40.24 with a range from 18 to 72 years old. The most common symptom experienced by the patients was abdominal mass (34.69%). This was followed by increase in abdominal girth (30.61%), pelvic pain (22.45%), weight loss (6.12%), ascites (4.08%) and edema (2.04%). Majority of the patients had an intraoperative and final stage of IA (63.27%). The rest of the patients had a final stage of IB (2.04%), IC (12.24%), IIIB (4.08%), IIIC (14.29%) and IV (4.08%). The largest tumor size was 60 cm in its widest diameter and the smallest was 8 cm. Most of the tumor sizes were >20cm (69.30%), followed by 11-20cm (28.57%) and <10cm (2.04%).

There were 49 patients with a final histopathologic result of mucinous tumor of low malignant potential. The mean age was 40.24 with a range from 13 to 69 years old. The most common symptom experienced by the patients was increase in abdominal girth (51.02%). This was followed by abdominal mass (42.86%) and pelvic pain (6.12%). Majority of the cases had an intraoperative and final stage of IA (77.55%). The rest of the patients had a final stage of IC (18.37%), IIIA (2.04%) and IV (2.04%). The largest tumor size was 48 cm in its widest diameter and the smallest was 9 cm. Most of the tumor size was >20 cm (79.59%) followed by 11-20 cm (16.33%) and <10 cm (4.08%).

There were 44 patients with a final histopathologic result of serous cystadenocarcinoma. The mean age was 49.41 with a range from 29 to 71 years old. The most common symptom was increase in abdominal girth (43.18%). This was followed by abdominal mass (31.82%), pelvic pain (20.45%) and gastrointestinal symptoms (4.54%). Majority of the patients had an intraoperative and final stage of IIIC (34.09%). The remaining patients had a final stage of IA (4.54%), IC (27.27%), IIB (2.27%), IIC (15.91%), IIIA (2.27%), IIIB (2.27%), IIIC (34.09%) and IV (11.36%). The largest tumor size was 38 cm in its widest diameter and the smallest size was 6 cm. Most of the tumor had a size of 11 to 20 cm (43.18%). This was followed by <10 cm (38.64%) and >20 cm (16.67%).

There were 4 patients with a final histopathologic result of serous tumor of low malignant potential. The mean age was 39.75 with a range from 33 to 53 years old. The most common symptom was increase in abdominal girth (50%), followed by abdominal mass (25%) and pelvic pain (25%). The patients had an intraoperative and final stage of IA (50%) and IC

(50%). The largest tumor size was 32 cm in its widest diameter and the smallest was 12 cm. Half of the samples had a tumor size of >20 cm (50%) and the other half ranged from 11 cm to 20 cm (50%).

There were 48 patients with a final histopathologic result of endometrioid adenocarcinoma. The mean age was 47.42 with a range from 28 to 64 years old. The most common symptom was abdominal mass (37.5%). This was followed by increase in abdominal girth (33.33%), pelvic pain (27.08%) and gastrointestinal symptom (2.08%). Majority of the patients had a final stage of IC (33.33%). The rest of the patients had a final stage of IA (6.25%), IB (4.16%), IIA (4.16%), IIC (10.41%), IIIB (4.16%), IIIC (27.08%) and IV (10.41%). The largest tumor size was 36 cm in its widest diameter and the smallest was 7 cm. Most of the tumor had a size of 11 to 20 cm (50%). This was followed by <10 cm (29.17%) and >20 cm (20.83%).

In the 194 paraffin-embedded blocks of the epithelial ovarian tumors included in the study, DNA ploidy was obtained. Aneuploidy was established in 14 (7.22%) epithelial ovarian tumors (Table 1). The average age of patients with aneuploid pattern was 48.64. The patients ranged in age from 29 to 71 years old. The ages of those with aneuploid DNA profile were found to be slightly older than those with diploid DNA profile (mean = 44.93) (Table 2). Furthermore, the association between aneuploidy and age was proven to be statistically significant as well (Table 3). Most of the patients were nulligravid (71.43%) as compared to the group with diploid pattern wherein only ¼ of the total sample were nulligravid. The largest tumor size was 40 cm in its widest diameter and the smallest was 8 cm. Of the 14 patients with aneuploid pattern, 6 had a tumor size of >20 cm (42.86%), 5 had a tumor size of 11 to 20 cm (35.71%), and 3 had a tumor size of <10 cm (21.43%). This pattern was also similar to the tumor sizes of those with diploid profile. However, no significant statistical association was found between tumor size and aneuploidy. The histopathologic distribution among the 14 epithelial ovarian tumors with aneuploid pattern were as follows: two from 49 mucinous cystadenocarcinoma (4.08%), two from 49 mucinous tumors of low malignant potential (4.08%), five from 44 serous cystadenocarcinoma (11.36%), and five from 48 endometrioid adenocarcinoma (10.42%). There were no aneuploid tumors obtained from serous tumors of low malignant potential. Aneuploidy was not significantly associated with histopathologic type. Most of the patients with aneuploidy had an intraoperative and final stage of I (50%), followed by II (21.43%), III (14.29%), and IV (14.29%). Similar to tumor size and histopathologic type, there was no significant association found between aneuploidy and stage at the time of diagnosis.

Table 1. DNA ploidy classification and clinicopathologic features.

Clinicopathologic Variables	DNA Ploidy Classification	
	Diploid	Aneuploid
Age (mean years)	44.93	48.55
Gravidity	G0 = 43	G0 = 10
Tumor size		
<10 cm	31	3
11-20 cm	62	5
>20 cm	87	6
Histologic type		
Mucinous cystadenocarcinoma	47	2
Mucinous tumor of low malignant potential	47	2
Serous cystadenocarcinoma	39	5
Serous tumor of low malignant potential	4	0
Endometrioid adenocarcinoma	43	5
Stage		
I	117	7
II	12	3
III	28	2
IV	23	2

Discussion

The significance of ploidy among patients with primary epithelial ovarian tumors using flow cytometric DNA analysis in relation to clinical and histopathologic variables were evaluated in a tertiary hospital from 2004 to 2011. DNA ploidy pattern were determined among the paraffin blocks of the 194 ovarian tumors obtained. There were 180 diploid tumors (92.78%) and 14 aneuploid tumors (7.22%).

This preliminary study revealed that there is a significant association between age of the patient and

aneuploidy. Aneuploidy was associated with older age compared to tumors with diploid DNA patterns. This result corresponds to the increasing incidence of ovarian cancer in older patients particularly rising steeply starting at the age of 40.[1,14] This finding is also consistent with the studies of Kaern and Kazlauskaite on ploidy and its relations to clinicopathologic variables, which showed that patients with aneuploid DNA profiles were older than their diploid counterparts.[10,15] In addition, this study revealed that most patients with aneuploid tumors were nulligravid (71.42%) as compared to those with diploid tumors (23.89%). The distributions of tumor size among aneuploid and diploid patterns were almost similar.

Table 2. DNA ploidy and clinicopathologic variables in terms of ratio.

Clinicopathologic Variables	DNA Ploidy Classification	
	Diploid	Aneuploid
Age (mean years)	44.93	48.64
Gravidity	¼	¾
Tumor size	-	-
<10 cm	16/100	2/100
11-20 cm	32/100	3/100
>20 m	47/100	3/100
Histologic Type		
Mucinous cystadenocarcinoma	24/100	1/100
Mucinous tumor of low malignant potential	24/100	1/100
Serous cystadenocarcinoma	20/100	3/100
Serous tumor of low malignant potential	2/100	-
Endometrioid adenocarcinoma	22/100	3/100
Stage		
I	60/100	4/100
II	6/100	2/100
III	14/100	1/100
IV	12/100	1/100

Table 3. Summary of relationship between aneuploidy and clinicopathologic variables.

Clinicopathologic Variables	Coefficient	P-value
Age	0.27	0
Histologic Type	-0.11	0.24
Tumor Size	0.15	0.43
Stage	0.18	0.24

In spite of this, the presence of aneuploidy appeared to have no significant association on tumor size. Previous studies have the same findings and have shown to emphasize the amount of residual tumor left after surgery. [16,17]

The present results showed greater frequency of aneuploidy among patients with serous cystadenocarcinoma and endometroid adenocarcinoma, consistent with previous studies of Silvestrini, et al. Furthermore, findings of this study concurred with the study of Harlow which concluded that only less than one-third of patients with mucinous tumors of low malignant potential show patterns of aneuploidy.[7] However, statistical analysis showed no significant association between DNA ploidy and histopathologic type of tumor. Similarly, Skirnisdottir in his study on prognostic factors of ovarian carcinoma concluded that histopathologic type was not associated with aneuploidy as well as prognosis.[6]

Previous studies have demonstrated that there is a strong association between tumor stage and ploidy, with all diploid tumors being of an early stage, while late-stage tumors were aneuploid.[9,18] These were not consistent with the present findings due to the fact that most of the patients with aneuploid profile had a FIGO stage I disease. There was no association between aneuploidy and stage at diagnosis.

In this study, no correlation was established between aneuploidy with the variables tumor size, histologic type and stage in view of the small numbers of samples with aneuploid profile. Since the required number of samples has not been reached, definite analysis of these variables cannot be made. These findings cannot be used to dismiss further evaluation of the association between clinicopathologic variables and tumor ploidy pending completion of this study.

Summary and Conclusion

The demographic data, clinicopathologic variables and tumor ploidy characteristics of patients with epithelial ovarian carcinoma were presented in this study. Preliminary results showed that there is a strong association between aneuploidy and age. This finding confirms that aneuploidy is found in older patients as compared to those with diploid patterns. Results also

showed that most patients with aneuploid pattern were nulligravid. In this study, there was no correlation between aneuploidy and the rest of the clinicopathologic variables identified such as tumor size, histopathologic type and stage. However, in view of the small numbers of epithelial ovarian cancer with aneuploid profiles, these findings cannot be definitely analyzed until the completion of the sample size is attained. It is therefore recommended that this study be continued to complete the required sample size in order to provide results on the major number of patients and more homogeneous patient's groups with respect to the clinicopathologic variables and its association with tumor ploidy.

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A Five Year Review of the Local Experience on the Response and Outcome of Treatment with Single Agent Carboplatin as an Adjuvant Chemotherapy in Patients with Epithelial Ovarian Carcinoma*

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Over 165,000 women develop ovarian cancer every year, making it the sixth most common cancer in women worldwide. Despite considerable improvement in the treatment of advanced ovarian cancer, the optimization of efficacy and tolerability remains an important issue. Standard treatment involves aggressive debulking surgery followed by adjuvant chemotherapy. The standard postoperative chemotherapy is combination therapy with platinum and paclitaxel. However, results of ICON trials supported that single agent carboplatin is acceptable as first line chemotherapy for ovarian cancer, with its superior toxicity profile and equivalent survival benefit compared with other regimens. No study so far has been done on outcome and response of single agent carboplatin in the treatment of epithelial ovarian carcinoma in this institution, thus, this study aimed to review the outcome of the diagnosed patients with epithelial ovarian carcinoma who were treated with single agent carboplatin AUC 5-7.

Methods: This is a descriptive study which aimed to determine the outcome of patients who were treated with single agent carboplatin AUC 5-7 as a first line treatment for patients with ovarian carcinoma. All patients who were given single agent carboplatin from 2006-2010 were included in the study. Data collection tools were provided in the study to record the demographic characteristics, type of surgery, histology, interval of chemotherapy, adverse reactions, and disease free interval, date of recurrence and progression of disease. Descriptive statistics such as means, medians and range of quantitative variables, e.g., age, body mass index, were computed. For qualitative variables such as occupation, history of disease, proportions were computed. Data were then presented in tables and graphs. STATA version 11 was used to perform the said analyses

Results: There were 67 patients included in the analysis. Forty three patients completed the 6 cycles of chemotherapy. Of these 37 patients (86%) had no evidence of disease and only 6 patients (14%) who initially exhibited no evidence of disease but eventually had recurrence during the study period. Among the 24 patients who did not complete

* Third Place, 2011 SGOP Fellows' and Residents' Research Contest.

the treatment, 14 patients (58%) were lost to follow up and 10 patients (42%) had tumor progression. Patients with borderline serous tumor, endometrioid adenocarcinoma, mucinous carcinoma and well-differentiated type histology had favorable outcome with majority of its population at its early stage resulted with no evidence of disease. Patients with advanced disease stage composed the highest proportion of tumor progression and recurrence. Adverse reactions were tolerable but contributed to the delay of treatment. Factors such as advanced disease stage, surgical treatment, delayed treatment and socioeconomic status may have contributed to the disease progression and disease recurrence. Despite these, majority of the patients in the early stage who completed the treatment were noted to have no evidence of disease at the end of the study.

Conclusion: This review suggests that single agent carboplatin AUC 5-7 offers good outcome in early stage of disease and in those who were able to complete their treatment.

Key words: carboplatin, adjuvant chemotherapy, epithelial ovarian carcinoma

Ovarian cancer is the most clinically challenging of all the gynecologic malignancies, with more than 15,000 deaths and 21,000 new diagnoses estimated in the United States in 2008.[1] The median age at diagnosis is 55 years old, so even a small improvement in survival could extend the lives of many thousands of women worldwide.

Definitive local surgery typically includes total hysterectomy, bilateral salpingo-ophorectomy and omentectomy.[2] This is carried out before chemotherapy. The chemotherapy agent varies depending on the histologic type, prognostic factors, and stage of disease. In our local setting, cost can sometimes be a factor in treating patients with ovarian carcinoma. The survival of these patients is poor, especially in advanced stage disease . Most of the patients are already on its advanced stage because of the lack of symptoms and at the same time, no standard tests or screening are recommended for the detection of ovarian carcinoma.

Many attempts and studies have been carried on to clarify the role of chemotherapy for the treatment of ovarian cancer. Meta analysis and randomized trials have been done to clarify the role of platinum-based chemotherapy in this disease. These studies have suggested that immediate platinum-based chemotherapy was better than non-platinum based chemotherapy. Platinum in combination was better than single agent platinum when used at the same time. There was no difference between carboplatin and cisplatin either as single agent or when substituted for one another in combination regimens.

Two meta analyses[3,4] have shown that the three-drug combination of CAP (Cisplatin , Adriamycin and Cyclophosphamide) was probably the most effective in terms of survival with women for ovarian carcinoma. However, platinum seems to be the single most active agent, thus raising a question whether a single agent platinum can provide equivalent survival when compared with the triple agent chemotherapy.

In 1991, the International Collaborative Ovarian Neoplasm Collaborators (ICON) initiated a randomized trial of immediate adjuvant chemotherapy for early stage (stage I and II) ovarian cancer (ICON1) and one for the more advanced-stage (stage II-IV) disease (ICON 2). The trials were designed to be complementary so that every patient with epithelial ovarian cancer could be considered an entry into one of these randomized trials. The protocol asked the following question of clinicians: In the opinion of the responsible clinician, does the patient require immediate chemotherapy? If the clinician was uncertain, he or she was asked whether to consider entering the patient to ICON 1, the earlier stage of the trial. If the clinician was certain about the need for immediate chemotherapy, he or she was asked to

consider entering into ICON 2, the more advanced stage of the trial. The two trials used single agent carboplatin and cyclophosphamide, doxorubicin and cisplatin (CAP) at intervals of three weeks. Carboplatin was chosen for the single agent dose because at optimally tolerated doses, it is less toxic, but with no evidence of inferiority in terms of efficacy on cisplatin. The recommended dose for carboplatin when used as a single agent was based on the dose required to obtain an area under curve (AUC) of 5mg/ml. The recommended dose for carboplatin when used in combination was 4mg/ml using the AUC method of Calvert, et al. in which the dose required is obtained by the formula (GFR + 25) x 5, where GFR is the measured glomerular filtration rate.

ICON 1,[5] the largest trial performed in early stage ovarian carcinoma, provides evidence that adjuvant treatment with platinum based regimens gets benefit because of improved survival in most of the patients with early stage ovarian carcinoma. It also improves overall survival and recurrence-free survival. In conclusion, the findings of this trial indicate that all patients with early stage ovarian cancer should be considered for platinum based adjuvant chemotherapy after optimal debulking. Most of the centers in this study also used carboplatin, thus recommending it to become the treatment of choice.

ICON 2[6] on the other hand, with majority of its subjects belonging to FIGO stage III and IV, provides reliable evidence of no difference in progression free or overall survival between CAP and single agent carboplatin with the absolute difference in 2 year survival is 0% for both groups and the 95% confidence interval is sufficiently narrow in 2 year survival of 4% for single agent carboplatin and of 6% for CAP. However, with the 1526 patients randomized, before the planned 2,000 patient maximum recruitment for the study of this large ramdomized trial, it was closed in 1996 due to the interest of testing combining paclitaxel and a platinum against platinum regimens. The interest in paclitaxel arose from GOG 111 comparing cisplatin (75mg/m^2) plus cyclophosphamide (750mg/m^2) with cisplatin (75mg/m^2) plus paclitaxel (135mg.m^2) in women with advanced stage ovarian carcinoma, the result of which proved the superiority of paclitaxel on the overall response rate and progression-free and overall survival. Thus ICON 3, which is the successor trial of ICON 2 (which was stopped in July 1996) started recruitment of data in February 1995 and compared the combination of paclitaxel and carboplatin with a control group of carboplatin or CAP. The results of ICON 3, suggested that CAP, single agent carboplatin and paclitaxel plus carboplatin are all safe and show similar effectiveness as first line treatment for women requiring chemotherapy in women with ovarian carcinoma. Of these treatments, carboplatin might be regarded as the preferred treatment because of its better toxicity profile, despite the fact that it was given in a dose intense 3-weekly schedule and that, some clinicians were able to escalate and tailor the dose of carboplatin to their respective patients.

