The Accuracy of Ultrasound in Pre-operative Assessment of Poor Prognostic Factors in Endometrial Carcinoma: A Preliminary Report

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Ultrasound is the most commonly used imaging modality in the diagnosis and pretreatment management of endometrial carcinoma. **Objective**: The objective of this study was to evaluate the diagnostic accuracy of pre-operative transvaginal sonography in determining prognostic variables in endometrial carcinoma such as lower uterine segment involvement, myometrial invasion, cervical extension, parametrial spread and lymph node metastasis. **Methods**: Twenty eight patients with histologically confirmed endometrial cancer were enrolled. All patients underwent abdominal hysterectomy, pelvic lymph node dissection or sampling and peri-aortic lymph node assessment. Two-dimensional pelvic ultrasound was performed before surgery to evaluate tumor involvement of the lower uterine segment, cervix and parametria, depth of myometrial invasion and lymph node metastases. Sonologic findings were correlated with histologic findings on the definitive specimen. Standard statistical calculations were used to determine accuracy, sensitivity, specificity, positive and negative predictive values, false-positive and false-negative rates and likelihood ratio of the procedure. **Results**: The sensitivity of ultrasound in detecting lower uterine segment involvement, myometrial invasion and cervical involvement were 76.5%, 83.3% and 66.7%. It failed to detect 2 cases with parametrial involvement and 5 cases with lymph node metastasis. **Conclusion**: Transvaginal ultrasound provides comparably accurate assessment of lower uterine segment involvement, myometrial invasion and cervical extension of endometrial carcinoma. The surgeon can rely on this procedure to decide pre-operatively on the extent of surgery and the need for subspecialist consult and/or referral to a higher center. However, this study had demonstrated that it has a low sensitivity in evaluating parametrial involvement and lymph node metastasis.

Key words: endometrial carcinoma, ultrasound

Cancer of the endometrium is the third most common gynecologic malignancy in the Philippines. In the 1998 Philippine Cancer Facts and Estimates, cancer of the corpus uteri ranks 9th among females. In contrast, incidence of endometrial carcinoma in the western countries has already exceeded that of ovarian and cervical cancer. In the Surveillance Research of the American Cancer Society, the estimated number of new cases for 2004 is 40,320 compared to 10,520 and 25,850 for cancers of the cervix and ovary, respectively. Thus, it is now the

leading gynecologic malignancy in the United States and the 4th most common cancer among American women. In the year 2003, our institution had seen a total of 173 newly diagnosed cases of endometrial cancer at the outpatient clinic, 50% of which were classified as stage I. There were 106 in-patient endometrial cancer cases, 78 of which were admitted for surgery.

For stage I disease, the prognosis and management of women with endometrial carcinoma are based on the prognostic variables related to pathologic features of their tumor, primarily grade and depth of myometrial invasion. In addition to these, histologic type, isthmic and cervical involvement are the major prognostic factors in carcinoma of the endometrium confined to the corpus.

The diagnostic factors necessary for the preoperative evaluation of endometrial cancer include (1) determination of the risk of lymph node metastasis in order to have skilled surgical consultation available; (2) diagnosing cervical extension, which requires preoperative radiation therapy or a different treatment plan, i.e., radical hysterectomy instead of simple total abdominal hysterectomy; and (3) detection of advanced disease.[1]

Sonography is one of the baseline diagnostic work-ups and the most common imaging modality being utilized in our center in the management of endometrial carcinoma. It has been used to evaluate endometrial abnormalities and proved to be fairly accurate in the preoperative assessment of endometrial cancer spread and in predicting the presence of deep myometrial invasion and extrauterine tumor spread. Transvaginal sonography has been shown by studies to have an overall accuracy of 60-70% in predicting extent of myometrial invasion.[2] However, sensitivity of transvaginal ultrasound for predicting myometrial invasion is highly dependent on operator experience.

Preoperative knowledge of these prognostic factors (depth of myometrial invasion, isthmic involvement, cervical involvement, parametrial involvement and lymph node metastasis) allows the gynecologists an appropriate planning and consultation in terms of extent of surgery and to select patients who might benefit from referral to gynecologic oncology centers or specialists. Intra-operatively, depending on the presence of the prognostic parameters, including the gross evaluation of the uterus, the surgeon decides whether to continue the operation by performing lymphadenectomy. There have been reports that pelvic and para-aortic lymphadenectomy should be performed routinely as part of the definitive surgical management to estimate the patient's prognostic risk and to individualize the postoperative schedules.[3] However, others maintain that routine pelvic and para-aortic lymphadenectomy cannot be justified because patients with a well differentiated tumor are at low risk for retroperitoneal lymph node metastasis and probably do not benefit from routine pelvic and para-aortic lymphadenectomy. In medically inoperable cases, determination of these prognostic factors would help in tailoring the radiotherapeutic intervention.

A commonly held belief is that tumor location affects patient outcome. At many centers, including our institution, involvement of the lower uterine segment or the uterine isthmus is perceived to increase the risk of pelvic recurrence and is an indication for adjuvant radiotherapy, even in the absence of other high-risk features.

Accurate preoperative assessment of cervical involvement is mandatory for determining the most appropriate surgery, or in the other words, to avoid oversurgery and undersurgery. Stage II endometrial carcinoma requires more aggressive surgical treatment than stage I disease. Patients with disease confined to the uterus do well with limited surgery; however, those with extension of the disease to the cervix may need radical hysterectomy or preoperative radiation. Pre-operative determination of cervical involvement of the cancer has been based mainly on endocervical curettage, which has been shown to be inaccurate with a false negative rate of 35%. In the study by Artner, et al., transvaginal sonography was able to predict cervical involvement with fairly high accuracy with 3 false negative and no false positive results out of 69 patients.[4]

Demonstration of involvement of the parametria and lymph node metastases would likewise affect the pre-operative planning as well as intra-operative decision-making in terms of extent of surgery. For endometrial cancers, surgically adequate evaluation of pelvic and para-aortic lymph node metastases might be essential to provide important prognostic information for patients, select suitable postoperative adjuvant treatment and perform accurate FIGO staging.

Lampe, et al. reported prognostic factors predictive of pelvic lymph node metastasis from endometrial cancer. In their report, serous papillary type, histologic grade, myometrial invasion, lymph-vascular emboli and cervical invasion were shown to be independently associated with pelvic lymph node metastasis.[5] However, these prognostic

or predictive data were all obtained from the postoperative pathologic findings. None of these data provided information from preoperative evaluation. Cheng, et al. evaluated efficacy of ultrasound in predicting lymph node metastases in endometrial cancer patients using tumor size, depth of myometrial invasion and intratumoral arterial resistance index as parameters.[6] Their use of color Doppler flow improved the predictive value of ultrasound. The American College of Radiology recommends magnetic resonance imaging (MRI) as the diagnostic tool of choice in detecting lymph node metastasis in endometrial carcinoma. Ultrasound has a significantly lower sensitivity for detection of lymph node metastases compared to MRI and CT-scan.

Materials and Methods

The general objective of this study was to determine the accuracy of ultrasound in predicting the poor prognostic factors in patients with endometrial carcinoma who will undergo primary surgical treatment. The specific objectives were to determine the specificity, sensitivity, positive predictive value, negative predictive value and likelihood ratios of sonographic examination in pre-operative assessment of the following prognostic variables of endometrial carcinoma:

a. Involvement of the lower uterine segment or the uterine isthmus
b. Depth of myometrial invasion
c. Cervical involvement
d. Involvement of the parametria
e. Lymph node metastasis

From December 15, 2003 to August 15, 2004, all patients with endometrial carcinoma undergoing primary surgical treatment (including abdominal hysterectomy with bilateral salpingooophorectomy, pelvic lymph node dissection or sampling and paraaortic lymph node sampling) in a tertiary institution were enrolled in the study.

The pre-operative diagnosis of endometrial cancer was based on the histopathologic report of endometrial curettage or biopsy. In addition, all patients included in the study have undergone a pre-operative ultrasound examination in the same institution. Patients excluded from the study were those who underwent pre-operative radiotherapy, or who had received pre-operative hormonal therapy or chemotherapy, those with sarcomatous histologies, those who underwent surgery at outside institutions and those without intra-operative assessment of the lymph nodes.