With the validation of the ICON trials in 2008, the Society of Gynecologic Oncologists of the Philippines (SGOP) included single agent carboplatin as one of the recommended first line chemotherapeutic regimens for the treatment of epithelial ovarian carcinoma with a minimum of AUC 5 every 21 days for 6 cycles. It is also recommended for platinum sensitive persistent or recurrent disease of ovarian carcinoma with an AUC of 5-7 every 21 days for 6 cycles.[7]

In the Section of Gynecologic Oncology of the Philippine General Hospital, approximately 900-950 consults of patients with ovarian carcinoma are seen yearly .Of these, 150-200 are new cases. . In 2010, a total of 187 ovarian carcinoma new cases and 916 consults were seen with the bulk of 15 % of the total number of gynecologic malignancies seen for the year. Most of them are operated in the institution. Of the new cases, 77.72% needed adjuvant chemotherapy.[8] They are either advised standard combination chemotherapy in the form of carboplatin paclitaxel or if with limited budget, the single agent carboplatin. Though the standard treatment of epithelial ovarian carcinoma still remains to be the double agent chemotherapeutic drug carboplatin paclitaxel, one of the options include single agent carboplatin which is based on the randomized trials (ICON trials) which have shown effectiveness and safety as first line treatment for women requiring chemotherapy for this disease. Aside from this, majority of the patients

presenting with this disease belonged to middle class family who find more affordable for them to choose a single agent drug than the double agent chemotherapeutic regimen. At present, there are no data on the outcome of the use of single agent carboplatin in the institution, more so, in the country. It was the aim of the authors to review the data of the patients who used single agent carboplatin in the treatment of epithelial ovarian carcinoma and know the outcome of this drug in the institution.

Significance of the Study

Since there has been no study and review of the outcome and response of carboplatin in the treatment of epithelial ovarian carcinoma in this institution as well as in the Philippines, the authors intended to do this descriptive study to be able to determine and review the outcome of the diagnosed patients with ovarian carcinoma who were treated with single agent carboplatin. By ascertaining the profile and results of this chemotherapeutic agent as the treatment of ovarian carcinoma in the institution, the authors would be able to correlate the response of this chemotherapeutic drug with the other countries such as the United Kingdom that use widely the optimal dose single agent carboplatin. Since no data have been extrapolated as to the result of single agent carboplatin for the treatment of patients with epithelial ovarian carcinoma in the country, the result of this study may be a basis of justification of the guidelines for further recommendation of the use of single agent carboplatin as the first line treatment of epithelial ovarian carcinoma in the country where financial resources are scarce.

Review of Related Literature

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States. Data from the Surveillance, Epidemiology, and End Results (SEER) program of the U.S. National Cancer Institute (NCI) suggest that 21,650 new cases of ovarian cancer and 15,520 deaths from ovarian cancer were expected in the United States in 2008.[1]

In the Philippines, cancer of the ovary is the 10th leading site for both sexes combined and the 5th among women with 2,165 new cases in 2010. The incidence rate rises steeply starting at age 40 and continues to increase with age.[9]

Our knowledge of the natural history and patterns of spread of epithelial ovarian cancer forms the basis for staging the disease and for the surgical management of ovarian cancer. The stage of ovarian carcinoma is surgicopathologic, thus, can be determined only following exploratory laparotomy and thorough evaluation of all areas at risk using the 2009 FIGO (International Federation of Gynecologic Oncology) staging classification of ovarian carcinoma.

Standard protocols have emerged for the management of ovarian carcinoma. The standard care for ovarian cancer includes surgical exploration for primary staging and cytoreduction or debulking. However, this disease is detected at a later stage and adjuvant treatment in the form of chemotherapy is needed. The standard postoperative chemotherapy is combination therapy with platinum and paclitaxel. Studies have shown its effectivity in the treatment of ovarian carcinoma. However, randomized studies have proven that other chemotherapeutic regimens result in equivalent survival rates. One of these is the use of single agent carboplatin in our institution.

Carboplatin is an inorganic heavy metal complex containing a central atom of platinum. It is an analog of cisplatin and contains a platinum atom surrounded in a plane by two ammonia groups and two other ligands in the cis position. The other two ligands in carboplatin are present in a ring structure rather than as two chloride atoms in cisplatin. This difference makes carboplatin more stable and with less nephrotoxicity, neurotoxicity, ototoxicity and emetogenesis.The exact mechanism of action of carboplatin is not known. Carboplatin undergoes intracellular activation to form reactive platinum complexes which are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Carboplatin is a radiation-sensitizing agent and is cell cycle-phase non-specific.[10]

The primary determinant of carboplatin clearance is glomerular filtration rate (GFR) and this parameter of renal function is often decreased in elderly patients.

Dosing formulas incorporating estimates of GFR to provide predictable carboplatin plasma AUCs should be used to minimize the risk of toxicity.[11]

Randomized controlled trials have shown that it is a comparable treatment as that of the double standard chemotherapeutic agent carboplatin and paclitaxel for the treatment of ovarian carcinoma. Published in 1998, the Large ICON 2 Trial is a series of meta-analyses of randomized controlled trials in 1526 patients in over 132 centers in 9 countries and raised the question of whether the three drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) was more or less effective than optimal-dose single-agent carboplatin for women with advanced ovarian cancer. It was found out that CAP or carboplatin had the same effectiveness in different subgroups defined by age, stage, residual disease, differentiation, histology, and coordinating centre. Results have indicated a median survival of 33 months and a 2-year survival of 60% for both groups. CAP was substantially more toxic than carboplatin, causing more alopecia, leucopenia and nausea. However, thrombocytopenia occurred with carboplatin. They concluded that single-agent carboplatin, with the dose calculated by the area-under-the-curve method, is a safe, effective, and appropriate standard of treatment for women with advanced stage ovarian carcinoma.[6]

Since carboplatin-paclitaxel combination has become a widely acceptable treatment for ovarian carcinoma, the ICON 3 trial aimed to compare the safety and efficacy of paclitaxel plus carboplatin with a control of either CAP or carboplatin alone. This is a randomized controlled trial of 2074 patients from 130 centers coming from eight countries. Results have shown that single-agent carboplatin and CAP are as effective as paclitaxel plus carboplatin as first-line treatment for women requiring chemotherapy for ovarian cancer. The favorable toxicity profile of single-agent carboplatin suggests that this drug is a reasonable option as first-line chemotherapy for ovarian cancer.[12]

Furthermore, in the study of toxicity of the drug, a randomized trial of dose intensity with single agent carboplatin in patients with epithelial ovarian cancer examined the role of an increase in cisplatin dose intensity in patients with advanced epithelial ovarian cancer by means of single agent carboplatin therapy. It was shown that carboplatin can be delivered at an AUC of 12 for four courses without granulocyte colony-stimulating factor support, although significant hematologic toxicity can occur. Non-hematologic toxicities were not clinically significant. They concluded that carboplatin offers an opportunity to intensify cisplatin therapy, but a greater than two fold increase in dose intensity probably needs to be achieved before significant effects on survival will be produced and hematologic support will be required.[13]

A North Thames Ovary Group Study performed a randomized trial comparing single-agent carboplatin with carboplatin followed by radiotherapy for advanced ovarian cancer. This study was done for advanced ovarian carcinoma whether consolidation therapy with whole-abdominal radiotherapy (RT) after chemotherapy improves survival and disease-free survival compared with the continued chemotherapy. In this study, they concluded that there is no significant advantage for consolidation whole-abdominal RT compared with the continuation of the same chemotherapy in the management of advanced epithelial carcinoma of the ovary, even when no macroscopic residual disease is apparent at second-look surgery.[14]

Objectives

General Objective

The general objective of the study was to determine the overall response and outcomes of patients with ovarian carcinoma who were treated with single agent carboplatin as a first line treatment for patients with epithelial ovarian carcinoma in the tertiary institution.

Specific Objectives

1. To describe the sociodemographic, clinical characteristics and the surgico-prognostic factors of patients with epithelial ovarian carcinoma who were treated with single agent carboplatin.
2. To determine the treatment outcomes of the patients (e.g. no evidence of disease, recurrence,

progression) with epithelial ovarian carcinoma who were given single agent carboplatin
3. To determine the toxicity effects or toxicity profile of single agent carboplatin in these patients

Definition of Terms

Progression-free survival (PFS): denotes the chances of staying free of disease progression for a group of individuals suffering from a cancer after a particular treatment. It is the percentage of individuals in the group whose disease is likely to remain stable (and not show signs of progression) after a specified duration of time. Progression-free survival rates are an indication of how effective a particular treatment is. Progression-free survival is often calculated for treatment of diseases that are slow growing and difficult to cure, like low grade lymphomas. This term is also used when salvage treatments are offered in situations where the intention is not cure but the control of disease.
Adjuvant Chemotherapy: cancer chemotherapy employed after the primary tumor has been removed by some other method.
Combination Chemotherapy: combination of several different agents simultaneously in order to enhance their effectiveness.
Disease Free Survival: Period after successful treatment in which there is no appearance of the symptoms or effects of the disease.
No Evidence of Disease: for the purpose of this study, no evidence of disease is defined as the complete resolution of the disease at the end of the complete cycle of chemotherapy to the time of the last check up of the patient.
Overall Survival: subjects in a study who have survived for a defined period of time. Usually reported as time since diagnosis or treatment. It is also a term that denotes the chances of staying alive for a group of individuals suffering from a cancer. It denotes the percentage of individuals in the group who are likely to be alive after a particular duration of time. At a basic level, the overall survival is representative of cure rates.
Debulking Surgery: it is a surgery that removes a portion, though not all, of a cancerous tumor. It is used in certain situations when removing an entire tumor may cause damage to an organ or the body.

Materials and Methods

Study Design

This is a descriptive study.

Population

All patients diagnosed with epithelial ovarian carcinoma who were treated with single agent carboplatin as their first line treatment in a tertiary hospital from 2006 to 2010.

Participants

Inclusion Criteria

a. Patients who were diagnosed with epithelial ovarian carcinoma FIGO stage I-IV in this institution who completed the treatment
b. Patients who were operated from other hospitals with staging data available and treated in this institution using single agent carboplatin.
c. Patients who were given single agent carboplatin but were lost to follow up and did not complete the treatment.
d. Patients who were initially treated with carboplatin but recurrence or persistence were observed during the treatment , thus shifting to second line chemotherapy.

Exclusion Criteria

a. Patients who used single agent carboplatin for persistent or recurrent ovarian carcinoma
b. Patients who initially used carboplatin as neoadjuvant treatment for ovarian carcinoma after which interval debulking surgery was done.
c. Patient with other malignancies other than epithelial ovarian carcinoma who used single agent as the drug of choice for their disease.

Methods

Charts of the patients with epithelial ovarian carcinoma of FIGO stage I-IV based on 2009 FIGO staging and underwent chemotherapy with single agent carboplatin AUC 5-7 at a tertiary hospital were reviewed. Data collection tools were developed by the researcher based on the objectives of the study. Charts of the patients meeting all the inclusion criteria were retrieved. Data collections were encoded using the data collection tool provided by the investigators. All data sheets were retrieved and encoded by the investigator for analysis.

Statistical Analysis

The three objectives do not need any statistical analysis. They simply required descriptive profiling of patients at baseline, and during their visits. Hence, descriptive statistics such as means ± S.D., medians and range of quantitative variables, e.g., age, BMI, etc. were computed. For qualitative variables such as occupation, history of disease, etc., proportions were computed. Data were then presented in tables and graphs. STATA version 11 was used to perform the said analyses.

Ethical Consideration

The research was conducted in accordance with the principles of the Hospital Ethics Committee.

Limitations of the Study

Since this is a 5-year chart review, data of the surgery done were only reviewed through operative findings available in the chart. Residual tumor was not measured if ever present, before the start of chemotherapy. Response to treatment is measured through subsequent internal examination, imaging studies and tumor markers, either of CA 125 and CA 19-9.

Results

A total of 67 female patients, 21 to 78 years of age, were included in this analysis. The median age was 46 years with 16 patients (23.88%) having ages below 40 years and only 2 patients (2.99%) having an age equal to or above 70 years (Table 1).

Table 1. Age distribution of the respondents.

Age (Years)	Number	Percent
<40	16	23.88
40-49	23	34.33
50-59	20	29.85
60-69	6	8.96
70 & over	2	2.99
Total	67	100.00
Mean SD	47 ± 11	
Median	46	
Range	21 - 78	

The mean body mass index (BMI) of the patients was 22.2 ± 3.3kg/m^2 with a range of 15kg/m^2 to 28kg/m^2. More than half of the patients were married, while about two-fifths of the patients were single. A vast majority (82.09%) of the patients were unemployed (Table 2).

Table 2. Socio-demographic characteristics of the respondents.

Variable	Number	Percent
Civil Status (n=67)		
Single	24	38.52
Married	39	58.21
Separated	0	0.00
Widowed	4	5.97
Employment Status (n=67)		
Employed	12	17.91
Unemployed	55	82.09

Table 3 presents the obstetric history of the respondents. The mean number of pregnancies experienced by the respondents was 2 ± 2, while the mean number of offsprings was also 2 ± 2. Age of menarche ranged from 11 years to 18 years. Twenty nine patients (43%) were already menopausal upon diagnosis of ovarian carcinoma. Among those who were already menopausal, mean age was 49 ± 3 years.

Table 3. Obstetric history of the respondents.

Variable	N	Mean	SD	Range
Gravidity	67	2	2	0-10
Parity	67	2	2	0-7
Age of menarche	67	14	2	11-18
Age of menopause	29	49	3	44-55
OCP use (n=67)	Number		Percentage	
Yes	24		35.82	
No	43		64.18	

Table 4 shows the lifestyle and clinical profile of the respondents. Majority of the patients were non-smokers (94.03%) and also non-drinkers (98.51%). No one admitted having drug abuse in the past. About 12% of the patients have hypertension. None of them have diabetes and only 2 patients (2.99%) have asthma.

Table 5 presents the procedure done on the patients according to cancer stage. Majority of the patients (62.69%) underwent combination of exploratory laparotomy, peritoneal fluid cytology, total abdominal hysterectomy with bilateral salpingo-oophorectomy, bilateral lymph node sampling, infracolic omentectomy, and random peritoneal biopsy. Most of the patients who underwent procedures 1, 2 and 3 had stage I cancer, while those who underwent procedures 5 and 6 had stage III cancer.

Among those whose surgery was performed by either the Surgery Department or the General OB-Gyn Department (83.58%), 61% (34 out of 56) were referred to the Gynecology-Oncology Department for completion surgery and staging.

The interval between date of surgery and first course of chemotherapy ranged from 18 days to 22 months with an average of 4 ± 4 months (n=67).

Table 4. Lifestyle and clinical profile of the respondents.

Variable	Number	Percent
Smoking Status (n=67)		
Smoker	4	5.97
Non-smoker	63	94.03
Alcoholic Intake (n=67)		
With	1	1.49
Without	66	98.51
History of Substance Abuse (n=67)		
Yes	0	0.00
No	67	100.00
Presence of Hypertension		
Yes	8	11.94
No	59	88.06
Presence of Diabetes		
Yes	0	0.00
No	67	100.00
Presence of Asthma		
Yes	65	97.01
No	2	2.99

Table 5. Procedure done on the patients according to cancer stage.

Cancer Stage	I		II		III		IV		TOTAL	
Procedure	N	%	n	%	n	%	n	%	N	%
Procedure 1[a]	26	61.90	9	21.43	6	14.29	0	2.38	42	62.69
Procedure 2[b]	7	41.18	3	17.65	7	35.29	1	5.88	18	26.86
Procedure 3[c]	2	100.00	0	0.00	0	0.00	0	0.00	2	2.99
Procedure 4[d]	2	66.67	1	33.33	0	0.00	0	0.00	3	4.48
Procedure 5[e]	0	0.00	0	0.00	1	100.00	0	0.00	1	1.49
Procedure 6[f]	0	0.00	0	0.00	2	100.00	0	0.00	2	2.99
TOTAL	37	55.22	13	19.40	16	22.88	1	1.49	67	100.00

[a] EL, PFC, THBSO,BLND, PALS, IO, RPB
[b] EL, THBSO, IO
[c] EL, THBSO
[d] EL, RSO/LSO
[e] biopsy of mass
[f] EL, PFC, THBSO,LN palpation, tumor debulking

The interval between the date of the first course of chemotherapy and the date of the second course of chemotherapy ranged from 21 days to 74 days with an average of 34 ± 15 days (n=58)

The interval between the date of the second course of chemotherapy and the date of the third course of chemotherapy ranged from 21 days to 127 days with an average of 40 ± 23 days (n=53).

The interval between the date of the third course of chemotherapy and the date of the fourth course of chemotherapy ranged from 21 days to 66 days with an average of 33 ± 12 days (n=50).

The interval between the date of the fourth course of chemotherapy and the date of the fifth course of chemotherapy ranged from 21 days to 97 days with an average of 39 ± 17 days (n=44).

The interval between the date of the fifth course of chemotherapy and the date of the sixth course of chemotherapy ranged from 20 days to 106 days with an average of 37 ± 16 days (n=41).

Among those who were able to complete their chemotherapy treatment (64.18%), the length of time they are disease-free (NED) from the date of their last course of chemotherapy ranged from 66 days to about 5 years with an average of 24 ± 12.6 months (n=43).

Most the patients were diagnosed with papillary serous carcinoma (38.81%), endometrioid cancer (22.39%), or mucinous carcinoma (22.39%) based on the histopathology results. Roughly two-fifths of the patients with papillary serous carcinoma had stage III cancer. On the other hand, most of the patients with mucinous carcinoma (80%) and endometrioid cancer (80%) had early stage (I-II) disease. More than half of the patients had stage I cancer upon enrolment in the study. Patients with borderline serous tumor, endometrioid adenocarcinoma, mucinous carcinoma and well-differentiated type of disease had favorable outcomes with majority of its population resulted with no evidence of disease at the end of the study period. The most favorable histologic type noted in this study are borderline serous tumor (1 patient), well-differentiated type (1 patient) and endometrioid adenocarcinoma (12 patients) with all of the patients on its early stage exhibiting no evidence of disease. One patient with early stage was noted to have disease recurrence in endometrioid carcinoma. It was observed 6 months after having no evidence of disease. Papillary serous tumor and clear cell carcinoma had a poor overall outcome of treatment and it was noted that only less than 50% of the patients respond to treatment even at early stage of the disease. Seven of the 11 patients (63.63%) with papillary serous carcinoma histology had tumor progression at its advance stage (stage III).

Forty three patients were able to complete the 6 courses of chemotherapy and became disease-free at the end of the study period. Thirty seven of this patients had no evidence of disease until the time of last follow up. Among these patients, more than one half (73%) had stage I cancer at baseline. No patient with stage IV cancer became disease-free at the end of the study period.

Among the 43 patients who have completed the treatment, only six patients had cancer recurrence during the study period. An equal number of these patients either had stage I, II or III cancer.

Among those who did not complete the treatment, 14 out of 24 (58.3%) were lost to follow-up without completing the treatment, while 10 out of 24 (41.67%) were not able to complete the treatment due to disease progression.

The most common adverse reaction ever experienced by the patients during the entire course of chemotherapy was anemia (42.10%), followed by electrolyte imbalance (28.94%), infection (14.47%) and thrombocytopenia (10.52) and afebrile neutropenia (3.94%).

Discussion

Ovarian cancer is the fifth leading cause of death in women in the United States and the most common cause of death in women with gynecological malignancies in most Western countries. Despite the significant advances in surgery, chemotherapy and radiotherapy, the resulting overall 5-year survival is about 40%-50%.[15]

Unfortunately at present, results of treatment are still far from optimal. Integration of surgery with chemotherapy are crucial in the treatment of ovarian cancer and the recommended treatment strategy for

patients with advanced ovarian cancer is radical cytoreductive surgery followed by 6 cycles of platinum-based combination chemotherapy.[16]

The standard treatment for ovarian carcinoma is the combination chameotherapy in the form of carboplatin AUC 5-7 and paclitaxel 175mg/m^2 given at a 21 day interval.[17-19] However, carboplatin has demonstrated single-agent efficacy in advanced ovarian cancer and has been the cornerstone for most combination regimens[2]. This was the basis of using the single agent carboplatin in our institution as one of the first line treatment for epithelial ovarian carcinoma patients who cannot afford the double agent chemotherapy with the same efficacy as the combination regimens. Aside from that, patients given with carboplatin adjuvant chemotherapy are done at the outpatient clinic, thus it would be convenient for the patient to comply with such treatment.

Review of the patients' demographic characteristics in this study showed that majority of the patients are 40 year old and above, 29 of the 67 patients (43%) were already postmenopausal at the time of diagnosis. This is consistent with the age distribution of the patients who were diagnosed with epithelial ovarian carcinoma. The risk of ovarian cancer goes up with age, mostly in postmenopausal women. While some women in their 20's and 30's get ovarian cancer, the majority of cases are diagnosed in women over 45 years old.

Most of the patients had papillary serous carcinoma (38.81%), endometrioid cancer (22.39%), or mucinous carcinoma (22.39%) based on the histopathology results. This correlates with most of the review in the literature as the most common histology in epithelial ovarian carcinoma. In the literature, serous papillary tumors are the most widespread forms of ovarian cancer. They account for 40% of common epithelial tumors. About 50% of these tumors are malignant, 33% are benign, and 17% are of borderline malignancy. Endometrioid tumors represent approximately 20% of common epithelial tumors. In 5% of cases, they also are linked with endometriosis, an abnormal occurrence of endometrium (womb lining tissue) within the pelvic cavity. Mucinous tumors make up about 1% of all common epithelial tumors.

Majority of the patients received completion surgery and staging upon diagnosis of the ovarian carcinoma. Majority of them (55.22%) were at the early stage of the disease when completion surgery and staging was done. This is because most cases were also done by obstetrician gynecologists (83.58%) and 61% of these patients were referred to the gynecologic oncologist for completion staging. Aside from this, most of the surgeries were done at the tertiary institution where availability of gynecologic oncology services are present. Thus, importance of complete surgical staging and tumor debulking was emphasized among these obstetricians. Patients benefited from these procedures. This is supported by the study of Goldie, et, al. and Pagano, et al.[20, 21] In order to minimize the tumor burden before chemotherapy, cytoreductive (or debulking) surgery is usually performed upfront. Possible benefits from upfront cytoreductive surgery include: a) improvement of tumor response to further therapy due to improved tumor perfusion and increased growth fraction. Smaller tumor masses require fewer cycles of chemotherapy with less chance of induced drug-resistance. Clones of phenotypically resistant cells may be removed also; b) immediate treatment, or prevention of complications arising from tumor masses, i.e. bowel obstruction and ascites; c) enhancement of the immunological competence of the patient. The immunogenicity of ovarian cancer has been demonstrated in vivo and cytoreduction may help the patient to mobilize her own immune response to the cancer [20]; d) psychological benefit to the patient of knowing that the tumor bulk has been removed.[21]

Patients who underwent biopsy of the mass and EL, THBSO, LN palpation and tumor debulking were all at the advanced stage. This can be explained by the extensive nature of the disease spreading through, thus, suboptimal debulking or biopsy were only done.

The mean interval between the time of surgery to the time of chemotherapy was 4 months. Furthermore, the interval of the successive chemotherapy in every cycle ranges from 21 days to 71 days. Ideally, interval on each chemotherapy should be 21 days in each cycle. With regards to the timing from the time of surgery to the first chemotherapy, retrospective studies have assessed the influence of survival of delaying chemotherapy. Since it will not be ethically acceptable

to perform a trial of early vs late start of chemotherapy, data from other types of studies are needed to provide evidence on the effect of delays in chemotherapy and survival. Two small studies from the 1980s reported an improved disease-free interval (DFS) for patients starting chemotherapy within 4-5 weeks compared with the patients treated later (Brooks, et al. 1983; Pronzato, et al. 1989). This finding was further supported by a Turkish study (Altumdag, et al. 2000). If the chemotherapy is delayed for more than 5 months, then the concept of being adjuvant no longer holds.[22]

Among the 43 patients who completed the six courses of chemotherapy, 6 patients (16.2%) had recurrence during the study period. These patients initially had no evidence of disease for more than 6 months, however, on follow up disease recurrence was noted, either by increasing tumor markers, palpation of tumor mass on internal examination followed by confirmation on imaging studies. Two patients (33%) were noted to have recurrence in stage I, II, III respectively. Though of equal distribution, looking at the total number of patients who had no evidence of disease per stage (Table 6), only 2 of the 31 patients (6.4%) had recurrence in early stage disease (I-II), 4 of the 6 patients (66.67%) in advanced stage (III-IV) had recurrence, thus, the higher the stage is, the higher the percentage of recurrence. No stage IV was recorded as tumor recurrence because the only patient in the study with stage IV disease had disease progression. The mean duration of patients with no evidence of disease until the time of their last check up, ranged from 66 days to about 5 years with an average of 24 ± 12.6 months (n=43). Among those who did not complete the treatment (35.82% or n=24), more than half (58.33% or 14 out of 24) was lost to follow-up without completing the treatment, while the rest (41.67% or 10 out of 24) had incomplete treatment due to disease progression. Most of the patients in this study were unemployed, thus securing funds for chemotherapy is difficult and would need government and private agencies for medical assistance that would take months, contributing for further delay of treatment. Factors such as advanced disease stage, interval from surgery to the time of first chemotherapy and chemotherapy interval on each cycle may have contributed to the disease progression and recurrence of the disease. Despite these, majority of the patients who completed the treatment in the early stage of the disease were noted to have no evidence of disease at the end of the study.

The most common adverse reaction ever experienced by the patients during the entire course of chemotherapy was electrolyte imbalance, thrombocytopenia and afebrile neutropenia .These adverse reactions were manageable but contributed to the delay in treatment due to lack of funds and patients' compliance to GCSF (granulocyte colony stimulating factor) or blood products.

Conclusion

The result of this study showed that patients who were given single agent carboplatin for treatment of epithelial ovarian cancer had either no evidence of disease, recurrence or progression. Patients with borderline serous tumor, endometrioid adenocarcinoma, mucinous carcinoma and well differentiated type of disease had favorable outcome with majority of its population at its early stage resulted with no evidence of disease at the end of the study period. Patients with advanced stage of the disease had a higher percentage of disease progression. Factors such as advanced disease stage, residual disease, delayed treatment, interval between chemotherapy cycles and socio-economic status may have contributed to the disease progression and recurrence. Despite these, majority of the patients in the early stage of disease who completed the treatment were noted to have no evidence of disease at the end of the study.

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Validity of Nutrition Risk Screening (NRS 2002) as a Nutrition Screening Tool in Ovarian Cancer Patients at a Tertiary Hospital

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Malnutrition is common among hospitalized patients, but more so in patients with malignant disease. The association between cancer and malnutrition is tremendous, such that patients may die because of malnutrition rather than the disease itself. There is no locally available screening tool used to detect malnutrition among ovarian cancer patients.

Objective: The study primarily aimed to determine the validity and reliability of Nutrition Risk Screening (NRS 2002) (Appendix 1) as a nutrition screening tool in ovarian cancer patients.

Methods: Thirty five preoperative ovarian cancer patients participated in the study. NRS 2002 was the instrument used in this study. Nutritional status was determined using the Subjective Global Assessment (SGA) grading and was combined with measures of Body Mass Index (BMI), serum albumin levels, and total lymphocyte count (TLC) to determine the over- all nutrition risk level. Reliability and validity of the NRS 2002 was assessed using the Cramer's V coefficient and Bootstrap analysis.

Results: Final screening showed that 65.7% of the subjects were nutritionally at risk. Assessment of nutrition status showed that 30 subjects (85.7%) were assessed with SGA B, and 4 (11.4%) patients with SGA C; this accounted for an overall prevalence of malnutrition of 97.1%, showing that the majority of the patients were at further risk of undernutrition, postoperatively. Nutritional risk level assessment showed that 14 (40%) of the patients were at moderate risk for malnutrition, and the remaining 60% were at high risk. Cramer's V coefficient showed values between 0.1- 0.3, signifying a low association between NRS 2002 and SGA grade (nutritional status; $r = 0.237$, $P=0.16$). Bootstrap results imply significant relationship between NRS 2002 and SGA, implying a valid measure for screening. However, the coefficient is still not large enough to conclude that NRS 2002 is a reliable measure for malnutrition screening.

Conclusion: The NRS 2002 is a valid measure for nutrition screening among ovarian cancer patients, although its reliability is uncertain. To date, there is still no locally established nutrition screening tool for patients with ovarian cancer.

Key words: malnutrition, Nutrition Risk Screening 2002, nutrition screening, ovarian cancer

Malnutrition is common among hospitalized patients, but more so in patients with malignant disease. They are at a nutritional risk or may develop malnutrition due to the disease itself, or due to its treatment, and it is a very important predictor of morbidity and mortality. It has been suggested that up to 20% of patients die of the effects of malnutrition rather than of the malignancy itself.[1] The association between cancer and malnutrition has many consequences, including increased risk of infection, increased length of hospitalization, poor wound healing, reduction in muscle function and its consequences, decreased response to treatment, a lower quality of life, and reduced survival and higher health-care costs.[2,3] In patients requiring surgery, the clinical impact of malnutrition includes an increased risk of perioperative complications, increased post-operative residual tumor after initial surgery, and increased length of hospital stay[4].

The incidence of malnutrition amongst patients with cancer has been estimated between 30% and 85%.[2,3,5] A significant proportion of patients with gynecological malignancies seem to experience malnutrition and patients with advanced ovarian cancer are particularly at risk.[4] The prevalence of malnutrition depends on the tumor type, location, stage and treatment.[3] For example, patients with ovarian malignancies were 19 times as likely to present with a poor nutritional status before treatment than were patients with benign conditions.[1] In a local study by Montoya, et al. at the National Kidney and Transplant Institute, about 47.7% of cancer patients suffer from malnutrition, as classified by Subjective Global Assessment (SGA), with cancer stage and Karnofsky performance status scoring as predictors of malnutrition.[6]

Ovarian cancer is the fifth leading site among women.[7] No screening test has been identified, which leads to late detection of the disease, and with the patients already diagnosed in the advanced stages. The disease itself triggers deterioration of health, and this is complicated by the fact that patients would have to undergo surgery, chemotherapy and radiotherapy to improve survival. Careful evaluation of the nutritional status through nutritional screening and assessment is essential to identify patients who are at risk of developing malnutrition or who are already malnourished. Through screening and assessment, early nutritional interventions can be implemented, which can improve the response to treatment, performance status, quality of life and reduce morbidity and mortality in patients with ovarian cancer. Thus, the determination of the preoperative nutritional status of these patients is of paramount importance, as this could affect the management of these patients.

Nutritional assessment is the first step in identifying and treating malnutrition and should be a part of pretreatment routine, however, the ideal method of evaluation has yet to be established, and association of various indicators is required to improve the accuracy of nutritional diagnosis.[2] Some of the nutrition assessment tools used for gynecologic patients include the scored Patient-Generated Subjective Global Assessment (PG-SGA), Serum albumin, skinfold thickness measurements, total- body potassium, and body density measurements. Other anthropometric and biochemical measurements, used either alone or in combination include arm circumference, total protein, transferrin, hemoglobin and vitamins. The disadvantage of these nutritional assessment tools is that they are too detailed and too time-consuming to complete on all hospitalized patients, therefore, nutrition screening is a feasible alternative for identifying patients at risk of malnutrition.[8]

Nutrition screening is the process of identifying parameters known to be associated with nutritional problems, the purpose of which is to identify individuals who are malnourished or at risk of becoming malnourished and who may benefit from nutritional support[7] and whether nutritional treatment is likely to influence this.[9] The usefulness of screening tools can be evaluated by a number of methods. Predictive validity is of major importance[9], such that an individual identified to be at risk will most likely benefit from the intervention. The screening tool must also have a high degree of content validity, high reliability, rapid, simple, purposeful and it should be linked to specified protocols for action.[9] However, there is no locally available standardized nutritional screening tool designed specifically for use in patients with ovarian cancer.

The NRS 2002 was developed in an attempt to establish a screening system, using a retrospective analysis of controlled trials and the nutritional criteria or characteristics and clinical outcomes in these studies.[10] The purpose of the NRS 2002 is to detect the presence of undernutrition and the risk of developing undernutrition in the hospital setting.[9] It is meant to cover all possible patient categories in a hospital.

The predictive validity was documented by applying the NRS 2002 to a retrospective analysis of randomized controlled trials (RCTs) of the effect of nutritional support vs no support or spontaneous intake on clinical outcome. A Medline search on RCTs published as full papers or reviews was done. A total of 128 RCTs of nutritional support were obtained. Analysis showed that patients fulfilling the risk criteria had a higher likelihood of a positive clinical outcome from nutritional support that RCTs of patients who did not fulfill these criteria.[9,10] In addition, it has been applied prospectively in a controlled trial with 212 hospitalized patients selected according to this screening method, which showed a reduced length of hospital stay among patients with complications in the intervention group.[9] Its content validity has been maximized by involving ESPEN ad hoc working group in the literature based validation.[9] It has also been used by nurses and dietitians in a 2 years implementation study in three hospitals in Denmark, which indicated that staff and investigators seldom disagree about a patient's risk status.[9] Its reliability was validated by inter- observer variation between a nurse, a dietitian and a physician with a K=0.67.[9] Its practicability was shown by the finding that 99% of 750 newly admitted patients could be screened.[9]

This study was conducted to evaluate the effectiveness of a NRS 2002 as a screening tool in determining malnutrition among ovarian cancer patients.

Objectives

General Objective

The study primarily aimed to determine the validity and reliability of NRS 2002 as a nutrition screening tool in ovarian cancer patients.

Specific Objectives

1) To determine the nutritional status of preoperative ovarian cancer patients admitted at a tertiary hospital
2) To determine the prevalence of malnutrition among preoperative ovarian cancer patients admitted at a tertiary hospital
3) To determine the risk status of developing further malnutrition among pre- operative ovarian cancer patients admitted at a tertiary hospital

Materials and Methods

Patient Population

The study was conducted at the gynecologic wards of a tertiary hospital. All pre- operative patients admitted from January to June 2011, with an admitting diagnosis of "Ovarian New Growth probably malignant", or "Ovarian New Growth rule out malignancy" were invited to participate in the study. Other inclusion/ exclusion criteria were as follows:

Inclusion Criteria:

Any age, as long as parental consent is given if < 18 years old

Stage I to IV ovarian malignancy of any histology

Exclusion Criteria:

Pregnant patients

Recurrent or persistent ovarian malignancy, previously treated for ovarian malignancy

Procedure

The Nutrition Risk Screening 2002 (Form A) system was chosen to be the instrument used in this study.