Ultrasound examination was performed at most 8 days before the patients underwent the surgical intervention. Transvaginal sonography was performed with a Medison or Aloka unit with a 5-, 6- or 7.5-MHz probe by one examiner. The uterus was scanned both sagittally and coronally to measure tumor size and depth of myometrial invasion and to note involvement of the lower uterine segment, cervix, parametria and pelvic and paraaortic lymph nodes. Hysterectomies were performed within 8 days of sonographic examinations. Intraoperative findings as reported by the surgeons in the operative record were reviewed and encoded in the Intra-operative Findings Portion of the Endometrial Carcinoma Data Sheet. Histologic examination of the surgical specimens was performed by pathologists who were blinded to the results of transvaginal sonography. The prognostic variables noted in the sonography and surgery were compared with the final histopathologic report. Stage was classified according to the 1988 FIGO Staging System. The carcinomas were classified using a three-grade system based on the architectural features.

Outcome measures of interest included the following surgicopathologic prognostic factors: involvement of the lower uterine segment or the isthmus, depth of myometrial invasion, involvement or extension of the tumor to the cervix, involvement of the parametria and lymph node metastases.

Lower uterine segment or isthmic involvement was determined in terms of distance of the lowest edge of the tumor from the internal cervical os or by involvement of the lower third of the uterus, taking into consideration the total uterine length.

Depth of myometrial invasion was the degree or depth of invasion of the endometrial tumor into the myometrium in relation to the myometrial thickness. It was calculated as deepest distance between myometrial invasion to the endometrium divided by whole thickness of myometrium from serosa to endometrium by sagittal scanning. In this study, it was categorized as either less than 50% or more than 50% invasion of the myometrium.

Cervical involvement or tumor extension to the cervix was determined sonologically based on irregular and heterogeneous echogenicity of the tumor in the cervix extending from that of the endometrium. When the tumor was seen in the cervical stroma, diagnosis of

cervical stromal invasion would be made. On the other hand, when the tumor was seen in the cervical canal or within the homogeneous endocervical glandular area, diagnosis of cervical glandular involvement was made.

Parametrial involvement was demonstrated sonographically by thickening of the parametria or distortion of the parametrial vessels. By gross examination, parametrial extension was considered when the tumor is unequivocally present within the parametrial tissue or dissected parametrial lymph nodes. Lastly, lymph node metastases would be seen as enlargement of the pelvic and para-aortic nodes or distortion of the iliac vessels and aorta by echogenic structures overlying or surrounding them. Lymph node metastasis, whenever present, was specified regarding location.

Data were collected using the data collection form. Tables were constructed comparing the sonologic findings and histopathologic examination findings, according to the different prognostic variables being studied. Likewise intra-operative assessment was compared with the final histologic evaluation. Accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratios of ultrasound were calculated using standard statistical formulas. Additionally, the false-positive (1-specificity) and the false-negative (1-sensitivity) rates of the procedure were calculated. An estimated sample size of 280 subjects was necessary to obtain the sensitivity of 76% cited in literature with an alpha value of 0.50.

Results

A total of 28 patients were included in the study. (Table 1) The mean age was 52.1 years with a range from 32 to 70 years, 8 patients were 61 years of age or older. The mean gravidity was 3.8 (range 0-11) while the mean parity was 3.4 (range 0-11) with 5 patients being nulligravid. The histologic types were adenocarcinoma (n = 21), adenocarcinoma with squamous differentiation (n = 4), clear cell carcinoma (n = 2) and serous papillary adenocarcinoma (n = 1). The histologic grade was well differentiated in 5 cases, moderately differentiated in 10 cases and poorly differentiated in 13 cases. Majority of the patients were classified as stage I (n = 16), 2 were stage II, 9 were stage III and 1 was stage IV having a tumor implant in the omentum. Three underwent radical hysterectomy with bilateral salpingo-oophorectomy and lymph node dissection for a pre-operative diagnosis of tumor extension to the cervix, the rest were treated with total hysterectomy with bilateral salpingooophorectomy and lymph node dissection or sampling.

Table 1. Patient demographics

Patient Characteristics (n = 28)	
Age (median, range)	52.1, 32-70
Gravidity (median, range)	4. 0-11
Parity (median, range)	3. 0-11
Tumor type	
Endometrioid	21
Endometrioid with squamous differentiation	4
Clear cell	2
Papillary serous	1
Tumor grade	
G1	5
G2	10
G3	13
Stage I	16
II	2
III	9
IV	1
Procedure	
RHBSO PFC with lymph node assessment	3
EHBSO PFC with lymph node assessment	25

Assessment by sonography and histology of the involvement of the lower uterine segment produced comparable results in 21 of 28 patients. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the sonographic evaluation of isthmic involvement were 76.5% (95% CI 0.50 – 0.92), 72.7% (95% CI 0.40 – 0.93), 81.3% and 66.7%, respectively (Table 2). On the other hand, intra-operative gross examination of the specimen yielded more accurate assessment of lower uterine segment involvement with sensitivity, specificity, PPV and NPV of 82.4% (95% CI 0.56 – 0.95), 100% (95% CI 0.72 – 0.99), 100% and 78.6%, respectively (Table 3).

Table 2. Determination of lower uterine segment involvement: transvaginal sonography versus histology.

	Histology		
	(+) lower uterine segment involvement	(–) lower uterine segment involvement	Total
TV UTZ: (+) lower uterine segment involvement	13	3	16
TV UTZ (–) lower uterine segment involvement	4	8	12
Total	17	11	

Sensitivity = 76.5% (95% CI 0.50-0.92)
Specificity = 72.7% (95% CI 0.40-0.93)
Positive predictive value = 81.3%
Negative predictive value = 66.7%
False negative = 23.5%
False positive = 27.3%
Accuracy = 75%
LR+ = 2.804 (95% CI 1.03-7.62)
LR– = 0.324 (95% CI 0.13-0.82)

Table 3. Determination of lower uterine segment involvement: intra-operative gross assessment versus histology.

	Histology		
	(+) lower uterine segment involvement	(–) lower uterine segment involvement	Total
Intra-op assessment: (+) lower uterine segment involvement	14	0	14
Intra-op assessment: (–) lower uterine segment involvement	3	11	14
Total	17	11	

Sensitivity = 82.4% (95% CI 0.56-0.95)	False negative = 17.6%
Specificity = 100% (95% CI 0.72-0.99)	False positive = 0
Positive predictive value = 100%	Accuracy = 92.8%
Negative predictive value = 78.6%	LR+ = 19.33 (95% CI 1.27-294.36)
	LR– = 0.20 (95% CI 0.08-0.52)

Sonography and gross examination (Tables 4 & 5) had similar accuracy in determining depth of myometrial invasion with identical values for the sensitivity, specificity, PPV and NPV of 83.3% (95% CI 0.51 – 0.97), 75% (95% CI 0.48 – 0.91), 71.4% and 85.7%, respectively.

Table 4. Determination of myometrial invasion: transvaginal sonography versus histology.

	Histology		
	>50% myometrial invasion	<50% myometrial invasion	Total
TV UTZ: >50% myometrial invasion	10	4	14
TV UTZ <50% myometrial invasion	2	12	14
Total	12	16	

Sensitivity = 83.3% (95% CI 0.51-0.97)	False negative = 16.7%
Specificity = 75% (95% CI 0.48-0.92)	False positive = 25%
Positive predictive value = 71.4%	Accuracy = 78.6%
Negative predictive value = 85.7%	LR+ = 3.33 (95% CI 1.38-8.08)
	LR– = 0.22 (95% CI 0.06-0.81)

Table 5. Determination of myometrial invasion: intra-operative gross assessment versus histology

	Histology		
	>50% myometrial invasion	<50% myometrial invasion	Total
Intra-op assessment: >50% myometrial invasion	10	4	14
Intra-op assessment: <50% myometrial invasion	2	12	14
Total	12	16	

Sensitivity = 83.3% (95% CI 0.51-0.97)	False negative = 16.7%
Specificity = 75% (95% CI 0.48-0.92)	False positive = 25%
Positive predictive value = 71.4%	Accuracy = 78.6%
Negative predictive value = 85.7%	LR+ = 19.33 (95% CI 1.27-294.36)
	LR– = 0.22 (95% CI 0.08-0.52)

Sonography was able to detect more cases with cervical involvement (Tables 6 & 7) than intra-operative gross examination with sensitivity, specificity, PPV and NPV of 66.7% (95% CI 0.24 – 0.94), 95.4% (0.75 – 0.99), 80% and 91.3%, respectively compared with that of gross examination's 33.3% (95% CI 0.06 – 0.76), 95.4% (0.75% – 0.99), 66.7% and 84%.