The nutritional status (Form B) of the patients was determined using the Subjective Global Assessment (SGA) grading. This grading system classifies patients subjectively on the basis of data obtained from history and physical examination. The over- all nutritional risk assessment (Form B) was determined combining the SGA grading, Body Mass Index (BMI), serum albumin levels and total lymphocyte count (TLC).

Patients included in the study signed a voluntary, written consent form signifying their willingness to participate in the study. Chart reviews were done to obtain information concerning age, marital status, gravidity, educational background and BMI. Surgical pathology reports were retrieved to confirm the diagnosis of ovarian malignancy and determine the histology.

Outcome Measurements

The NRS 2002 consists of two components: the Initial (undernutirtion) and Final Screening (disease severity). Patients are scored in each of the two components: 1) undernutrition and 2) disease severity. Undernutrition was estimated using three variables used in most screening tools: BMI, percent recent weight loss and change in food intake.[10] Any "Yes" answer to these questions qualifies the patient to proceed to the final screening. The patient can have a score of 0-3 for each component, a total score of 0-6, and any patient with a total score of ≥3 is considered at nutritional risk[10] and is believed to benefit from nutritional support.

Form B of the questionnaire is the nutritional assessment form, which used the Subjective Global Assessment (SGA) system to determine the nutritional status of the patients. Five features of the history were elicited: 1) weight loss in the past six months, 2) dietary intake, 3) presence of significant gastrointestinal symptoms, 4) functional capacity and 5) metabolic demands of the patient's underlying disease.[11] Four features of the physical examination were included: 1) loss of subcutaneous fat measured in the triceps region and the mid- axillary line at the level of the lower ribs (measurements are not precise, but rather a subjective impression), 2) muscle wasting in the quadriceps and deltoids, 3) presence or absence of edema and/ or 4) ascites.[11]

The nutrition risk level was then determined based on the total scores of the SGA grade, BMI, albumin levels and TLC, giving a total score of 0-9. Patients with a total score of ≥3 are classified as high risk.

Data Analysis

The validity and reliability of the NRS 2002 were analyzed using the Bootstrapping method and the Cramer's V coefficient. Table 1 shows the level of association based on the coefficient.

Table 1. Cramer's coefficient with corresponding levels of association.

Coefficient	Level of Association
> 0.5	High association
0.3- 0.5	Moderate association
0.1- 0.3	Low association
0- 0.1	Little, if any association

Corresponding P-values were determined based on the computed coefficient (significant relationship: P> 0.7).

Results

During the study period, a total of 50 patients were interviewed; only 35 (70%) were histopathologically confirmed ovarian malignancy. The distribution of the study population based on demographic factors is shown on Table 2.

All patients interviewed had at least one "yes" answer to the questions based on the initial screening, making 100% of the subjects with nutrition risk (Table 3). All patients underwent the final screening.

Final screening showed that 65.7% of the subjects were nutritionally at risk (Table 4).

Nutritional status of the subjects was determined using the Subjective Global Assessment tool. Patients with SGA grades B and C were considered to be malnourished. Table 5 shows that 30 subjects (85.7%) were assessed with SGA B, and 4 (11.4%) patients with SGA C; this accounted for an overall prevalence of malnutrition of 97.1%, showing that the majority of the patients were malnourished, and were at further risk of undernutrition, postoperatively.

Over- all nutritional risk level assessment showed that 14 (40%) of the patients were at moderate risk for malnutrition, and the remaining 60% were at high risk (Table 6).

Table 2. Demographic profile of ovarian cancer patients at a tertiary hospital.

Variables		Frequency	Percent
Age	<18	3	8.57
	18-30	4	11.43
	31-40	7	20.00
	41-50	10	28.57
	51-60	9	25.71
	61-70	2	5.72
Educational Status	< Elementary	4	11.43
	Elementary	5	14.28
	< High School	1	2.86
	High School	19	54.29
	< College	3	8.57
	College	3	8.57
Marital Status	Single	13	37.14
	Married	20	57.14
	Widow	2	5.72
Gravidity	G0	10	28.57
	G1	7	20.00
	G2	18	51.43
Histologic Type	Epithelial	30	85.71
	Germ cell	4	11.43
	Sex cord stromal	1	2.86
Body Mass Index	18.5 - 25	21	60.00
	25.1 - 30	8	22.86
	<18.5 or > 30	6	17.14

Table 3. Initial nutrition risk screening of the ovarian cancer patients at a tertiary hospital.

Initial Screening	Frequency	Percent
Without Nutrition Risk	-	-
With Nutrition Risk	35	100.00

Table 4. Nutritional status indicator and clinical condition of the ovarian cancer patients at a tertiary hospital.

Final Screening	Frequency	Percent
Nutritionally not at risk (<3)	12	34.3
Nutritionally at risk (≥3)	23	65.7
Total	35	100.0

Table 5. Assessment on nutritional status of the ovarian cancer patients at a tertiary hospital.

Status	Frequency	Percent
Normal (SGA A)	1	2.9
Moderate (SGA B)	30	85.7
Severe (SGA C)	4	11.4
Total	35	100.0

Table 6. Assessment on nutritional risk level of the ovarian cancer patients at a tertiary hospital.

Level	Frequency	Percent
Low Risk (0)	0	0.0
Moderate Risk (1-2)	14	40.0
High Risk (≥3)	21	60.0
Total	35	100.0

The ability of the NRS 2002 to predict SGA is shown in Table 7. Patients with a score of 3 or more were subsequently classified as at risk of malnutrition and patients with a score of 1 or 2 were classified as not at risk of malnutrition. A total of 23 patients were correctly classified as being malnourished and 1 patient was correctly classified as being well nourished. A total of 12 patients were misclassified as being well nourished, giving a misclassification rate of 34.3%.

Based on this table, NRS 2002 was able to correctly classify 23 patients as being nutritionally at risk. Twelve patients were misclassified as being at no risk of malnutrition, giving a misclassification rate of 34.3%.

Table 9 shows the summary of the results of the NRS 2002 as compared to the Nutrition Assessment form. This shows an over-all misclassification rate of 34.3%.

Table 7. Comparison of the number of patients classified as being at risk of malnutrition using the NRS 2002 and the number of patients rated as malnourished using SGA.

NRS 2012	At Risk of Malnutrition?	SGA Grade	
		A	B and C
1	No		1
2	No	1	11
3	Yes		6
4	Yes		8
5	Yes		4
6	Yes		5

Table 8. Comparison of the number of patients classified as being at risk of malnutrition using the NRS 2002 and the over-all nutrition risk level assessment based on SGA, BMI, albumin and TLC.

NRS 2012	At Risk of Malnutrition?	Nutrition Risk Level	
		Low Risk	Moderate/High Risk
1	No		0
2	No		12
3	Yes		6
4	Yes		8
5	Yes		4
6	Yes		5

Table 9. Cross-tabulation of NRS 2002 with Nutrition Assessment Form.

		NRS 2002		Total
		Nutritionally not at Risk (<3)	Nutritionally at Risk (≥3)	
Nutrition Assessment Form	Normal	1	0	1
	Moderate/ High Risk	11	23	34
Total		12	23	35

Table 10 shows that there is a positive correlation between the two forms. Although the correlation is not perfect (perfect = 1), there is moderate correlation between the two forms.

Cramer's V coefficient showed values between 0.1-0.3, signifying a low association between NRS 2002 and SGA grade (nutritional status; r = 0.237, P = 0.16) (Table 11). The association between NRS 2002 and over-all nutrition risk level cannot be computed due to two 0 observations. Bootstrap results imply significant relationship between NRS 2002 and SGA, implying a valid measure for screening. However, the coefficient is still not large enough to conclude that NRS 2002 is a reliable measure for malnutrition screening.

Table 10. Symmetric measures showing the correlation of the NRS 2002 with the Nutrition Assessment Form.

		Value	Asymp. Std. Error	Approx. T	Approx. Sig.
Nominal by Nominal	Phi	0.237			0.16
	Cramer's	0.237			0.16
Interval by Interval	Pearson's	0.237	0.118	1.404	0.17[a]
Ordinal by Ordinal		0.237	0.118	1.404	0.17[a]
Total # of Valid Cases		35			

[a]based on normal approximation

Table 11. Reliability and validity of nutrition risk screening 2002 (NRS 2002) as a nutrition screening tool in ovarian cancer patients at a tertiary hospital.

Variables		NRS 2002		Cramer's V Coefficient	P-value	Bootstrap* BCA 95% C.I.
		Total Score < 3	Total Score ≥3			
SGA	Normal	1	11	0.237	0.16	.157 - .568
	Moderate/ High Risk	0	23			
Nutrition Risk	Moderate Risk	0	0			
	High Risk	12	23			

*Bootstrap results are based on 10,000 bootstrap samples.

Discussion

For ovarian cancer patients, optimal nutrition is essential. As previously mentioned, at least one-third of all cancer deaths can be linked to malnutrition, thus, the importance of proper nutrition in cancer care cannot be overstated. In ovarian cancer patients, the poor nutritional status and cachexia are caused by the metabolic effects of the enlarging tumor masses and bowel obstruction.[12]

Ovarian cancer and its treatment can deplete the patient's body nutrients, suppress the appetite, and even affect the ability to digest foods. When fighting ovarian cancer and when recovering from ovarian cancer treatments such as surgery, radiation, or chemotherapy, the body is in a more vulnerable condition and requires a higher nutrient intake. Subsequently, aside from addressing the malignancy itself, one should take into consideration the nutritional status of these patients, therefore, nutrition assessment is vital to the management of ovarian cancer patients. Each ovarian patient should receive a nutrition assessment, and an individualized plan for nutritional support should be followed throughout the treatment. The plan should be customized to the unique nutritional needs, attempting to prevent malnutrition, reduce side effects and enhance the over all well being of the patient. Addressing the malignancy as well as the nutritional requirements of ovarian cancer patients provides a more holistic approach to the treatment of these patients.

Since nutrition assessment is too tedious to be done on all patients, a nutrition screening tool is a practical alternative for identifying patients at risk for malnutrition. To date, there is no established nutrition screening tool for ovarian cancer.

The NRS 2002 system was chosen for this study since it was meant to cover all possible patient categories. Based on the analysis of controlled trials, it can detect the presence of malnutrition, the risk of developing malnutrition, and identify patients who are likely to benefit from nutritional support.

In the study, NRS 2002 identified 65.7% of patients with nutrition risk. Nutrition assessment, however, revealed that 100% of the patients were moderate to high risk of developing malnutrition. It is prudent to say that majority of pre- operative ovarian cancer patients will present with malnutrition, and are at an increased risk of developing malnutrition. A nutrition care plan should be initiated for these patients, as this could have positive effect on the disease course, management and quality of life of these patients.

Correlation and validity studies show a positive association between the NRS 2002 and the Nutrition Assessment Form, therefore, NRS 2002 is a simple, quick, valid screening tool which can be used to identify patients at risk of malnutrition. Inter- observer reliability studies should further be conducted to assess its reliability.

Conclusion

The NRS 2002 is a valid measure for nutrition screening among ovarian cancer patients, although further studies are recommended to test its reliability. Most pre- operative ovarian cancer patients present in a malnourished state. These patients are at further risk of malnutrition postoperatively and during chemotherapy.

To date, there is still no locally established nutrition screening tool for patients with ovarian cancer.

Recommendations

The validity and reliability of the NRS 2002 could be further tested by increasing the sample size population. The interobserver reliability of the NRS 2002 could also be investigated by testing the agreement of at least two healthcare workers (nurse, dietitian, physician) using the screening tool.

Another screening tool found in the literature was the Malnutrition Screening Tool (MST). This screening tool however, has not been validated in ovarian cancer patients. This could be the subject of another research. Furthermore, studies have been conducted on developing a nutrition screening tool specific for a disease category. Studies on developing a nutrition screening tool specific for ovarian cancer could aid in the effective nutritional intervention and management of patients with ovarian cancer.

APPENDIX A

NUTRITION RISK SCREENING (NRS 2002) (Form A)

Patient Data		
Last Name	Height (meters)	
First Name	Weight (kg)	
Room Number	BMI	
Attending MD		
Clinical Impression		

STEP 1 – Initial Screening		
Questions	YES	NO
Is the BMI < 20.5?		
Has the patient lost weight within the last three months?		
Did the patient have a reduced dietary intake in the last week?		
Is the patient severely ill (e.g. intensive therapy)		
Current risk status: no Nutritional Risk		
If YES to any question, go to STEP 2		

STEP 2- Final Screening		Place score if YES
Nutritional Status Indicators (choose one only)	Score	
Normal nutritional status	0	
Weight loss > 5% in 3 months/ or food intake below 50-75% of normal requirement in preceding week	1	
Weight loss > 5% in 2 months/ or BMI 18.5- 20.5 + impaired general condition/ or food intake 25-60% of normal requirement in preceding week	2	
Weight loss >5% in one month (or >15% in 3 months)/ or BMI < 18.5 + impaired general condition/ or food intake 0-25% of normal requirement in preceding week	3	
Clinical Condition (may choose more than one)		
Hip fracture chronic patients, in particular with acute complication; cirrhosis; COPD, chronic hemodialysis, diabetes, oncology	1	
Major abdominal surgey, stroke, severe pneumonia, hematologic malignancy	2	
Head injury, bone marrow transplantation, intensive care patients (APACHE > 10)	3	
Total Score		

ACTION TO BE TAKEN	
Total Score ≥ 3: The patient is nutritionally at risk and a nutritional care plan is initiated	
Total Score < 3: Weekly re- screening of the patient/ if the patient is scheduled for major operation, a preventive nutrition care plan is considered to avoid associated risk status	
Performed by:	Date:

NUTRITIONAL ASSESSMENT (Form B)

LAST NAME		**ROOM**		
FIRST NAME		**DATE ADMITTED**		
MIDDLE NAME		**AGE**		
ATTENDING MD		**SEX**		
HEIGHT (m)	**Weight (kg)**	**BMI**		**IBW**
		OB	**UW**	
DIAGNOSIS				

CRITERIA	**NORMAL/ MILD**	**MODERATE**	**SEVERE**
Weight loss	None	<10% of usual wt.	>10% of usual weight
Food intake (last 1-2 months)	No change	Suboptimal	Starvation
Gastrointestinal symptoms >2weeks	None	Nausea, vomiting	Anorexia, diarrhea, severe
Functional Capacity	No change	Dysfunction < 3wks Suboptimal work Bedridden < 2wks	Bedridden > 2weeks
Disease and relation to nutritional requirements	No or low stress	Moderate stress	Severe stress
Physical examination	0 subcutaneous fat and/ or muscle loss	+1 to +2 subcutaneous fat and/ or muscle loss	+3 subcutaneous fat and/ or muscle loss
Edema/ ascites	None	None	

SGA GRADE	**A (0)**	**B (1)**	**C (3)**
BMI	18.5- 25 (0)	25.1- 30 (1)	<18.5 or >30 (2)
Albumin g/dL	>3.4 (0)	2.5- 3.4 (1)	<2.5 (2)
TLC	≥1500	900 <1500	<900

Total Score	Nutritional Risk Level	0: Low risk (level 1)	≥3: high risk (level 3)
		1-2: moderate risk (level 2)	

NUTRITIONAL STATUS: ☐ **NORMAL** ☐ **MODERATE**

☐ **SEVERE**

RISK LEVEL 1 or 2, WOULD YOU LIKE TO REFER YOUR PATIENT TO THE NUTRITION SUPPORT TEAM FOR FOLLOW UP?

☐ **YES** ☐ **NO**

NAME & SIGNATURE OF RIC

DATE SIGNED

☐ **THE** **RISK LEVEL 3: REQUIRED TO BE FOLLOWED UP BY NUTRITION SUPPORT TEAM**

ASSESSMENT PERFOMED BY (Name/ signature):

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Spontaneous Pregnancy Following Surgery and Chemotherapy for Mixed Germ Cell Tumor of the Ovary in a 29 year old: A Case Report*

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Malignant germ cell tumors of the ovary account for only 0.6% of all ovarian tumors which have the propensity to develop in women in the second and third decades of life. Hence, the issue of conservation of fertility should be addressed in the choice of appropriate treatment. This is a case report of a 29 year-old patient who underwent fertility-sparing surgery and chemotherapy for malignant mixed germ cell tumor of the ovary comprising of endodermal sinus tumor and dysgerminoma at 25 years of age, then without child. The patient spontaneously conceived after 3 years of remission and subsequently undergone primary cesarean section with second-look laparotomy at term. Histopathologic findings were initially suggestive of tumor recurrence, however immunohistochemistry confirmed benign mesothelial reaction instead. This report likewise illustrates the need for thorough gross and histologic review in determining the proper approach for management and prognostication.

Key words: malignant mixed germ cell tumor, endodermal sinus tumor, fertility-sparing surgery, second-look laparotomy, reactive mesothelial cells, pregnancy outcome

Germ cell tumors account for 20% of ovarian neoplasms, of which 3% are malignant.[1] Asians have been documented to have a greater predilection for this type of tumor with an incidence of 8% to 19% usually occurring in younger women, primarily during their second and third decades of life.[2] Patients present with a palpable abdominal mass, often associated with pain and the diagnosis is confirmed during the initial surgical intervention. Monitoring of tumor markers and imaging techniques aid in the diagnosis, prognosis and follow-up of the disease.

This is a case of malignant mixed germ cell tumor of the ovary comprising of endodermal sinus tumor and dysgerminoma occurring in a nulligravid during her early reproductive years who eventually conceived spontaneously after having underwent fertility-sparing surgery and adjuvant chemotherapy. A primary cesarean section was done and subsequently, partial omentectomy, peritoneal biopsies and palpation of abdominopelvic organs. On histopathology, tumor cells were noted. Immunohistochemistry played an essential role in this dilemma negating presence of

* Second Place, 2011 SGOP Fellows' and Residents' Interesting Case Contest.

malignancy, thereby liberating patient from undergoing salvage treatment.