Table 6. Determination of cervical involvement: transvaginal sonography versus histology.

	Histology		
	(+) cervical involvement	(–) cervical involvement	Total
TV UTZ: (+) cervical involvement	4	1	5
TV UTZ (–) cervical involvement	2	21	23
Total	6	22	

Sensitivity = 66.7% (95% CI 0.24-0.94)	False negative = 33.3%
Specificity = 95.4% (95% CI 0.75-1.00)	False positive = 4.6%
Positive predictive value = 80%	Accuracy = 89.3%
Negative predictive value = 91.3%	LR+ = 14.67 (95% CI 1.99-108.02)
	LR– = 0.35 (95% CI 0.11-1.09)

Table 7. Determination of cervical involvement: intra-operative gross assessment versus histology.

	Histology		
	(+) cervical involvement	(–) cervical involvement	Total
Intra-op assessment (+) cervical involvement	2	1	3
Intra-op assessment (–) cervical involvement	4	21	25
Total	6	22	

Sensitivity = 33.3% (95% CI 0.06-0.76)	False negative = 66.7%
Specificity = 95.4% (95% CI 0.75-1.00)	False positive = 4.6%
Positive predictive value = 66.7%	Accuracy = 82.1%
Negative predictive value = 84%	LR+ = 7.33 (95% CI 0.79-67.81)
	LR– = 0.20 (95% CI 0.39-1.24)

With regards to assessment of parametrial involvement, ultrasound failed to detect 2 cases with extension of tumor to the parametria. Intraoperative gross evaluation also missed the tumor involvement. Accuracy of ultrasound is 92.8%. However, sensitivity and specificity cannot be calculated since no positive result was obtained by this diagnostic procedure. (Tables 8 & 9).

Table 8. Determination of parametrial involvement: transvaginal sonography versus histology.

	Histology		
	(+) parametrial involvement	(–) parametrial involvement	Total
TV UTZ: (+) parametrial involvement	0	4	0
TV UTZ: (–) parametrial involvement	2	26	28
Total	2	26	

Sensitivity = N.A.
Specificity = N.A.
Positive predictive value = 50%
Negative predictive value = 92.8%
False negative = N.A.
False positive = N.A.
Accuracy = 92.8%
LR+ = 9.00 (95% CI 0.22-376.66)
LR– = 0.20 (95% CI 0.51-1.412)

Table 9. Determination of parametrial involvement: intra-operative gross assessment versus histology.

	Histology		
	(+) parametrial involvement	(–) parametrial involvement	Total
Intra-op assessment: (+) parametrial involvement	0	0	0
Intra-op assessment: (–) parametrial involvement	2	26	28
Total	2	26	

Sensitivity = N.A.
Specificity = N.A.
Positive predictive value = 50%
Negative predictive value = 91.4%
False negative = N.A.
False positive = N.A.
Accuracy = 92.8%
LR+ = 9.00 (95% CI 0.22-376.66)
LR– = 0.20 (95% CI 0.51-1.412)

Ultrasound was also not able to detect the 5 cases with lymph node metastasis. The computed accuracy is 82.1%. Similarly, sensitivity and specificity values cannot be computed. (Table 10)

Table 10. Determination of lymph node involvement: transvaginal sonography versus histology.

	Histology		
	(+) lymph node involvement	(–) lymph node involvement	Total
TV UTZ: (+) lymph node involvement	0	0	0
TV UTZ: (–) lymph node involvement	5	23	28
Total	5	23	

Sensitivity = N.A.
Specificity = N.A.
Positive predictive value = 50%
Negative predictive value = 82.1%
False negative = N.A.
False positive = N.A.
Accuracy = 82.1%
LR+ = 4.00 (95% CI 0.09-181.79)
LR– = 0.94 (95% CI 0.73-1.20)

Discussion

This study investigated whether preoperative transvaginal ultrasound could sufficiently detect poor prognostic variables in patients undergoing surgery for endometrial cancer. The stage of the disease is the most significant prognostic variable, but a number of other parameters also determine the existence of a more aggressive behavior of the disease and consequently, the need for additional surgical interventions. These prognostic factors include poor histological tumor types, poor differentiation (G3), deep (< 50%) myometrial invasion, involvement of the cervix and radiological indications of pelvic and/or paraaortic lymph node metastasis. Since the adoption of surgicopathologic staging by the FIGO in 1988, surgery in the form of total abdominal hysterectomy has been the primary treatment for endometrial cancer. The presence of the poor prognostic parameters determine the need for additional surgical intervention such as pelvic and/or paraaortic lymph node dissection or performance of radical instead of simple abdominal hysterectomy in case with cervical and/or parametrial extension, for both therapeutic and staging purposes. Furthermore, adjuvant treatment has been instituted after primary surgical intervention based on the presence of poor prognostic variables.

Endometrial carcinoma is a disease most commonly found in women in the advanced age with presence of co-morbidities like obesity, diabetes mellitus and hypertension. Diagnostic imaging may be instrumental in the decision making regarding management of a primarily obese, elderly population in which radiation therapy, with or without hormonal and/or chemotherapy, rather than surgery might be advocated as a primary treatment or as a preoperative adjuvant to surgery. In patients who will undergo surgery, preoperative determination of these variables may tailor staging laparotomy and hysterectomy. Surgical management of cervical extension or stage II endometrial cancer would include radical hysterectomy and paraaortic node sampling. Such extended surgical staging requires advanced surgical skills. A number of patients with endometrial carcinoma is primarily diagnosed and managed by general gynecologists. Preoperative knowledge of prognostic factors would allow these gynecologists to identify patients who requires a more radical surgery so that they could be referred to gynecologic oncologists for co-management or to centers where the skills and necessary facilities are available.

Knowledge of these prognostic factors combined with the operative findings and evaluation would also aid the surgeon in intra-operative decision-making regarding additional surgical intervention.

In this study, ultrasound has a fairly high accuracy (75%) of detecting lower uterine segment involvement, with sensitivity of 76.5% and specificity of 72.7%. In the literature reviewed, there had been no studies done on assessing accuracy of ultrasound in determining tumor involvement of the lower uterine segment. Location of the tumor within the lower uterine segment has been considered by some investigators as a poor prognostic factor. Mayr, et al. noted a high rate of pelvic recurrence (50%) in low-risk patients with isthmic involvement treated with surgery alone compared to 3% with the addition of adjuvant radiotherapy.[7] Thus, it has been the practice to institute post-operative radiotherapy to patients with endometrial carcinoma involving the isthmus or the lower third of the corpus. If behavior of tumor involving the lower uterine segment would be likened to that of tumor extending to the cervix, then surgical management of cancers assessed to have isthmic involvement should also include radical hysterectomy. In a similar manner, this would obviate the need for adjuvant radiotherapy. However, this is subject to controversy since presently this would be considered overtreatment of a stage I cancer. Phelan and co-workers in their investigation of pathological stage I endometrial cancer with isthmic involvement concluded that the involvement of lower uterine segment does not adversely impact on patient outcome and should not be used as an indication for adjuvant therapy in the absence of other unfavorable pathologic features.[8]

The depth of myometrial invasion is an important prognostic factor and directly correlates with the incidence of pelvic and/paraaortic nodal metastasis. In stage IA and IB disease, when the tumor is confined to the endometrium or to the superficial myometrium, the incidence of para-aortic lymph node metastases is only 3%. On the other hand, in stage IC disease, when there is deep myometrial invasion, lymph node metastases occur in 6%-46%.[9]

The use of transvaginal sonography has shown potential in the evaluation of myometrial invasion. Reported accuracy for myometrial invasion in stage I range from 69%-85% in differentiating deep invasion (IC) from absent or superficial invasion (IA-IB) and from 68%-69% in differentiating stage IA versus stage IB and versus stage IC.[9] Our study showed an accuracy of ultrasound of 78.6% in distinguishing deep myometrial invasion (<50%) from superficial or absent invasion with a sensitivity of 83.3% and specificity of 75%. These findings are also comparable to the results obtained by San Juan, et al. in a retrospective study done in this same institution. The values they calculated for the sensitivity, specificity, positive predictive value and negative predictive value of ultrasound in evaluating myometrial invasion were 76.47%, 82.35%, 81.25% and 77.77%, respectively.

The limitations of ultrasound appear to be in suboptimal soft tissue contrast resolution (when the tumor and the adjacent myometrium have similar echogenicity), a relative small field of view that precludes assessment of large tumors and patient physique (since patients with endometrial carcinoma are often obese and have short stature). False positive results of myometrial invasion have been reported in the presence of other uterine pathology like polyps, pyometra, myomas, or focal adenomyosis mimicking myometrial invasion and myometrial/uterine atrophy. False negative results may occur in cases of superficial growth or microinvasion.[9]

In this study, intra-operative gross assessment of myometrial invasion demonstrated same rate of accuracy as ultrasound. Since the gross evaluation has a comparable accuracy, some gynecologic oncologists choose to evaluate patients with endometrial cancer clinically confined to the corpus intra-operatively and make a decision about extent of lymph node sampling based on knowledge of histologic grade and a frozen section to assess myometrial invasion. However, this may be less ideal if a local hospital lacks reliable frozen section facilities or when consultations have to be arranged in advanced to perform adequate staging with pelvic and paraaortic lymph node dissections.[2] Frozen-section examination predicts the final result of myometrial invasion with an underestimation rate (false negative) of 3-30%, thus being directly comparable to gross evaluation.[3] Moreover, the high rate of sensitivity obtained in this study may be biased since the surgeons who evaluated the specimens were subspecialists in training who might have more experience and expertise in gauging depth of myometrial invasion compared to a general gynecologist.

FIGO stage II endometrial cancer is defined on the basis of tumor spread to the cervix. Endometrial carcinoma that infiltrates the cervix has a poorer prognosis than disease confined to the corpus uteri and presents with a higher rate of lymph node involvement. The

reported 5-year survival of patients with endometrial cancer involving the cervix is approximately 65%.[10]

Because of the inaccuracy of clinical staging in diagnosing cervical involvement, surgical treatment is considered an important primary step in the management of suspected stage II endometrial cancer. However, no consensus exists about the best surgical treatment for women with tumor invasion of the cervix. Some authors have emphasized the therapeutic importance of parametrial dissection in managing these cases and others have advocated adjuvant radiotherapy to improve prognosis, independently of the type of hysterectomy performed. The possible therapeutic advantage of surgical parametrial dissection is supported by the finding that parametrial involvement has been demonstrated histologically in 11.5% of cases of stage II disease and in 52% of cases of stage III disease. Futhermore, the importance of achieving local control of disease has been demonstrated by higher local recurrence rates in patients with stage II disease than in those with stage I disease.[10]

Dilation and curettage (D & C) or fractional curettage is used to make the diagnosis of endometrial carcinoma, but also to evaluate tumor grade, histologic type and involvement of the endocervix. Unfortunately, cervical invasion is misdiagnosed by this procedure with false-positive results of up to 25% and false-negative results of up to 10% being reported.[3] Intraoperative gross inspection of the uterus upon removal from the operating field is a cheap and fast way to evaluate both myometrial invasion and extension of the tumor to the cervix.. Tumor involvement of the cervix not only changes the stage of cancer but also if deep stromal invasion is present, it alters the natural behavior of the endometrial carcinoma, making it similar to adenocarcinoma of the cervix. This results to an increased risk of pelvic lymph node metastasis to approximately 35-40%. On the other hand, if only the superficial or glandular part of the cervix is affected, or if disease is occult (stage IIa), the behavior and prognosis are similar to that of stage I disease and consequently, these patients can be treated in the same way as the latter.[3] Gynecologic cancer centers in North America utilized extended hysterectomy (Class II-III) in the presence of cervical involvement and/or to avoid radiotherapy in younger patients. In our setting, where radiotherapeutic facilities are lacking, the use of radical surgery would obviate the need for adjuvant radiotherapy and administer a curative intervention to the patient with a single procedure.

With respect to evaluation of cervical involvement, our study demonstrated a relatively lower sensitivity (66.7%) and positive predictive value (80%) of ultrasound than what has been reported by other investigators but with a high specificity (95.4%) and negative predictive value (91.3%) that are comparable with that of other studies. San Juan, et al. retrospective study demonstrated both high sensitivity ad positive predictive value at 85.71% and high specificity and negative predictive value of 96.29%. The intra-operative gross evaluation of cervical extension in our study had a much lower sensitivity of 33.3% in contrast with the values obtained by Maggino, et al. with overall accuracy reaching 98.5% and only 11.5% false negative. Although, at the point of the surgery, when the surgeon inspects the uterus that has already been amputated, radical hysterectomy is no longer possible, performance of lymphadenectomy might have considerable positive effect on patient outcome.[3]

Cervical extension can be diagnosed reliably with accuracy ranging from 86%-95%.[9] Ultrasound has been found superior to intra-operative gross evaluation and even fractional/endocervical curettage in detecting cervical extension, which has been associated with 40-50% false positive rates.[4] Subtle changes in the echogenicity of the cervix which are interpreted by a skilled sonologist as cervical extension could be missed by gross inspection of cervix in a surgical specimen.

The parametrium is regarded as an important tissue, through which extrauterine tumor spread occurs either by direct invasion of cancer cells to the connective tissues or by lymphatic channels in endometrial carcinomas. The incidence of parametrial involvement increased with the advancing stage of endometrial carcinomas.[11] In this study, parametrial spread was identified in 2 patients, one with a pre-operatively known cervical involvement and the other one had been clinically diagnosed as Stage I disease but was post-operatively upstaged due to presence of ovarian metastasis. Parametrial involvement was significantly related with other histopathological factors such as tumor grade, depth of myometrial invasion, lymphovascular space invasion (LVSI) in the myometrium, cervical involvement, and pelvic lymph node metastases.[11] It has been recognized that both the depth of myometrial invasion and LVSI in the myometrium are important prognostic factors in patients with endometrial cancer that is apparently confined to the uterus. Even in cases without cervical involvement, there may be extensive lymph node metastases if myometrial invasion is deep

or LVSI is prominent because there are numerous anastomotic lymphatics between the uterine muscular layer and the parametrium, which will facilitate various patterns of metastases based on the anatomic location of the cancerous growth within the uterus.[11] Therefore, it is likely that parametrial spread may contribute to occult metastases and subsequent local pelvic recurrence.

Ultrasound failed to detect involvement of parametria in any of the patients in this study. This low sensitivity of the diagnostic procedure might be accounted for by a bias in selection of patients enrolled in this study. Patients who were diagnosed clinically with parametrial extension of the endometrial carcinoma were elected to undergo neoadjuvant pelvic radiation instead of primary surgical intervention and thus, excluded from enrollment this study. Therefore a valid conclusion cannot be drawn at this point regarding accuracy of sonography in assessment of parametrial extension.

One of the major concerns in endometrial cancer therapy is the value of lymphadenectomy. Some centers that have the skilled surgeons and facilities perform it routinely, while others reserve it for specific pathological risk factors such as grade, histologic type and myometrial invasion. There is a need for postoperative adjuvant treatment in pathological stage I disease when lymph nodes are positive.[3]

Various investigators have categorized endometrial carcinoma patients as either low risk or high risk. Low risk groups consisted of patients with disease confined to the uterine corpus, histologic grade 1 or 2, endometrioid histologic subtype and inner half myometrial invasion. They are characterized by those factors in relation to pelvic lymph node metastasis to discriminate a subgroup of patients who would not require pelvic lymphadenectomy.[12]

Patients with lymph node metastases demonstrated higher incidence of poor histologic grade, deep myometrial invasion and positive LVSI. Risk of lymph node metastases increases to more than 10% in well-differentiated lesions invading into outer third of myometrium or moderately differentiated lesions with middle third invasion, affecting choice of treatment and outcome.