The Case

A. B., a 29 year old primigravid, on her 38 weeks and 5 days age of gestation, was admitted in a tertiary hospital in the Philippines for elective primary cesarean section.

On review of her medical history, the patient was a non-diabetic and non-hypertensive, and was not maintained on any medications. She has no known food or drug allergies. The patient has a family history of malignancy on her paternal side, affecting the liver and stomach of her aunt and grandmother, respectively. Her father was a known diabetic. Socio-personal history showed that she was a non-smoker, a non-alcoholic beverage drinker, with no history of illicit drug use. She was working as a hotel personnel in Dubai. Her menstrual history revealed menarche at 15 years old, with menses occurring at irregular intervals of 30 to 60 days, lasting for 3 days, consuming 2 moderately soaked napkins per day. She had her first coitus at 27 years old with one sexual partner, with no known history of sexually transmitted diseases. The patient denied oral contraceptive pill use.

Five years prior to admission, the patient underwent right salpingo-oophorectomy and left oophorocystectomy in another institution for which histopathology revealed ovarian mixed germ cell tumor (endodermal sinus tumor and dysgerminoma) of the right ovary and left dermoid cyst. Staging was inadequately done. She was asymptomatic until two months post-operatively, the patient presented with a rapidly enlarging abdomen accompanied with constipation and body weakness. She sought consult in this institution with a gynecologic oncologist and was noted to be cachectic, pale and weak-looking. Her abdomen was enlarged with a palpable mass, approximately 10cm in diameter in the suprapubic area, with limited mobility. Fluid wave sign was positive. No lymph nodes were palpated. On rectal examination, the inferior pole of the abdominal mass was not palpated.

Transrectal ultrasound revealed several irregular solid masses in both adnexa. Serum α-feto protein (AFP) and lactate dehydrogenase (LDH) were elevated, while β-human chorionic gonadotropin (β-HCG) was normal. Chest radiograph revealed minimal fluid on her left lower lung field. On Computed Tomography (CT) of the abdomen, a hepatic cyst was noted which measured 5cm in widest diameter.

She then underwent chemotherapy with Bleomycin, Etoposide and Cisplatin (BEP) and response to treatment was monitored with tumor markers and imaging. After the second cycle of BEP, the largest documented abdominal mass was noted to have decreased in size to 5cm. Ascites and pleural effusion were noted to resolve. Serum AFP and LDH showed a downward trend approaching normal limits as treatment was being given. Chemotherapy was further given to complete seven cycles affording resolution of symptoms. A referral to a gastroenterologist led to biopsy of the hepatic cyst which revealed calcified tissue. She was on close follow-up with biannual pelvic ultrasound and monitoring of serum AFP, β-HCG and LDH for one year, then annually thereafter. Abdominal CT scan was done yearly.

Her menses resumed 10 months after the last cycle of chemotherapy. She subsequently got married and within one year of marriage, the patient spontaneously conceived. She regularly sought consult for prenatal care with good compliance to medical advice. Serial ultrasound done revealed a well-grown fetus with no congenital anomalies.

The patient was received at 38 weeks and 5 days age of gestation, without labor signs, where she was eventually admitted under the care of a gynecologic oncologist for elective abdominal delivery and second-look laparotomy. She then underwent elective primary cesarean section under epidural anesthesia and delivered a live female, with APGAR score of 9, 9 weighing 3,290 grams, with a birth length of 48cm, 37 weeks, appropriate for gestational age. Intra-operatively, there was no ascites noted. The liver, gallbladder, subdiaphragmatic surface, stomach, spleen, kidneys, appendix and intestines were all grossly normal. A greenish kidney-shaped, solid mass measuring 1.5cm x 1cm was seen intra-abdominally with no noticeable attachments to any abdominal organ. Part of the omentum was adherent to the anterior abdominal wall. Adhesions

were also noted between the intestine and pelvic side wall. The right ovary was surgically absent, and the left ovary was grossly normal, approximately 1cm x 0.5cm in size. The left fallopian tube was grossly normal. The surgery included partial omentectomy, peritoneal biopsies, resection of adhesion and palpation of abdomino-pelvic organs under epidural anesthesia. The procedure was well tolerated by the patient and no postpartum morbidity was noted.

The following specimens were sent for histopathology: omentum, intestinal adhesion, kidney-shaped intra-abdominal mass, bladder peritoneum and anterior abdominal peritoneum. Peritoneal fluid washing was also sent for cytologic review. Histopathology revealed tumor implants in sections from the omentum. Peritoneal fluid yielded positive malignant cells.

A rigorous review was performed in order to confirm post-operative histopathologic findings. Immunostaining was employed to further determine recurrence of malignancy and to delineate it from reactive mesothelial cells, an entity that may have the same presentation histologically.

After comprehensive evaluation, the initial histopathologic diagnosis was subsequently revised. Immunostains with α-fetoprotein (AFP), placental alkaline phosphatase (PLAP) and low-molecular weight cytokeratin (CK) were all negative whereas stain for calretinin was positive. Thus, final histopathologic diagnosis showed the omentum was negative for tumor, and positive for reactive mesothelial cells. Cytology of peritoneal fluid was likewise negative for tumor, and revealed reactive mesothelial cells. Intra-abdominal mass was composed of degenerated and necrotic tissues, and was negative for tumor. Sections from bladder peritoneum and anterior abdominal peritoneum were likewise negative for tumor cells.
The final diagnosis was *Pregnancy Uterine delivered term, cephalic, live birth via Elective Primary Cesarean Section with Partial Omentectomy, Peritoneal Biopsies, Resection of Adhesion, Palpation of abdomino-pelvic organs; Mixed Germ Cell Tumor (Endodermal Sinus Tumor, Dysgerminoma) S/P Right Salpingo-oophorectomy, Left Oophorocystectomy – Dermoid Cyst (2005); S/P Chemotherapy (Bleomycin-Etoposide-Cisplatin) x 7 cycles; No evidence of disease.*

Three months post-partum, on follow-up, the patient was asymptomatic with a good sense of well-being. Her tumor markers were normal and her latest CT scan of the whole abdomen revealed no noted abnormalities within the uterus and right adnexal area, and a normal-sized left ovary. No other masses, lymphadenopathy and other signs of metastasis were seen. Her baby was healthy.

Discussion

Germ cell tumors are the second most common group of ovarian malignancies that occur across all ages comprising 15% to 20% of reported cases worldwide.[3] These consist of several histologically different tumor types derived from primitive germ cells of embryonic gonads and are classified based on the existing degree of differentiation of the tumor cells (Figure 1).

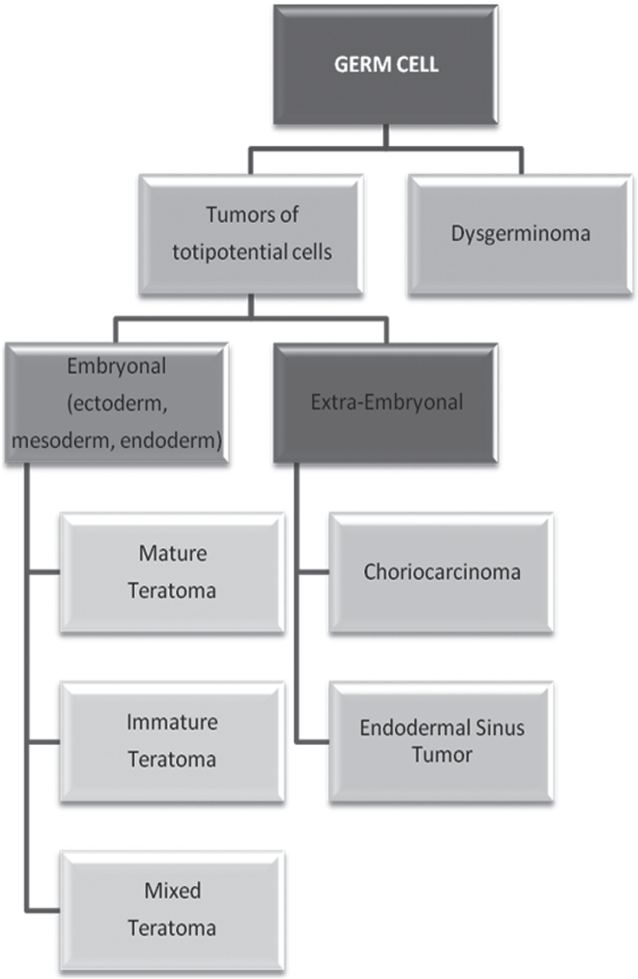


Figure 1. Classification of germ cell tumors.

Malignant germ cell tumors of the ovary account for only 0.6% of all ovarian tumors. These tumors clinically behave depending on whether they are histologically pure, consisting of one cell type, or mixed, of which behavior conforms to the most aggressive subtype.[4] From 1973 to 2002, the Surveillance Epidemiology and End Results (SEER) revealed the following distribution for these types of tumors: 32.8% dysgerminoma, 35.6% immature teratoma, 2.9% mature teratoma with malignant degeneration and 28.7% mixed germ cell carcinoma.[5]

Mixed germ cell tumors which show almost any combination of germ cell elements are common in the testis, but rare in the ovary.[4] This occurs in 5% to 10% of ovarian malignant germ cell tumors. Females in the age group of 4 to 28 years old, with median age of 12 years are commonly affected.[6] The patient in this case report was diagnosed with ovarian mixed germ cell tumor consisting of dysgerminoma and endodermal sinus tumor. Of the two, the latter exhibits greater malignant germ cell elements. The clinical course in most patients with tumors of this combination does not differ greatly from that in patients with pure endodermal sinus tumors.[1]

Dysgerminoma occurs in 3% to 5% of ovarian malignancies which consists of germ cells that have not differentiated to form embryonic or extraembryonic structures. It may involve the contralateral ovary in 10% to 20% of cases.

Endodermal sinus tumor (or yolk sac tumor) is the second most common type of ovarian malignant germ cell tumor occurring among women with a median age of 19 years old. These patients are initially seen complaining of abdominal pain with a rapidly enlarging palpable abdominal or pelvic mass. Most patients have early stage disease: 71% stage I, 6% stage II, and 23% stage III.[7] These tumors are highly malignant. Early metastasis and invasion to surrounding structures is its usual course. Intra-abdominal spread causes extensive involvement of abdominal structures with tumor deposits and metastasis also occurring via lymphatic system. Therefore, there is a need to employ immediate and adequate treatment since cure from this malignancy is within reach.

Generally, the surgical approach should be tailored to every patient. Since occurrence of this type of cancer is more predominant in girls and young women, fertility preservation is a major concern among patients undergoing treatment. Fortunately, despite the aggressive nature of this tumor, they tend to involve only one ovary. In this regard, conservative surgery followed by chemotherapy compared with radical surgery has been reported to be equally effective for patients with stage I tumors.[8]

Every attempt should be made to perform a careful surgical staging procedure followed by a unilateral salpingo-oophorectomy. It is necessary to evaluate the contralateral ovary since this may occasionally be pathologic, especially in cases of dysgerminoma, which has the propensity for bilaterality in 10% to 20% of cases. If the contralateral ovary appears diseased, biopsy or cystectomy is warranted, and should frozen section confirm a diagnosis of malignancy, this ovary should likewise be removed. However, given that a careful inspection is conducted revealing a normal contralateral ovary, this should be left alone. Performing wedge biopsy in normal-looking contralateral ovaries has the potential for surgical complications such as hemorrhage or adhesion formation that may affect fertility and is not recommended.[1] In the case of the patient, she underwent right salpingo-oophorectomy and inspection of her left ovary revealed another cystic mass. Left oophorocystectomy was performed for dermoid cyst and normal ovarian tissue was then conserved. However, complete surgical staging was not performed.

Recent studies showed that, with surgery and aggressive combination chemotherapy, the 5-year survival for patients with stage I tumors and more advanced disease were 92% and 29% to 44%, respectively.[3] Approximately 20% of patients with germ cell malignancies treated with surgery alone will be expected to recur. Adjuvant chemotherapy after completely resected tumor can afford cure in nearly 100% of patients with early stage disease, and at least 75% for those with advanced-stage disease.[7] Hence, this speaks of the vital role of chemotherapy in the treatment of patients with malignant germ cell tumors.

Cisplatin-based regimen and the use of Etoposide were initially noted to be successful in the treatment of testicular germ cell tumor; consequently the current

combination platinum-based chemotherapy for ovarian germ cell malignancies has evolved to utilize Bleomycin, Etoposide and Cisplatin (BEP). The Gynecologic Oncology Group (GOG) prospectively assessed this regimen among women with stage I to III disease, given as three cycles of adjuvant chemotherapy. Ninety-one of 93 were noted to be free from recurrence upon follow-up establishing the effectiveness of this regimen. The chemotherapeutic drug toxicity incurred in the study was considered acceptable. This study paved the way for BEP regimen to become the standard chemotherapeutic regimen for the adjuvant treatment of malignant germ cell tumors. In many cases, only 3 or 4 courses have placed patients into remission with long term survival.[1]

In general, germ cell tumors possess the unique property of producing biologic markers. Accurate measurements of these markers prove to be useful for monitoring the results of treatment and for detecting subclinical recurrences. Mixed germ cell tumors may produce either both or none of the markers depending on the type and quantity of elements present. Endodermal sinus tumor secretes AFP and serves as a guide to the number of chemotherapy courses needed by the patient. This tumor marker has been reported to be 57% sensitive and 78% specific for endodermal sinus tumor.[9] Dysgerminoma is commonly devoid of hormonal production although a small percentage of tumors may tend to produce low levels of β-HCG if multinucleated syncytiotrophoblastic giant cells are present within the tumor tissue. LDH and CA-125 levels can be elevated, however these are less specific.[10]

In the latest 2011 National Comprehensive Network Clinical Practice Guidelines in Oncology (Figure 2), it is generally recommended to treat endodermal sinus tumor, of any stage, even in cases that were incompletely surgically staged, with BEP - regimen. For patients who show complete clinical response, they are observed and tumor markers are

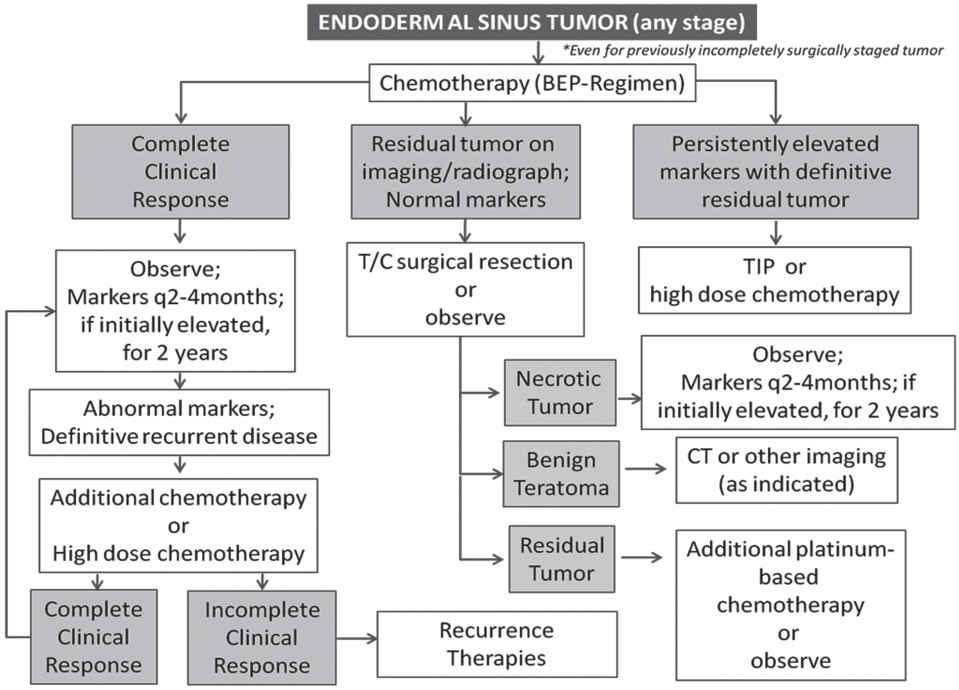


Figure 1. 2011 NCCN guidelines on treatment and follow-up of patients with endodermal sinus tumor[11]
BEP - Regimen: Bleomycin 30 units per week, Etoposide 100 mg/m^2/d daily for days 1-5, Cisplatin 20mg/m^2/d daily for days 1-5 for 3 to 4 cycles
Recurrence Therapies: 1) High-dose chemotherapy: Cisplatin/etoposide; Docetaxel; Docetaxel/Carboplatin; Paclitaxel; Paclitaxel/Ifosfamide; Paclitaxel/Carboplatin; Paclitaxel/Gemcitabine; VIP (Etoposide, Ifosfamide, Cisplatin); VeIP (Vinblastine, Ifosfamide, Cisplatin); VAC (Vincristine, Dactinomycin, Cyclophosphamide); TIP (Paclitaxel, Ifosfamide, Cisplatin; 2) Radiation therapy; 3) Palliative care

measured every 2 to 4 months for 2 years if the markers are initially elevated. Should tumor markers fail to normalize after 3 to 4 cycles of BEP, additional chemotherapy may be given or high dose chemotherapy may be started. Persistently elevated markers despite BEP - chemotherapy with identified residual tumor should undergo high dose chemotherapy. Among patients who show incomplete clinical response, recurrence therapies have been enumerated which includes high dose chemotherapy, radiation therapy and palliative care.[11]

After completion of treatment, the Society of Gynecologic Oncologists of the Philippines recommends follow-up as frequent as every 3 months for 4 visits, every 4 months for 3 visits, every 6 months for 6 visits and annually thereafter. Tumor marker determination is advised every visit. Transvaginal ultrasound with or without color Doppler studies should be done every 4 to 6 months and an annual CT scan or MRI for the first 3 years post-treatment.[12]

In the patient, AFP, β-HCG and LDH were monitored to assess her response to treatment. This was accompanied by pelvic ultrasound to evaluate initially noted abdominal masses. Although not yet normal after the fourth cycle of chemotherapy, serum AFP and LDH showed a downward trend on monitoring. Further, serial pelvic ultrasound performed revealed a drastic decrease in size of the abdominal masses. BEP - chemotherapy was continued for 7 cycles based on the levels of tumor markers obtained on close follow-up. After complete clinical response was noted, monitoring with tumor markers and imaging revealed no evidence of disease.

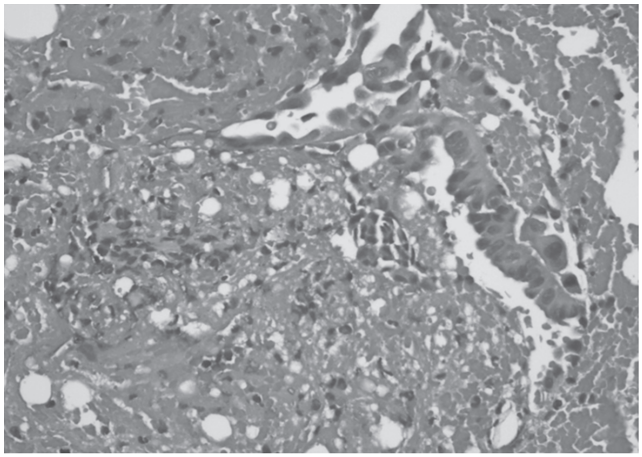
Frequently, chemotherapeutic drugs are used in combination to improve anti-tumor effects, however, with increasing toxicity. Late complications include secondary malignancies and adverse effects in the ovaries. Ovarian damage and subsequent failure is a common long term side effect of curative chemotherapy. Clinical studies have emphasized the importance of age as a pertinent factor in determining the effects of chemotherapy in ovarian function. Older women were documented to have a higher incidence of complete ovarian failure and permanent infertility, whereas young girls and adolescents are considered to be more resistant probably due to larger follicle stores prior to treatment. With many young patients, cyclic menses may proceed with discontinuation of treatment. Studies have observed a significant number of younger patients who continued to have regular menses, however, after chemotherapy, they were at risk for undergoing premature menopause. Patients are subsequently encouraged childbearing however, should be beyond 6 to 12 months after treatment to avoid toxicity on growing oocytes.[13]

Several studies have documented successful pregnancies in young patients with malignant ovarian germ cell tumors who underwent fertility-sparing surgery and combination chemotherapy. In a questionnaire study conducted by Gershenson, 33 out of 40 patients (83%) who were treated with fertility-sparing surgery followed by chemotherapy were noted to have regular menses. Of 16 patients who had attempted pregnancy since chemotherapy, 11 delivered 22 healthy infants, with no noted major birth defects. In a study conducted by Brewer, of the 26 patients who underwent fertility-sparing surgery and platinum-based chemotherapy for ovarian dysgerminoma, 71% maintained normal menstrual function during and after chemotherapy, and 93% had returned to their normal menstrual pattern. Several live births were reported in each of these series.[14] In a retrospective study performed by de La Motte Rouge, regular menstruations were noted after achieving a complete remission in 39 of 40 (97%) patients treated with conservative surgery followed by BEP - chemotherapy for pure and mixed endodermal sinus tumor. The median time to full recovery of regular menses was five (1 to 8) months after chemotherapy. During the follow-up period, 19 pregnancies were recorded in 12 of 16 (75%) of women who attempted conception. Ultimately, 15 children free of any malformations or developmental problems were born to 11 patients.[15] A recent retrospective study conducted by Weinberg among patients who had fertility-sparing surgery revealed that 8 out 10 patients had 11 successful spontaneous pregnancies, resulting to subsequent live births. All patients had normal menstrual cycle within one year of completing chemotherapy.[16] In the patient presented in this report, her menses resumed 10 months after her last cycle of chemotherapy. Two years after, the patient spontaneously conceived.

Second-look laparotomy was originally included in the management of patients with epithelial ovarian cancer to assess disease status after completion of a fixed number of chemotherapy treatments. This practice was extended to patients with other ovarian tumors, including the germ cell types. The role of second-look laparotomy is not established in patients with endodermal sinus tumors. In a study conducted by Williams, they reported on 117 patients with malignant ovarian germ cell tumors that underwent second-look laparotomy after treatment with Cisplatin-based chemotherapy in 3 trials of the GOG. They concluded that patients with either completely resected tumors or advanced-stage, incompletely resected tumors without elements of teratoma, rarely, if ever, benefit from second-look laparotomy.[17] It may be reasonable to omit a second-look operation among patients whose AFP values return to normal during the course of treatment. However, there have been reported cases in which AFP titers have returned to normal in spite of persistent measurable disease and some of these cases have been mixed germ cell tumors[7]. At 38 weeks and 5 days age of gestation, the patient underwent primary cesarean section and second-look laparatomy in order to survey and determine evidence of malignancy, if any. This was likewise performed given that the previous operation was done by another physician. Partial omentectomy, peritoneal biopsies and palpation of abdomino-pelvic organs were performed.

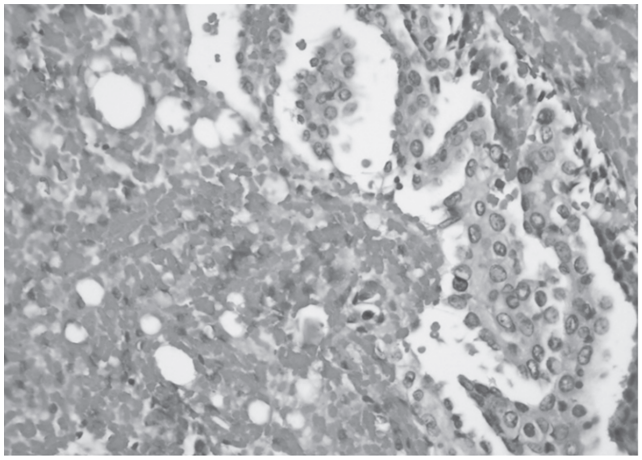
The patient was initially diagnosed with tumor recurrence based on the findings of malignant cells on the following specimens sent: omentum and peritoneal fluid. In the omentum, a cluster of viable cells were noted on higher magnification. The cells were composed of a strip of tall columnar epithelium, with stratified nuclei, and noticeable nuclear enlargement was exhibited by some cells. Cytoplasm was noted to be scanty and blood elements were entrapped within these cells. Peritoneal fluid cytology revealed atypical cells forming short papillae. Nuclei were vesicular, with partial clearing and varied sizes (Figure 3). This diagnosis was ultimately revised on second opinion, as these findings were adjudged as reactive mesothelial cells, more than cancer.

Mesothelial cells normally line peritoneal, pleural, and pericardial cavities of the body as well as the surface epithelium of the ovary. Irritation of serosal surfaces, with or without subsequent effusion, induces the proliferation of mesothelial and often sub-mesothelial cells, giving rise to a variety of hyperplastic appearances. In some instances, the degree of hyperplasia may be so severe as to suggest a malignant process. The invasion of intraperitoneal organs or fat is the most reliable indicator for malignancy, but this may be mimicked by mesothelial cells entrapped in



40x: Omentum

Atypical cells noted were composed of a strip of tall columnar epithelium with stratified nuclei and noticeable nuclear enlargement exhibited by some cells. Blood elements were trapped within. This was read as positive for tumor.



40x: Peritoneal Fluid

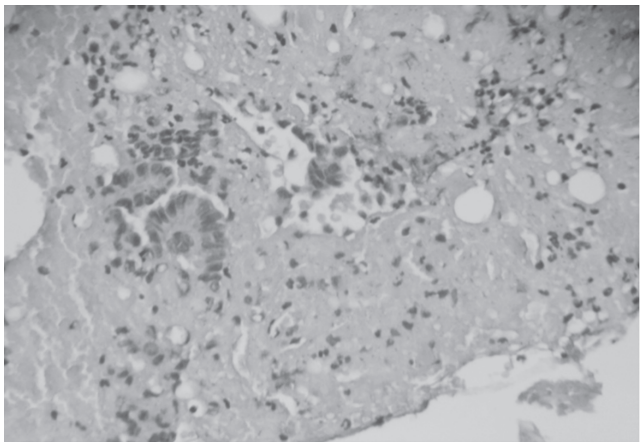
Atypical cells form short papillae with round nuclei which were vesicular with partial clearing and variation in size. This was read as positive for tumor.

Figure 3. H & E.

organizing granulation tissue or between fat lobules. These benign cells usually arrange themselves in a more orderly fashion and parallel to the peritoneal surface, and they are associated with perpendicular blood vessels and abundant histiocytes; however all manner of exceptions can occur. Malignancy is highly suspected if atypical cells cluster within the stroma, particularly arranged in cords, nodules, papillae or gland-like structures. However, benign reactive, entrapped mesothelial cells may also focally present with this malignant appearance. *Hyperplasia* of the omental or adnexal *mesothelium* may accompany different pathologic conditions of the female genital tract, such as endometriotic cysts, tubal *pregnancy*, pelvic inflammatory disease, and *ovarian* tumors. Pregnancy causes a decidual reaction which causes metaplasia involving the submesothelial stroma[18] which may have predisposed the patient to have these benign histopathologic findings. With this dilemma of differentiating carcinoma from reactive mesothelial cells, further evaluation is necessary. Immunohistochemistry study is of utmost importance. Calretinin shows the best sensitivity and specificity to determine the presence of mesothelial cells.[19] Calretinin is a calcium adhesion protein that is mainly expressed in the nervous system, however its expression in mesothelial cells allows it to be a powerful discriminator of mesothelial cells from other cell types.[20] Reactive mesothelial cells exhibit nuclear and cytoplasmic calretinin positivity. A study conducted by Kachali, et al. revealed calretinin to have as much as 95% sensitivity and 86% specificity. However, values vary from one study to another. During the United States and Canadian Academy of Pathology 94th Annual Meeting, the sensitivity of calretinin as a mesothelial marker was declared to be 84%.[19]

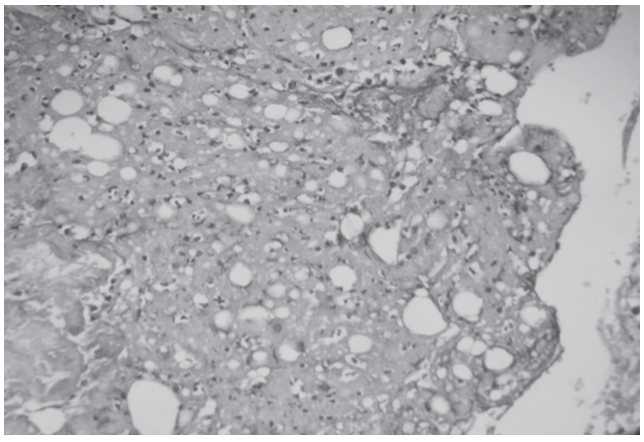
In addition to using positive markers for mesothelial cells, it is also prudent to include in the panel antibodies which are negative mesothelial markers and should be positive in the type of cancer considered. In the case of the patient, immunostain panel included α-fetoprotein (AFP), placental alkaline phosphatase (PLAP) and low-molecular weight cytokeratin (CK). AFP and CK are useful markers in the diagnosis of endodermal sinus tumor and PLAP for dysgerminoma.

Had the patient been diagnosed with tumor recurrence after second-look laparotomy, salvage treatment may have been employed with high dose chemotherapy accompanied with monitoring of response through imaging techniques and tumor marker determinations. Further, this will also lead to emotional and psychological stress brought about by the recurrence of disease. However, on utilization of immunostains, AFP, CK and PLAP all tested negative (Figures 4, 5, 6). Calretinin was positive, confirming presence of reactive mesothelial cells, and ultimately absence of disease (Figure 7). Thus, in such case, annual follow-up and continued determination of tumor markers and imaging will be done on every visit.



Omentum

Negative for tumor.



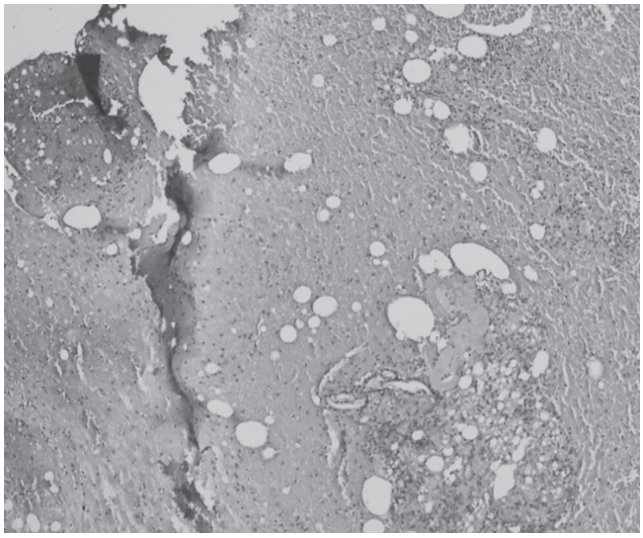
Peritoneal Fluid

Negative for tumor.

Figure 4. Immunostain, AFP

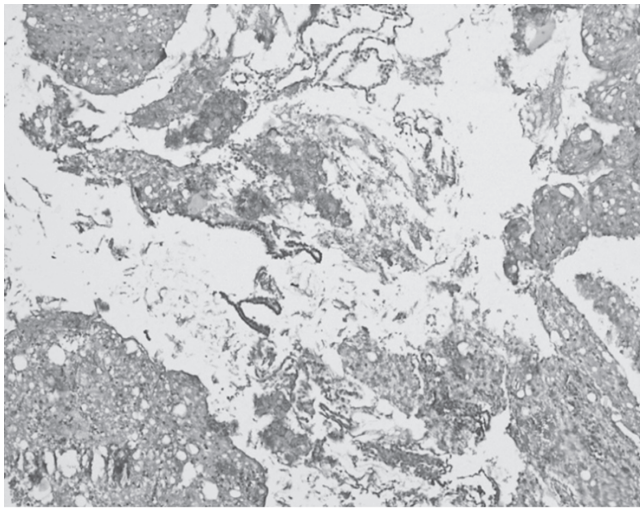
Conclusion

Malignant germ cell tumors of the ovary are rare, more frequently affecting young girls and women of early reproductive age, hence sparing the patients' reproductive potential is of essence. The patient is an example of a cancer survivor who underwent fertility sparing surgery and had a successful pregnancy outcome. Her case illustrates that combination chemotherapy is an effective therapeutic regimen to address cure in cases of tumor progression. Treatment must always be individualized to every patient. Moreover, a thorough histopathologic review should always be conducted, since a reactive physiologic process, though uncommon, may be mistaken for malignancy.



Omentum

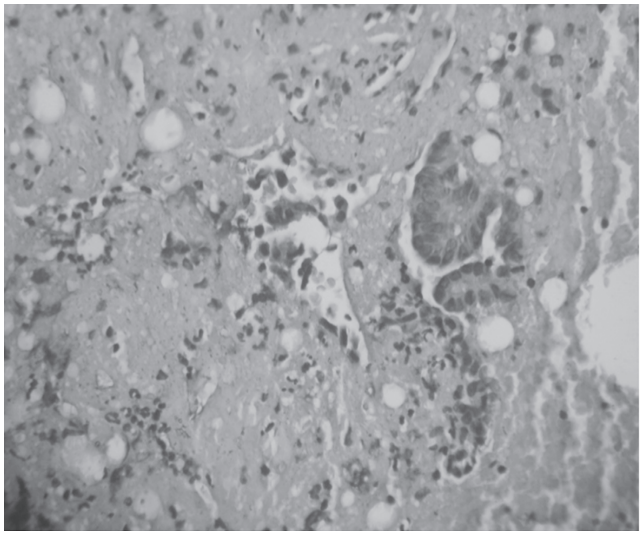
Negative for tumor.



Peritoneal Fluid

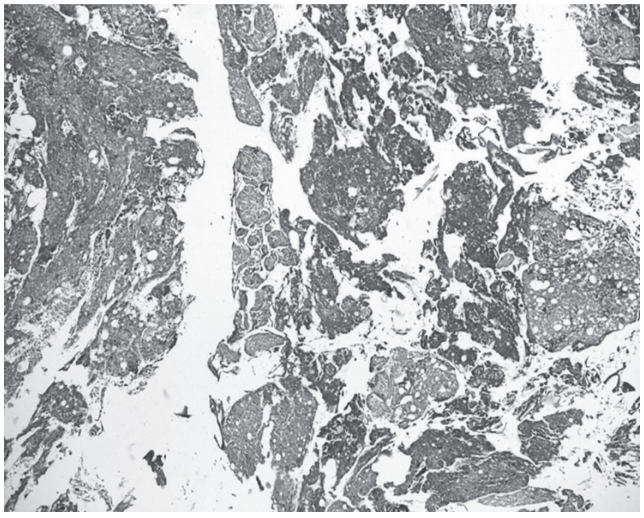
Negative for tumor.