In the evaluation of lymph node metastases, compared with either CT scan or MRI, ultrasound has a significantly lower sensitivity. The efficacy of CT and MRI in the evaluation of lymph node metastases is similar and both modalities rely on anatomic findings of nodal size, (equal to or greater than 1 cm on short axis).[9] Ultrasound can easily miss lymph nodes that are less than 1 cm in size. Other factors that have to be considered are the thickness of the abdominal wall and the adequacy of the bowel preparation. A thick abdominal wall, which is often encountered in obese endometrial cancer patients, would hinder adequate sonographic evaluation of paraaortic and paracaval nodes since a transabdominal technique is utilized. Shadows of unprepped bowels would also affect sonographic assessment of pelvic nodes rendering ultrasound less sensitive.

Conclusion

The data and statistical analysis obtained from this study suggest that ultrasound provides comparably accurate estimates of lower uterine segment involvement, myometrial invasion and cervical extension of endometrial carcinoma. The surgeon can rely on this procedure to decide pre-operatively on the extent of surgery, the need for subspecialist consult and/or referral to a higher center. However, this study had demonstrated that it has a low sensitivity in evaluating parametrial involvement and lymph node metastasis.

Ultrasound, especially with the use of transvaginal sonography, is oftentimes considered to be the primary imaging approach. In patients in whom ultrasound is suboptimal or in whom the results of imaging studies will directly influence the choice of therapy and guide in therapeutic planning, the higher accuracy of contrast-enhanced MR imaging warrants its use. If lymph node involvement is the major clinical concern, MRI is the study of choice. Additionally, one must not forget that MRI, which is the most accurate radiological method, is not available at all hospitals and is quite expensive to be considered as a primary or routine imaging modality.[8] In a low resource setting, all patients with endometrial cancer who are taken to the operating room for primary therapy should be prepared to undergo extended surgical staging, including selective pelvic lymph node dissection on the basis of the intraoperative assessment of risk of lymph node metastasis or other extrauterine spread.

Limitations

This study was conducted in a span of 8 months with a calculated accrual rate of 4 patients per month

based on the number of patients with endometrial cancer undergoing surgery in this institution. It would take several years of accrual to reach the target estimated sample size of 280 subjects. Considering the low incidence of lymph node metastasis and parametrial involvement in endometrial cancer, the number of subjects enrolled in this study is quite small to draw a definitive conclusion from regarding accuracy of ultrasound in evaluation of these two variables.

Recommendations

This paper presents the preliminary result of an ongoing study. It is recommended that investigation and accrual of subjects be continued to reach the estimated sample size so that more meaningful analysis and conclusion can be drawn from a greater pool of data. Efforts should be raised in pursuing primary surgical treatment for patients with clinical and/or radiographic evidence of parametrial involvement so that histologic confirmation of parametrial involvement would be done.

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Intraoperative Morphologic Characterization of Ovarian Disease: Evaluation of a Proposed Scoring System to Predict Ovarian Malignancy

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The aim of the study was to assign a probability of malignancy for any patient with an ovarian mass by the application of multivariate regression analysis to intra-operative variables recorded at the time of surgery. **Methods**: One hundred seventy one (171) cases were reviewed from January 1 to December 31, 2002. **Results**: Of these, 110 women had benign cysts and 61 had malignant ovarian tumors. For each patient, the variables included: (1) papillary projections, (2) size/tumor volume of the mass, (3) presence of ascites, (4) presence of extraovarian implants, (5) presence of adhesions, (6) presence of locules, (7) bilaterality, (8) presence of rupture, (9) wall thickness and (10) consistency of the mass. These ten independent variables and the final histopathologic diagnosis for each patient (the dependent variable) were used for regression analysis. Regression analysis on the ten variables resulted in the retention of only 'papillary projections', 'tumor volume,' 'presence of ascites,' 'wall thickness' and 'presence of extraovarian implants' as significantly contributing to predicting the presence or absence of malignancy. Also a proposed weighted scoring scheme was presented. A cut-off score of ≥ 6 is indicative of high likelihood of ovarian malignancy. Cross validation of the scoring model on the test data gave a sensitivity of 78.62% and specificity of 91.73% and positive and negative predictive values of 81.55 and 88.01, respectively. **Conclusion**: In conclusion, multivariate regression analysis enables the calculation of probability of malignancy for a patient with known adnexal/ovarian mass. The value of this scoring model needs to be tested prospectively.

Key words: ovarian malignancy, logistic regression analysis

Ovarian carcinoma remains to be the leading cause of death from gynecologic malignancies. It is the third most common type of malignancy among Filipino females (12.5 per 100,000 ASR). This is the 8th most frequent site in both sexes combined in the Philippines. The average age-standardized incidence rate for both sexes is 5.8 per 100,000. The incidence of ovarian cancer in the Philippines is somewhere between the high rates observed in Europe and the USA white females and the low rates in Thailand and Japan. The mortality rate adjusted by age, ranges from 3.02 in Italy to 11.02 in Denmark and 7.04 in the USA. Yet, there is no cost effective screening method for ovarian carcinoma.

Because symptoms of ovarian cancer are non-specific or even rare, the majority of patients have advanced disease-stage III or IV - at the time of diagnosis. The 5-

year survival rate for these women is only 15-20% (Society of Gynecologic Oncologists Report).

Accurate preoperative discrimination of benign and malignant adnexal masses remains difficult despite recent advances in medical imaging. The quality of cytoreductive surgery is one of the most important prognostic factors and it is argued that surgery for ovarian cancer should be performed in specialized oncology centers. However, the presence of an adnexal mass is a common problem encountered in clinical practice and referral of all women with such masses would be both impractical and unnecessary. Preoperative detection of malignancy would allow selective referrals to the appropriate centers for optimal care, whereas those women with benign masses could be offered more conservative surgery. In the past, individual sonographic, demographic and biochemical variables were used to distinguish between benign and malignant adnexal masses. However, these diagnostic facilities are not always available. Thus, a general obstetrician-gynecologist merely relies on his/her clinical "eye" pre-operatively and intraoperatively.

As befitting the weight of this disease entity, an exhaustive fathom of researches focused on the diagnosis of this disease. These studies range from pre-operative values of tumor markers, ultrasonography and pelvic examination. However, less has been written about the value of ovarian mass morphology during the operation as predictor of malignancy potential.

In a tertiary hospital, in year 2001 alone, based on the annual statistics of its Section of Gynecologic Oncology, eighteen percent (18%) of the referrals from the General Services of the Department of Obstetrics and Gynecology for the intra-operative assessment of ovarian mass were not accurate. Some of these masses diagnosed benign intra-operatively, turned out to be malignant and other cases were thought to be malignant but turned out benign in the final histopathologic report.

The rationale for intra-operative screening of ovarian masses is the close relationship between the extent of the cancer operation and patient survival. Accurate assessment of malignancy potential during operation would definitely affect the decision to perform more extensive staging procedures such as omentectomy, peritoneal fluid cytology and pelvic and aortic lymphadenectomy. It can also minimize unnecessary surgical procedures and morbidities from these procedures.

Of course, there will always be the help of frozen section in a tertiary hospital, which has a high accuracy rate, reaching above ninety percent (90%). However, it must be kept in mind that the Philippines, like any other low-resource countries, has areas where frozen section is not available.

The long term objective of accurate ovarian cancer diagnosis is to improve the treatment planning of patients with ovarian carcinoma by the judicious use of non-invasive, low-cost and valid tests or methods.

Objectives

The study has the following objectives:

A. General Objective

To identify intra-operative variables that are predictive of ovarian malignancy.

B. Specific Objectives

1. To determine the incidence of ovarian malignancy among patients who underwent primary surgery for gynecologic pathology.

2. To determine the value of the following intra-operative variables in predicting ovarian malignancy.
   a. Bilaterality
   b. Size of the mass
   c. Presence of ascites
   d. Presence of extra-ovarian implants
   e. Consistency of the mass (solid/cystic/ predominantly solid or cystic)
   f. Presence of adhesions between the mass and adjacent structures.
   g. Inner wall structures
      1. presence and size of papillary excrescencies
      2. presence of loculations
   h. Wall thickness

3. To determine the odds ratio of each of the above variables in its association with ovarian malignancy.

4. To determine the specificity, sensitivity, positive predictive values and negative predictive values for ovarian malignancy of each intra-operative variable.

5. To construct a multiple logistic regression model for the prediction of ovarian malignancy based on intra-operative findings.

This is a retrospective case control study.

Materials and Methods

A. Study Subjects

Population at Risk/Target Population

The study population consisted of female patients admitted to a tertiary hospital who underwent primary abdominopelvic surgery for gynecologic pathology whose final histopathologic report showed ovarian pathology/pathologies from January 1 to December 31, 2002.

Selection of Sample Population

Charts of all patients' admitted to the obstetric, gynecologic and gynecologic-oncologic services for emergency and elective abdominopelvic and gynecologic surgery were reviewed for eligibility into the study.

1. Inclusion Criteria:
   - Female patients with pre-operative diagnosis of ovarian neoplasms.
   - Female patients with incidental findings of ovarian neoplasms on exploratory laparotomy or laparoscopic operations.
   - Patients who underwent any of the following surgical procedures under general or regional anesthesia:
     - Abdominopelvic (gastro-intestinal)
     - Gynecologic (transabdominal)
     - Obstetric (caesarian)
     - Laparoscopic-gynecologic
   - Female patients with ovarian neoplasm/s as indicated in the final histopathologic report.

2. Exclusion Criteria

   Patients who underwent surgery for gynecologic pathology whose final histopathologic reports point to a non-ovarian neoplasm.

B. Methodology/Study Procedure

Names of subjects were retrieved from the files of the Department of Laboratories - Surgical Pathology Unit. The files to be reviewed were grouped under the "OVARY" and "UTERUS" files. Data from the histopathologic report were encoded in the Ovarian Histopathology Data Sheet. The inpatient charts of the recruited subjects were retrieved for the review of intraoperative findings. Intraoperative findings as reported by the surgeons were reviewed and encoded in the Ovarian Intra-operative Findings Data Sheet. The incidence of ovarian malignancy was computed. The odds ratios of each variable for the presence of malignancy were computed along with their 95% confidence interval to compare the effect of each individual variable.

For the purpose of multivariate analysis, variable with an odds ratio higher than 2 or less than 0.5, as well as variables for which the 90% confidence intervals excluded the value of null effect for at least one category were retained. A multiple logistic regression model was developed using a forward stepwise approach, starting with variable showing the most significant association in the univariate logistic regression. The specificity, sensitivity, positive predictive value and negative predictive value were then derived from the model and the receiver operating characteristic curve was traced.

C. Outcome Measurements

The outcome of interest was the presence of malignancy as reported in the final histopathologic report.

The following are the intra-operative variables studied: (1) bilaterality of the mass/es; (2) size of the ovarian mass/masses (in cm). The length, width and height (thickness) of the ovarian pathology were all measured. The volume of the tumor is defined as the product of three diameters taken in perpendicular planes using the formula for a prolate ellipsoid (Length x Width x Height x $\pi/6$); (3) consistency of the mass/masses (either solid, cystic, mixed-predominantly solid, mixed-predominantly cystic); (4) presence of ascites; (5) presence of extra-ovarian implants; (6) presence of adhesions between the ovarian mass and adjacent structures; (7) wall thickness, measured in centimeters; and (8) inner wall structures: presence of papillary excrescencies, presence of septations and/or loculations.

D. Data Analysis

Data were entered into an SPPS version 10-program database. Frequency tables were constructed comparing those classified as "*Benign*" to "*Malignant*" ones according to the different intraoperative variables being studied. Univariate and multivariate analyses were performed and a logistic regression

model for significant intraoperative variables was constructed using the same program.

Results

One hundred seventy one (171) cases were reviewed from January 1 to December 31, 2002. Of these, 110 women had benign cysts and 61 had malignant ovarian tumors. The mean age of women in the benign group was 42 years, compared with 53 years in the malignant group ($p = 0.03489$) (Table 1). Twenty-two (22) percent of women with benign cysts were postmenopausal, compared with 67 percent of women with malignant tumors. Similarly, a larger proportion of women with ovarian cancer have ascites and papillary excrescences present.

Table 1. Characteristics of benign tumors compared with malignant tumors.

Parameter	Benign Tumor N=110	Malignant Tumor N=61	p value p<0.05
Age			
Mean	42	53	0.03489
Range	10-75	12-75	
Postmenopausal (%)	22%	67%	0.0001
Intraoperative Findings%			
Tumor Volume (cm^3)*			
Mean	214.3	1210	0.0001
Range	6-2294	6-34300	
Papillary Projections	4	48	0.048
Unilocular	64	48	NS
Bilateral	24	58	NS
Ascites	6	58	0.0361
Adhesions	49	64	NS
Ruptures	28	48	NS
Extraovarian Implants	4	71	0.04314
Wall Thickness (cm)			
Mean	0.3	0.8	0.04972
Range	0.1-1.1	0.2-1.7	
Solid consistency	24	72	NS

* Tumor volume was calculated from three diameters taken in perpendicular planes using the formula for a prolate ellipsoid (Length x Width x Height x $\pi/6$)

Of the 110 benign cases, four (4) women had bilateral cysts of different histopathology. The majority of women with benign tumors had cystadenomas, dermoid cysts, endometriomas or functional cysts (Table 2).

Table 2. Histologic classification of benign tumors (n=110).

Histology	N%
Cystadenomas	37 (34%)
Dermoid Cysts	24 (22%)
Endometriomas	20 (18%)
Functional Cysts	14 (13%)
Fibroma/Thecoma	7 (6%)
Pelvic Inflammatory Disease/Abscess	7 (6%)
Adhesions	1 (1%)

Of the 61 women with malignant tumors, 40 invasive epithelial tumors, 10 had non-epithelial ovarian carcinomas and 11 had tumors of borderline malignancy.

Table 3. Histologic classification of malignant tumors (n=61).

Histology	N (%)
Bordeline Tumors	11 (18%)
Epithelial Tumors	
Serous Cystadenocarcinomas	24 (39%)
Mucinous Cystadenocarcinomas	12 (20%)
Endometrioid Adenocarcinomas	2 (3%)
Clear Cell Adenocarcinomas	2 (3%)
Non-epithelial Tumors	
Yolk Sac Tumors	2 (3%)
Granulosa Cell Tumors	8 (13%)

As shown in Table 4, the most significant intraoperative findings as determined by stepwise logistic regression analysis and odds ratio were: papillary projections, tumor volume, presence of ascites, presence of extra-ovarian implants and cyst wall thickness. The value of the odds ratio for the most significant intra-operative features were ranked and the relative weights of the categories in each variable were determined. This method was used to design the proposed predictive scoring system (Table 5).

Table 4. Multivariate stepwise analysis and estimated odds ratio.

Parameters	B	SE	Wald	Df	P value <0.05	R	Odds Ratio
Papillary Projections*	1.4509	0.6310	5.28731	1	0.0215	0.1100	4.2669
Tumor Volume*	0.5758	0.3583	8.53891	1	0.0053	0.1859	2.6839
Ascite*	0.5398	0.2115	6.5114	1	0.0107	0.1288	2.7157
Wall Thickness*	0.9348	0.2947	10.0604	1	0.0015	0.2722	2.5466
Extraovarian Implants*	0.9239	0.3422	7.29131	1	0.0069	0.1395	2.5192
Unilocular/Multilocular	0.0100	0.0170	0.3479	1	0.5553	0.0000	1.0101
Bilaterality	–0.0155	0.4808	0.0010	1	0.9743	0.0000	0.9846
Adhesions	0.2445	1.2949	0.03571	1	0.8502	0.0000	1.2770
Presence of Rupture	0.5656	0.4902	1.3309	1	0.2486	0.0000	1.7605
Consistence (Solid)	–0.0285	0.0238	0.0012	1	0.9956	0.0000	0.9933

* Significant Factors

Table 5. Proposed ovarian cancer intra-operative predictive scoring scheme.