Figure 5. Immunostain, PLAP.



Omentum

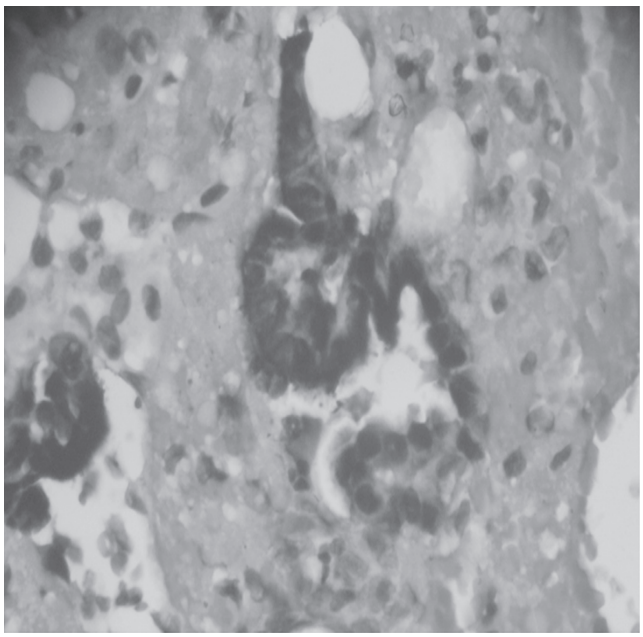
Negative for tumor.



Peritoneal Fluid

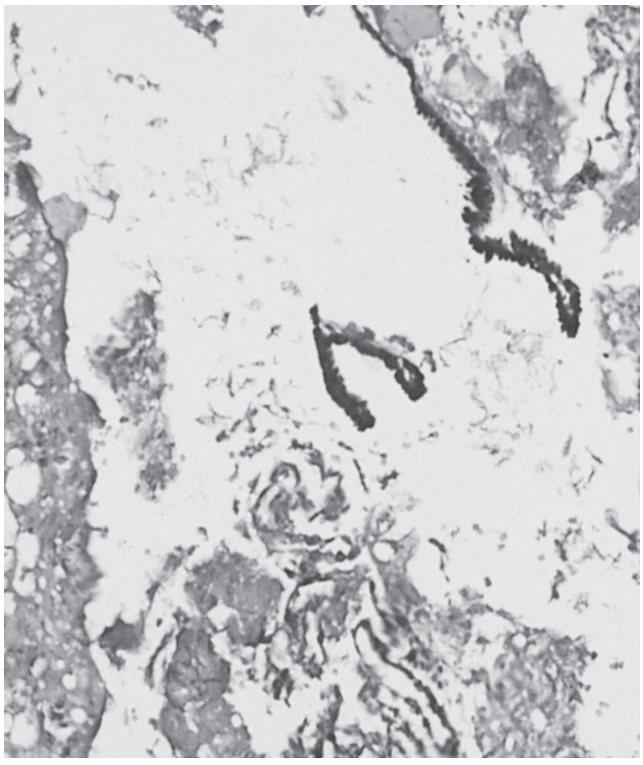
Negative for tumor.

Figure 6. Immunostain, CK.



Omentum

Positive for reactive mesothelial cells.



Peritoneal Fluid

Positive for reactive mesothelial cells.

Figure 7. Immunostain, Calretinin.

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Successful Pregnancy Following Radical Vaginal Trachelectomy for Early Stage Cervical Carcinoma*

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In the Philippines, cervical cancer is the second most common malignancy among women. For this reason much attention has been put to early detection and treatment of the disease. The importance of Pap smear and visual inspection with acetic acid as screening tools cannot be overemphasized.

The standard management for early stage cervical carcinoma remains to be radical abdominal hysterectomy plus pelvic lymphadenectomy, or chemoradiation. Young patients desiring fertility conservation, diagnosed with early stage cervical cancer may opt for radical vaginal trachelectomy as a method of management. It maintains the radicality required to excise the diseased cervix yet allowing future pregnancy to occur. In the Philippines, there have been two reported radical vaginal trachelectomies done for fertility preservation. This is the third case done in the country, the very first one performed outside of Manila, and the very first to achieve successful pregnancy and delivery following radical vaginal trachelectomy.

Key words: radical vaginal trachelectomy, early stage cervical cancer

In women worldwide, cervical cancer comprises 12% of all cancers. It is estimated that 231,000 women die of cervical cancer annually and over 80% of whom lives in developing countries like the Philippines. Locally, cancer ranks third among the leading causes of morbidity and mortality. Among women, cervical cancer is the second most common cancer following breast cancer.[1] In the annual report of the Filipino Cancer Registry in 2005, the incidence of cervical cancer remains the same over a period of 25 years (1980-2005), with an annual age-standardized incidence rate of 22.5 cases per 100,000 women. In the same report, it was cited that there were 7,277 new cases of cervical cancer, with 3,807 reported deaths in 2005, with an overall 5-year survival rate of 44% and the mortality rate was cited at one per 10,000 women.[2] Almost 75%

* Third Place, 2011 SGOP Fellows' and Residents' Interesting Case Contest.

of cervical cancers in the Philippines are diagnosed at an advanced stage, reflecting a poor implementation of an otherwise good screening method such as Pap smear. Mostly due to inadequate radiotherapy facilities, mortality is thus high. The good thing is cervical cancer is a preventable disease and to say the least, has a very good survival rate if detected at the pre-invasive stage.[1] A promising survival rate between 95% to 98% is cited with surgical intervention at an early stage with no lymph node involvement.[3]

The success of cervical cancer prevention, however, depends mostly on a well-organized screening program. To date, cervical cytology remains to be the only test known to reduce cervical cancer incidence in organized screening programs.[1] In the Philippines like most other developing countries, there is difficulty implementing such organized screening programs mainly due to scarcity of resources and the geographic limitations, among others. The importance of early detection of cervical cancer cannot be overemphasized. The disease has a long pre-cancerous period of at least 10 years and as long as 30 years wherein it can be detected by the conventional screening method of cervical cytology or Pap smear.[4] The use of adjunctive methods, such as visual inspection with acetic acid (VIA) has improved much the sensitivity of cervical cytology or Pap smear (from 57.4% to 83.3%) when used together as a screening method for cervical cancer.[5]

In the recent years, more women in the younger age group (24-35 years) comprise approximately 10% to 15% of cervical cancer cases and the quality of life following treatment is a major consideration.[6] In Western countries, women often delay childbearing for various reasons that when a diagnosis of carcinoma is made, fertility sparing treatment would be most favored option.[5] Although in most developing countries, including the Philippines, most women of the same age group will most probably have completed their family size, the issue of fertility preservation is still highly considered perhaps due to some social and cultural reasons. Hence, fertility preservation becomes a major issue in the management of early stage cervical cancer.

The standard management of early stage cervical carcinoma is radical hysterectomy plus pelvic lymphadenectomy, or chemoradiation. It poses a potential loss of fertility. A more conservative procedure was developed more than 20 years ago in the form of radical vaginal trachelectomy by Daniel Dargent, et al. It was followed by several other authors and experts. To date, there are 7 centers worldwide performing the procedure and the literatures are quite encouraging. Success in terms of oncologic as well as pregnancy outcomes is reassuring.[5] Overall recurrence rate in 4 published series including a total of 130 cases is in the range of 3.1% (4 out of 130) which is comparable to that reported after radical hysterectomy.[7] A number of case series of successful pregnancies following radical trachelectomy has already been published.[8] Few local journals featuring radical vaginal trachelectomy as a method of managing invasive cervical cancer are available, including those done in the Philippines. The first two cases done were abdominal radical trachelectomy for cervical stump cancer early stage disease. The same surgeon did two fertility-preserving vaginal radical trachelectomies for early stage cervical cancer. (Personal communication) A third case of fertility-sparing radical vaginal trachelectomy for minimally invasive cervical carcinoma in a 30 year old primipara was reported.[9] Among the cases of radical vaginal trachelectomy done for fertility-preservation in the country, the latter is the first case to achieve a successful pregnancy and delivery.

The Case

This is a case of a 32 year old, married, healthy primipara, diagnosed at age 30 with squamous cell carcinoma of the cervix stage 1, with a strong desire for another pregnancy who underwent the fertility-sparing radical vaginal trachelectomy in our institution. Earlier, she has had 3 early pregnancy losses, 2 were due to abortion and another one was an ectopic pregnancy, for which she underwent salpingotomy. There was a very strong family background for carcinoma. An aunt and a cousin on the paternal side died of brain tumor and thyroid carcinoma, respectively, and she had a sister who was diagnosed with cervical carcinoma at age 35, who died 2 years later. She had her sexual debut at the age of 24, with a total of 4 sexual partners. Annually for 3 years, the

patient had regular Pap smear which were all consistent with cervicitis and were subsequently treated.

Three years prior to admission, the patient was diagnosed with cervical carcinoma stage 1 (squamous cell, large cell keratinizing) by way of colposcopy-guided biopsy after persistent aceto-whitening on visual inspection using 5% acetic acid (VIA). She was subsequently referred to and seen by a gynecologic oncologist. Metastatic work-up was done. Chest radiography, liver and renal function tests were normal. An abdominopelvic CT scan was negative for pelvic and para-aortic lymph node involvement. Due to her strong desire to conceive again, she consented to undergo the fertility-sparing radical vaginal trachelectomy (Figure 1) with extra-peritoneal lymph node dissection (Figure 2) with frozen section biopsy (Figure 3) under subarachnoid block. Total operative time was 2 hours and 45 minutes. The post-operative course of the patient was otherwise uneventful and she was discharged free of any symptoms on the second postoperative day. The final histopathologic report of the permanent section revealed *Sinus Histiocytosis of both the right and left pelvic lymph nodes; Chronic Endocervicitis, Moderate, Endocervix; Minimally Invasive Squamous cell carcinoma, Large Cell Keratinizing at 6 & 12 o'clock positions. NO Lymphatic or Vascular Invasion.* (Figure 4) Hence, the final diagnosis at that time was squamous cell carcinoma of the cervix, large cell, keratinizing, stage 1A2, G4P1 (1031), status post salpingotomy (2004), status post extra-peritoneal bilateral lymph node dissection, radical vaginal trachelectomy with frozen section biopsy.

Patient had regular follow-up with the gynecologic oncologist and 3 months post-operatively, Thin-Prep Pap smear and HPV DNA test were negative. She has received three doses of HPV vaccine. The patient had no evidence of disease for over a year after the procedure was done. After thorough fertility work-up was done, 17 months post-trachelectomy, the patient spontaneously conceived. She had an elective prophylactic cerclage (Mc Donald's procedure) using Mersilene tape (0.5mm width) at 14 weeks and 3 days age of gestation. (Figure 5) The patient was given a full course of dexamethasone 12mg every 24 hours for two doses at 28 weeks. The pregnancy was otherwise uncomplicated, until she entered early third

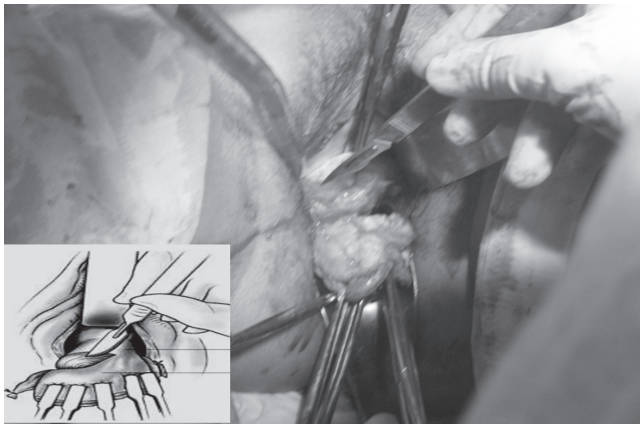

Figure 1. Radical vaginal trachelectomy. Cervical amputation 1 cm from isthmus after dissection of vesicouterine and rectovaginal mucosa.

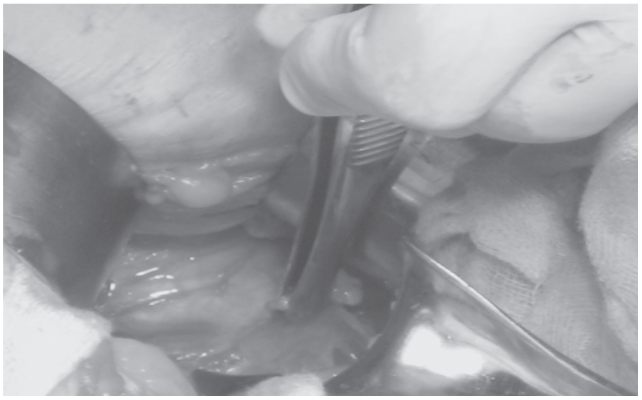

Figure 2. Extra-peritoneal bilateral lymph node dissection. Resection of iliac and obturator nodes en bloc along the vascular adventitia.

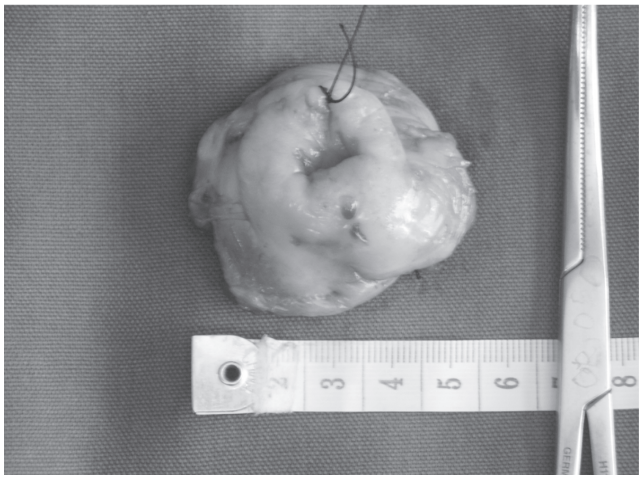

Figure 3. Specimen sent for frozen section biopsy.

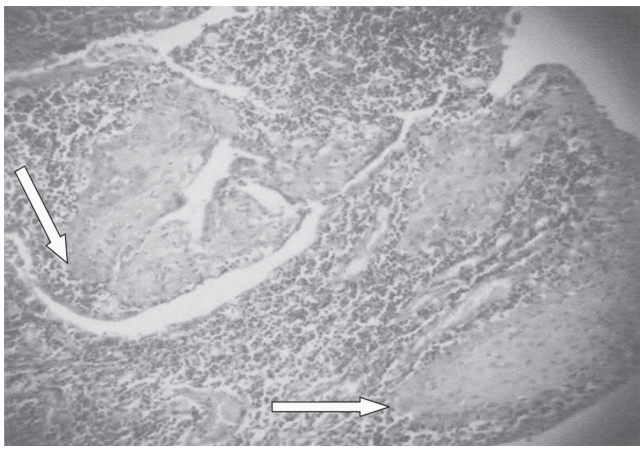

Figure 4. Section shows large atypical squamous cells invading stroma; invasion depth is 3mm.

trimester (at 31-32 weeks age of gestation), when she was admitted due to preterm labor. Co-managed with a perinatologist, tocolysis with nifedipine 30mg was instituted every 8 hours and she was put on complete bed rest. The patient was given rescue dose of steroid (dexamethasone 12 mg IVTT) for fetal lung maturity. However, on the fourth day of tocolysis there was note of spontaneous variable decelerations in the fetal heart tones, hence the patient underwent primary low segment caesarean section to deliver a live preterm baby girl weighing 1.9 kilograms, with APGAR score of 8 and 9, at one and five minutes of life, respectively, with Ballard score of 32 weeks. Subsequently, the team proceeded with total hysterectomy based on the patient's expressed decision made pre-operatively. Intra-operatively, the parous uterus measured 17cm x 12cm x 5cm in dimension, with the remaining cervical length measuring one centimetre from the lower uterine segment, with the Mersilene tape in place. (Figure 6) Both ovaries and fallopian tubes were noted to be grossly normal. Three days postoperatively, the patient was discharged improved. The histopathologic result revealed hypertrophy of the smooth muscles, myometrium, uterus. The final diagnosis was pregnancy uterine, cephalic delivered preterm livebirth baby girl by primary low segment cesarean section secondary to non-reassuring fetal heart rate pattern (variable deceleration); G5P2 (1132); status post radical vaginal trachelectomy with extra-peritoneal bilateral pelvic lymph node dissection for squamous cell carcinoma of the cervix stage IA2 (2008), no evidence of disease.

Discussion

The case of a 32 year old, married, primipara who had a successful pregnancy after she underwent the fertility-sparing radical vaginal trachelectomy for squamous cell carcinoma of the cervix, large cell keratinizing, stage 1, is presented.

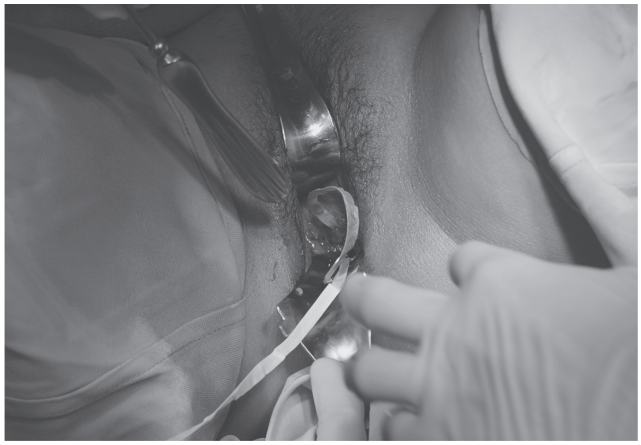

Figure 5. Elective cerclage (McDonald's Procedure) at 14 weeks and 3 days AOG.