Parameters	0	1	2	3
Papillary Projections	(–)			(+)
Tumor Volume		<250 cm^3	≥250 cm^3	
Ascites		(–)	(+)	
Wall Thickness		<.03 cm	≥0.3 cm	
Extraovarian Implant		(–)	(+)	

* If the score is ≥6, there is high likelihood for malignancy.

Each of the 171 women was scored according to the scoring system (Table 5). The sensitivity and the specificity curves were drawn in order to determine the positive predictive value and negative predictive value of each proposed cut-off. The proposed cut off for likelihood of malignancy was greater or equal to a score of 6 (Figure 1). At a cut-off of 6, the sensitivity was 78.62% and the specificity was 91.73% and the positive and negative predictive values were 81.55 and 88.01, respectively.

Table 6. Sensitivity, specificity, positive predictive value and negative predictive value of different proposed score cut-offs of the ovarian cancer intra-operative predictive scoring scheme.

Cut-Off Score	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
≥ 9				
< 9	6.14	99.90	84.51	82.24
≥ 8				
< 8	16.38	96.63	84.80	81.95
≥ 7				
< 7	41.84	92.85	81.88	84.25
≥ 6				
< 6	78.62	91.73	81.55	88.01
≥ 5				
< 5	81.46	79.62	70.18	90.32
≥ 4				
< 4	88.03	48.44	45.38	92.95
≥ 3				
< 3	92.75	15.72	26.65	95.13

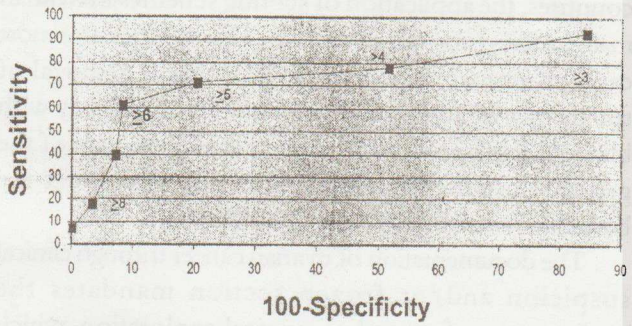

Figure 1. Receiver operator curve.

Discussion

There are no currently reliable procedures for the early detection of ovarian cancer. Available potential screening techniques have included pelvic examination (ovarian palpation), ultrasound examinations, serum CA-125 determination and other tumor markers and combined modality approaches. Numerous criteria have been established for useful screening tests.

The importance of delineating a benign from a malignant adnexal mass can not be underestimated. The utility of the frozen section in situations wherein the decision cannot be based on intra-operative picture alone is well indicated. If frozen section indicates the presence of ovarian cancer, a complete abdominal exploration should be carried out, including evaluation of all intestinal surfaces. Any suspicious areas should be biopsied. Omentectomy and random peritoneal biopsies should be performed. Routine pelvic lymph node dissection is indicated as well. Aortic lymph node sampling should also be performed. Standardized protocols are used to record the specific details of operative and pathologic

findings that have prognostic and therapeutic bearing on treatment and natural history.

In adnexal masses, there are many surgical findings that may point to a malignancy. Indeed, these intra-operative features show good predictive power in identifying the woman who may have an ovarian or any other pelvic malignancy. Many studies have combined clinical, as well as surgical findings and imaging features to predict ovarian malignancies. Most of these studies used logistic regression analysis to formulate models that can highly identify ovarian malignancy.

In the Philippines, like most other less developed countries, the application of scoring schemes in ovarian malignancies becomes significant. This is so because most cases of ovarian cancer undergo a simple removal of the ovaries or at the most, a simple hysterectomy with bilateral salpingo-oophorectomy under the care of the general obstetrician gynecologist and do not get the benefit of a complete surgical exploration.

The documentation of ovarian cancer through clinical suspicion and/or frozen section mandates the performance of complete surgical exploration, which includes pelvic and periaortic lymph node dissection. There are numerous centers in the Philippines wherein these special surgical skills are available. However, in centers wherein these skills and frozen section are not available, the ovarian cancer intra-operative predictive scoring scheme can be utilized. If the score based on the proposed model is greater than or equal to 6, the primary surgeon can do peritoneal fluid cytology, omentectomy, random peritoneal biopsies and thorough palpation of lymph nodes and abdominopelvic organs at the very least. In institutions where there is a gynecologic oncologist, referral can be made for surgical opinion and co-management.

Limitations of the Study

The study was a retrospective case control study. The findings were based mainly on the chart reviews. Most of the surgical features were not included in the written intra-operative findings.

Summary and Conclusion

The introduction of diagnostic models would allow a uniform approach when assessing an adnexal mass intraoperatively. The model would ensure reproducibility of diagnosis and reduce dependence on operator experience. Another important advantage is the ability to estimate the probability of malignancy that is helpful in both decision making and patient counseling. Therefore, the search for optimum diagnostic models should continue.

The utilization of the ovarian cancer intra-operative predictive score scheme allows involvement of the general obstetrician-gynecologist in the intervention of the disease in a low resource setting.

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A Comparison Between Separate Surgical Incision Technique and en Bloc Technique of Radical Vulvectomy and Inguinal Lymphadenectomy in Primary Squamous Cell Carcinoma of the Vulva: A Retrospective Cohort Study

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To compare the outcomes in vulvar cancer patients treated by radical vulvectomy and inguinal lymphadenectomy using the triple incision technique and those using the en bloc technique. **Materials and Methods**: A retrospective review of 18 patients with primary squamous cell carcinoma of the vulva was performed and follow-up data were collected from the patient's records. All pathology slides were reviewed by a single pathologist. Eight patients underwent radical vulvectomy and bilateral inguinal lymphadenectomy using the separate incision technique while 10 patients underwent the same operation using the en bloc technique. **Results**: There was no statistically significant difference between the two groups regarding age, gravidity, parity, stage, lesion diameter, grade of the tumor, status of margins, capillary lymph space invasion, depth of invasion and groin node metastasis. There were more patients in the en bloc group who underwent postoperative radiotherapy. There was a longer operating time, more blood loss and longer hospital stay in the en bloc group compared to the separate incision group ($P<0.05$). Complications were also more frequent among patients in the en bloc group compared to those in the separate incision group: wound breakdown, 50% versus 25% and leg edema, 20% versus 12%. Number of months with no evidence of disease between the two groups was not statistically significant ($P<0.05$). There were two recurrences in the separate incision groups which were attributed to invasion of the subcutaneous tissue and extracapsular groin node metastasis. **Conclusion:** Separate surgical incision technique of radical vulvectomy provides satisfactory survival results with less morbidity compared to the en bloc technique.

Key words: Radical vulvectomy, en bloc technique, separate surgical incision technique.

Cancer of the vulva accounts for 4 percent of gynecological malignancies, over 90 percent of which are squamous carcinoma.[1,2,3]

In the early part of the 20th century, patients commonly presented with advanced disease and surgical techniques were poorly developed; thus, the 5-year survival rate for vulvar cancer was 20-25 percent.[4] Taussg in the United States and Way in Great Britain clinically applied the principles of Bassets and developed the surgical technique en bloc. The 5-year survival rate improved 60-70 percent.

The morbidity of this surgical approach is very high. Bryan, et al. proposed the technique with three separate incisions as an alternative technique more than 35 years

ago.[5,6] This concept did not gain widespread acceptance until the landmark article by DiSaia, et al. in 1979.[7] Since then, conservative surgery has been successfully incorporated into the care of vulvar carcinoma.

Separate incision technique has been reported in several studies to have consistent local control and cure and with considerably less morbidity. This approach has gained widespread acceptance and has become the standard of therapy in most centers. Triple incision technique has been used in the management of vulvar carcinoma for several years. To date, no local studies have been done to compare the separate incision and en bloc techniques.

Objective

General Objective

To compare the outcome in vulvar cancer patients treated by radical vulvectomy and inguinal lymphadenectomy using the en bloc technique from those treated with triple incision technique.

Specific Objectives

To compare the intraoperative and postoperative outcome of vulvar cancer patients treated with radical vulvectomy and inguinal lymphadenectomy using the en bloc technique from those treated with triple incision techniques.