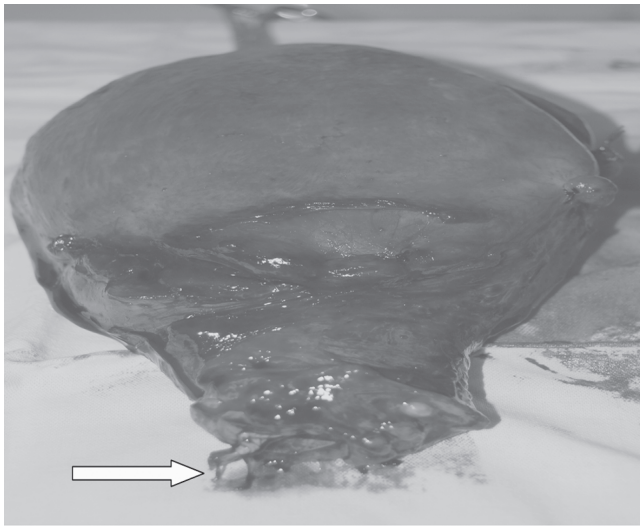

Figure 6. CS-hysterectomy specimen: parous uterus measured 17cm x 12cm x 5cm; remaining cervix measured one centimeter from the lower uterine segment, with the Mersilene tape in place (arrow).

Worldwide among women across ages, cervical cancer is the second most common cancer following breast cancer. Almost half a million cases are diagnosed each year, 80% of whom are from developing countries like the Philippines. The overall survival rate is 44% or 10 in 100,000 women die of the disease in five years. This is perhaps due to the fact that almost 75% of patients with cervical cancer in the country are diagnosed at an advanced stage.[1] This reflects the poorly implemented screening method of Pap smear as seen in the dismal 7.7% total Pap smear coverage among Filipino women 18-69 years of age.[2] On the other hand, in western countries where screening programs for cervical cancer is well-imposed and the pick-up rate for early stage carcinoma is relatively high, the incidence of advanced disease is markedly low.[5] With surgical treatment, there is a very good survival rate of between 95% to 98% among patients with early-stage cervical carcinoma when the pelvic lymph nodes are negative.[3] In the USA and UK, 43% of cervical cancer is diagnosed among women younger than 45 years.[5] Concurrently, the women in these countries are more career-oriented and often delay childbearing, so that a more conservative, fertility sparing treatment is favored when cervical carcinoma is diagnosed. For some cultural and social reasons, Filipino women of the same younger age group, including those with completed family size, when diagnosed with such invasive disease, would still opt to preserve the uterus.

Large randomized controlled studies using sensitive and specific polymerase chain reaction (PCR) assays strongly showed the causal relationship of Human Papillomavirus (HPV) infection to CIN and eventually to cervical carcinoma. HPV is a member of the Papovaviridae family and is a double-stranded DNA virus. The more high risk types, HPV 16 and 18 are consistently found in more than 90% of cervical cancers. They have the transforming viral oncogenes (E6 and E7) which integrate with the host genome coupling directly to the viral enhancer and promoter sequences in the HPV upstream regulatory region thereby allowing their continued expression.[10] Moreover, these oncoproteins up-regulates the telomerase causing disruption of the replicative senescence leading to immortalization of the cell and mitotic defects and genomic instability.[11] (Figure 7) All of these lead to cervical intraepithelial neoplasia which may exist in a non-invasive stage for as long as 20 years before eventually progressing to cervical cancer.

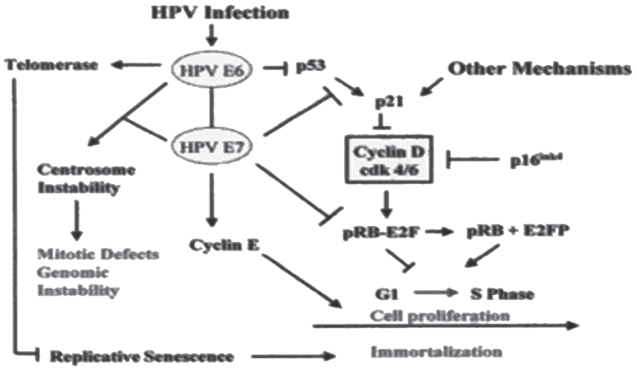

Figure 7. Diagram of mechanisms by which Human Papillomavirus (HPV) affects cell biology that leads to cell proliferation (Sternberg, et al. 2004).

The importance of a screening method in the detection of early stage or pre-invasive cervical carcinoma cannot be overemphasized since there is a big window of opportunity to treat women found with pre-malignant lesions. Germar MJ stated that Visual Inspection with Acetic acid (VIA) has similar sensitivity with cervical cytology in detecting pre-invasive disease but has lower specificity. The sensitivity of cervical cytology as a screening method has improved greatly, from 57.4% to 83.3%, with the use of VIA as an adjunctive test[5] and proves to be useful especially in a low-resource setting.[12] VIA, first described by Ottaviano and La Torre in 1981, is done by ocular inspection of the cervix before and after a 1-minute application of 3-5% acetic acid solution under a 100-watt lamp light source. Acetic acid dehydrates the cells, coagulating surface cellular proteins and reducing the transparency of the cervical epithelium. A positive test for VIA would show a well-defined, acetowhitening of the epithelium at the transformation zone close to the squamocolumnar junction.[14] With the case in point, the suspicious cervical lesion was noted on two occasions of acetowhitening on VIA, followed with confirmation of squamous cell carcinoma, large cell keratinizing, confined to the cervix on colposcopic-guided biopsy.

Data from several epidemiologic studies have long implicated a sexually transmitted agent to cause cervical cancer. The most common risk factors thus far identified include early age of sexual debut, multiple sexual partners, and a male partner with multiple previous sexual partners. Other potential co-factors for the development of cervical cancer include oral contraceptive use, cigarette smoking, parity, family history, associated genital infections and lack of circumcision of male partner.[10] The patient in this case had a total of 4 sexual partners since she had her first sexual intercourse at the age of 24, until she got married to a soldier; she had a sister who was diagnosed and died with cervical cancer at the age of 35; she had a history of using oral contraceptive pills; and at the time of diagnosis a gravida four with only one successful term pregnancy, with the other two ending up in abortion for which completion curettage was done. These placed her at a significantly increased risk of developing the cervical cancer.

Early stage cervical carcinoma with no lymph node involvement, has a very good survival rate (95% to 98%) following surgical management.[15] Early stage cervical carcinoma includes stages IA, IB, and some small IIA tumor. The standard management of early stage cervical cancer remains to be radical hysterectomy and pelvic lymphadenectomy or chemoradiation, or both. However, in both modalities fertility is lost.[5] Among the population of young women suffering the disease, including our patient, the desire to preserve childbearing capacity is very tangible and valid. Literatures of late revealed a number of innovative techniques or approaches that fulfill the necessity of radicality in treating gynecologic cancers, including cervical cancer, yet aim at preserving fertility potential.[16,15,5] Of particular note is radical vaginal trachelectomy (RVT) as a treatment option for young reproductive women, just like our patient, diagnosed with early stage (microinvasive) cervical cancer and who wished to conceive again.

Pioneered by Daniel Dargent, et al. in 1987, the procedure involves the removal of most, if not all, of the cervix, the contiguous parametrium, and the vaginal cuff following a laparoscopic pelvic lymphadenectomy with frozen section biopsy,[17] preserving the upper endocervix and the uterine corpus, thereby allowing future pregnancy to happen.[3] Published in French literature in 1994, radical vaginal trachelectomy is a relatively new surgical technique with over 535 cases performed worldwide in 7 different centers, particularly in UK, France, Germany, USA and Canada.[15] Although Dargent and his team pioneered the procedure in France in 1987 with a total of 95 cases. In 2002, Shepherd, et al. did the procedure with a total of 123 cases of radical trachelectomy until 2007.[15]

The feasibility of RVT as a procedure replacing the more radical hysterectomy for early-stage cervical cancer was based on a careful understanding of the nature of spread of the disease. It commonly spreads laterally from the cervix to the parametrium, along the cardinal ligaments[5] and inferiorly to the upper vagina. In rare occasions, it spreads superiorly to involve the uterus in small stage IB cervical cancers.[17]

The technique has two phases. In its original description, RVT starts with laparoscopic pelvic lymphadenectomy with frozen section biopsy of the nodes dissected.[5] Extraperitoneal approach to pelvic lymph node dissection is found to be an adequate technique complementing radical vaginal operations for cervical cancers and it showed a significantly reduced operating time and a greater number of nodes removed.[18] Hence it was used in this case. (Figure 2) The second phase of Dargent's technique, which was adapted in this case, involves the amputation of the cervix (Figure 1) approximately 1cm below the isthmus[3] with adequate margin of the vaginal cuff (about 2cm from the cervix), dissecting alongside the paravesical, rectovaginal and vesicovaginal spaces.[5,17] Frozen section biopsy of the cervix (Figure 3) is done to ensure a minimum 5mm tumor clearance at the superior margin of the specimen.[17] If there is lymph node involvement and if there is incomplete resection of the cervix with positive margins, a more definitive treatment (i.e., radical hysterectomy or chemoradiation) shall be pursued.[5]

During that time, the patient underwent radical vaginal trachelectomy, a temporary cerclage using a delayed absorbable suture (Vicryl 0) put in place instead of a permanent cerclage as described in literature.[17] The main reason was to avoid cervical stenosis which

is very likely with the latter (about 15%) and is associated with some degree of infertility.[19]

The decision to opt for a relatively conservative procedure for an otherwise potentially invasive condition, such as cervical cancer must be guided by a number of patient selection criteria.[5,20] The following criteria should be met if radical vaginal trachelectomy is considered for the management of cervical cancer: 1) Desire to preserve fertility; 2) FIGO stage IA1 if there's presence of vascular space invasion or IA2 and IB1; 3) Lesion size less than 2cm diameter confined to the cervix; 4) No involvement of the upper endocervical canal as determined by examination under anesthesia (EUA), colposcopy and MRI; 5) No evidence of pelvic node metastasis; 6) Squamous cell carcinoma or adenocarcinoma histological subtypes; 7) Patient's informed consent.[5,20] At the outset, our patient stood as a good candidate for radical vaginal trachelectomy at the time of diagnosis; she was relatively young and very much desirous for another pregnancy; she was diagnosed with the lesion at stage 1A (no gross lesion seen) and with the more favorable histological subtype of squamous cell carcinoma; and there were no evidence of pelvic node metastasis and upper endocervical canal involvement based on the CT scan done pre-operatively.

Follow-up of patients who underwent RVT consists of Pap smear and colposcopy on top of good physical examination each time the patient comes for clinic visit every 3 to 4 months for 3 years, then every 6 months for the next 2 years, then yearly thereafter.[15] Our patient had negative Thin Prep Pap smear and HPV DNA test 3 months later. She has completed the 3 doses of HPV vaccine. She was free of disease until she conceived spontaneously 17 months after her radical vaginal trachelectomy. Pregnancy rates after RVT are between 41% & 79%.[17] In another report, the 5-year cumulative pregnancy rate was found to be 52.8%.[5] Thirty-eight percent of the pregnancies were term deliveries (>37wks). While preterm delivery (<37 weeks) ranged between 16% and 20% in various studies, and in most a shortened cervical length has been implicated,[17] predisposing the pregnancy to subclinical chorioamnionitis secondary to inadequate mucus plug and exposure of the membranes to vaginal flora.[22] An update to the review made by Plante in 2008 including 256 pregnancies following RVT indicates that 62% will reach third trimester of which 65% delivered term. The preterm delivery rate (<37 weeks) of the said study was reported to be at 28%, with 12% ending up to deliver a significantly premature baby (<32weeks). Presumed etiologies of preterm labor in this subset of patients include either mechanical causes (e.g, cervical incompetence) or infectious nature (e.g, chorioamnionitis) or a combination of both.[5]

At 14 weeks and 3 days age of gestation, she had an elective prophylactic cerclage (McDonald's procedure) using Mersilene tape (0.5mm width). (Figure 6) There is substantial evidence that doing an elective cerclage for a documented short cervix (for this patient, 1cm from the isthmus) between 12 and 16 weeks of gestation is beneficial as it avoid the risk of stimulating preterm labor or membrane rupture inherent to more advanced pregnancy. The pregnancy of our patient was otherwise uncomplicated. However, at 31 weeks and 5 days age of gestation she was admitted at the high-risk unit of our institution's labor room for preterm labor. A perinatologic consultation was made and tocolysis was the initial goal of management. However, due to fetal indication, at 32 weeks and one day gestation the team had to expedite delivery by low segment cesarean section. Plante and associates showed that in a series of 50 pregnancies following RVT, 8 delivered prematurely (<37 weeks), comprising 16%.[5] Another combined studies documented preterm delivery (<37 weeks) at 20% of pregnancies following RVT. There is reason to believe that the previous amputation of the cervix in this patient put her at a significant risk of cervical incompetence and preterm labor. Possible mechanism predisposing a pregnancy to preterm delivery is exposure of the fetal membranes to ascending infection through a shortened cervix in addition to lack of protective mucus plug,[17,22] activating the cytokine cascade leading to premature rupture of membranes.[5] The rate of preterm birth varies among studies and is likely due to the variability of the amount of cervix excised.[19,5] A study showed that cervical length less than 25 mm confirmed through sonography is predictive of preterm birth among patients who underwent cervical procedures.[24] Mention has been made of a vaginal occlusion procedure but it did not appear to prolong gestation as it was hoped for.[25] At

present, there is no standardized protocol in the obstetric management of pregnancies following radical vaginal trachelectomy and there are very few published data recommending a unified approach. In a recent review of literature, some authors proposed a set of recommendations for obstetric management of post-radical vaginal trachelectomy women, which includes the following: 1) Early referral to consultant care (high-risk obstetrician and gynecologic oncologist) and high risk pregnancy unit; 2) Application of vaginal progesterone pessaries from 12 weeks age of gestation (200mg BID); 3) Ultrasonographic measurements of the lower uterine segment every two weeks from 12 weeks age of gestation, to assess thickness and funnelling; 4) Consider regular high vaginal swabs and/or prophylactic antibiotics at 16 and 24 weeks age of gestation; 5) Steroids from 26 weeks AOG onwards if labor is threatened; 6) Consider early admission and bed rest from 24 weeks AOG if labor is threatened; 7) Choice of classical cesarean section as mode of delivery at onset of labor or at 34 – 36 weeks since onset of uterine contractions is associated with serious risk of uterine rupture.[26]

The decision to proceed with simple hysterectomy following the cesarean section in this patient was governed by the patient's expressed decision made prior to the surgery to remove her uterus and not due to perceived risk of recurrence, with the confidence of a relatively long disease-free interval of 17 months. Where the issue of performing a definitive hysterectomy once the desired family size is achieved arise, recommendations should be individualized based on a thorough discussion with the patient as there are no data to support that it should (or should not) be done.[5] Big centers performing RVT made careful observations with regard tumor recurrences. It has been found that almost 40% of the recurrences involved the parametrium or pelvic side walls, possibly due to inadequate parametrial excision. For such recurrences, adjuvant chemoradiation or completion radical hysterectomy must be offered.[17]

Follow-up schedule in patients after completion of treatment for cervical carcinoma is every 3 months for the first 2 years; every 6 months from the 3rd to 5th year; then yearly thereafter. In each clinic visit, it is recommended that a thorough physical and pelvic examinations, including Pap smear be performed, and where deemed needed, colposcopy-guided biopsy should be done. Chest radiograph should be done annually or as indicated. Furthermore, recommendations include an annual CT scan, MRI or PET scan for the first 3 years post treatment. Annual vault smear is recommended indefinitely and is still the general practice for patients diagnosed and treated of cervical cancer.[27] In another study, it was suggested that follow-up, after hysterectomy for cervical cancer, should comprise regular vaginal vault smears at least every 3 months for the immediate 2 years following hysterectomy. Lifetime screening and vigilance is recommended.[28] To date, 7 months after completion hysterectomy, our patient is free of disease.

RVT is a relatively new technique, otherwise safe and feasible procedure for our patient who, at the time of diagnosis of early stage cervical cancer was still desirous of preserving her fertility potential. The tumor recurrence rate is 5% and the mortality rate from disease recurrence is about 3%.[17] Another data report recurrence and death rates at 4.3% and 1.5%, respectively, comparable to that with the standard radical hysterectomy.[5] The overall 5 year survival rate is excellent at 95%.[5] The most important risk factor for tumor recurrence is lesion size >2cm.

Summary and Conclusion

Presented was a case of a 32 year old, who underwent radical vaginal trachelectomy for squamous carcinoma of the cervix, large cell keratinizing, stage IA2 at the age of 30. Her desire to preserve her reproductive capacity spun the idea to opt for a procedure that maintains radicality of excising the diseased cervix along with conservativism of leaving much of the healthy uterus allowing pregnancy to occur 17 months later. During the interval time to pregnancy, our patient has been free of disease. Indeed radical vaginal trachelectomy though a relatively new procedure fulfills the aggressiveness called for in cervical carcinoma and its fertility-preserving nature. At present, there are about 700 cases being reported worldwide since it was pioneered by Daniel Dargent in 1987 in France.[26] In the Philippines, this is the third

in a case series of radical vaginal trachelectomy for fertility preservation in early stage cervical carcinoma since 2007.[29] The case demonstrates how early detection of a potentially invasive and lethal condition using inexpensive tools such as VIA and Pap smear allowed a more conservative procedure to be carried out.

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