To compare morbidity from radical vulvectomy and inguinal lymphadenectomy using en bloc technique with those using the triple incision technique.

To compare (1) number of months with no evidence of disease and (2) tumor recurrence between vulvar cancer patients treated with radical vulvectomy and inguinal lymphadenectomy using en bloc technique with those treated using the triple incision technique.

Materials and Methods

A retrospective review was performed on 18 patients with primary squamous cell carcinoma of the vulva treated between March 17, 1994 and March 7, 2003. The study included all previously untreated invasive squamous cell carcinoma of the vulva patients who underwent radical vulvectomy and inguinal lymphadenectomy. Patients with in situ vulvar carcinoma, recurrent vulvar carcinoma, non-squamous vulvar carcinoma and those who were previously treated with radiation therapy and/or chemotherapy prior to surgery were excluded from the study.

The study protocol was submitted and evaluated by the research coordinator of the section. Clinical and follow-up data were collected from the patient's records. All histopathologic slides were retrieved and reviewed again by one pathologist. All patients were reclassified according to the 1988 International Federation of Obstetricians and Gynecologists (FIGO) staging classification, taking into consideration the tumor size; depth of invasion; vaginal, urethral, or anal extension; lymph node involvement (number and location); and bladder and/or rectal invasion.[8,9]

A gynecologic oncologist performed all surgical procedures. Radical vulvectomy and inguinal node dissection employing separate incision technique was performed as described by Hacker, et al.[10] Specifically, inguinal node dissection was performed through an elliptical incision paralleling the inguinal ligament. The superficial nodes lying above the cribiform fascia were dissected en toto in all patients. When performed, the deep inguinal nodes were resected by removing the nodal fat overlying the femoral vessels. Vulvar resection in the separate incision technique commenced on the mons and extended posteriorly along the labial crural fold to the peritoneum. The medial incision extended around the vaginal mucosa at the introitus and anterior to the urethra. The vulva was resected to the level of the fascia overlying the urogenital diaphragm (total deep vulvectomy). In the other group, radical vulvectomy was performed employing an en bloc resection of the vulva and inguinal nodes as described by Stanley Way.[3] The skin incision consisted of a curvilinar incision from one anterior iliac spine to the opposite one, passing through the mons pubis just above the symphysis pubis. From the anterior superior iliac spine, the skin incision was carried down to the thigh below the crease of the groin, down to the medial aspect of the thigh below the femoral triangle. The upper and lower skin flaps were undermined to expose all the fatty tissues that harbor lymph nodes. The dissection involved opening the femoral sheath to expose the Cloquet's node. The radical vulvectomy portion followed.

Demographic characteristics, intraoperative and postoperative outcomes were compared using student T test. Results within a P value of <0.05 were regarded as statistically significant.

Results

Eighteen patients diagnosed to have primary squamous cell carcinoma of the vulva treated at the Section of Gynecologic Oncology, Department of Obstetrics and Gynecology of Philippine General Hospital were identified. Ten patients were treated with the standard en bloc technique and 8 patients were treated with separate incision technique. All patients were treated between 1994 and 2003.

There were no statistically significant difference in age, gravidity, surgical stage, grade, lesion diameter, status of margin, nodal status and capillary lymph space invasion.

There was a statistical difference in postoperative therapy with more patients in the en bloc group receiving post-op radiotherapy.

There were more positive capillary lymph space involvement and nodal invasion in the en bloc group (Table 1).

Table 1. Comparison of the two treatment modalities.

	En Bloc N=10	Separate Incision N=8	P value
Age (year)			
Median	59.5	56	NS
Range	47-68	35-78	
Gravidity			
Median	5.5	7	NS
Range	2-13	4-9	
Parity			
Median	5.5	6.5	NS
Range	1-13	3-9	
Stage			
II	7	6	NS
III	3	2	
Lesion Diameter			
2.2-3.0 cm	1	2	NS
3.1-4.0 cm	2	2	
4.1-5.0 cm	2	2	
> 5.1 cm	5	2	
Grade of Tumor			
1	8	7	NS
2	2	1	
Status of Margin			
Positive	0	0	NS
Negative	10	8	
Capillary Lymph Space Invasion			
Positive	2	0	NS
Negative	8	8	
Depth of Invasion			
2-5 mm	4	3	NS
>5 mm	6	5	
Groin Nodes			
Positive	3	2	NS
Negative	7	6	
Post-op therapy			
Yes	6	2	0.003241
No	4	6	

P value of alpha <0.05

Median duration of follow-up for the en bloc group was 11 months and for the separate incision group was 17.5 months.

All patients had bilateral inguinal node dissection. Three of the 10 patients (30%) in the en bloc group had inguinal node metastasis: 2 with metastasis to 3 nodes and 1 with metastasis to 4 nodes. Two of the 8 patients (25%) in the separate incision group had inguinal node metastasis: 1 with metastasis to 3 nodes and 1 with metastasis to 4 nodes.

There was a statistically significant difference in the intraoperative and postoperative outcomes between the two treatment groups. The operating time was longer for the en bloc group (225 minutes) compared to the separate incision group (184 minutes). A median blood loss of 1000 ml was seen in the en bloc group compared to a median blood loss of 900 ml in the separate incision group. There was a longer hospital stay in the en bloc group with a median of 13 days compared to a median of 8 days in the separate incision group (Table 2).

Table 2. Comparison of intraoperative and postoperative outcome between patients who underwent separate incision technique and en bloc vulvectomy and inguinal node dissection.

	En Bloc N=10	Separate Incision N=8	P value
Operating time (mins)			
Median	224	181.63	0.034289
Range	175-290	105-240	
Blood loss (ml)			
Median	1100	1018.75	0.034289
Range	600-1700	600-1500	
Hospital stay (days)			
Median	12.3	8.875	0.044978
Range	6-18	5-17	

P value of alpha <0.05

There were more morbidity noted on the en bloc group compared to the separate incision group: 50% (5/10) wound dehiscence and 20% (2/10) leg edema in the en bloc group compared to 25% (2/8) wound dehiscence, 12% (1/8) cellulitis and 12% (1/8) leg edema in the separate incision group (Table 3).

The duration of no evidence of disease between the two treatment groups was not statistically significant: 11 months for the en bloc group and 14.5 months for the separate incision group (Table 4).

There were two tumor recurrences in the separate incision group: one patient had recurrence in the vulvar

incision site and another patient had recurrence in the groin incision site. The patient with vulvar recurrence had tumor invasion up to the subcutaneous tissue while the patient who had groin recurrence had extracapsular lymph node invasion. Both patients had postoperative radiotherapy. No similar patients were seen in the en bloc group.

Table 3. Morbidity associated with separate incision technique and en bloc radical vulvectomy.

	En Bloc N=10	Separate Incision N=8	P value
Wound Dehiscence	5 (50%)	2 (25%)	NS
Cellulitis	0	1 (12%)	NS
Leg edema	2 (20%)	1 (12%)	NS

P value of alpha <0.05

Table 4. Number of months among patients with no evidence of disease and number of patients with tumor recurrence who underwent separate incision technique and en bloc radical vulvectomy.

	En Bloc N=10	Separate Incision N=8	P value
NED (months)			
Median	11	14.5	NS
Range	2-84	5-44	
Recurrence			
Vulva	0	1(12%)	
Groin	0	1(12%)	

P value of alpha <0.05

Discussion

As with other malignancies, a trend has existed to minimize the radicality of the surgical therapy without compromising survival. The initiating factor was the high incidence of postoperative complications associated with the standard radical incision. The changes in surgical therapy therefore have been primarily directed toward prevention and reduction of these complications.

The standard therapy for practically all stages of vulvar carcinoma has been the removal in one specimen of vulva, perineum, mons pubis and bilateral groin nodes and their overlying skin, the so called "en bloc vulvectomy." This has resulted in unacceptable rates of wound complications and has been shown to be over treatment in early stages of the disease.

Consequently, studies have addressed the results of lesser forms of radical surgery that were tailored to the location and extent of the lesion and with intent to decrease complications but provide similar survival as standard radical therapy.

After the landmark article of DiSaia in 1979, separate incision technique has been successfully incorporated into the care of vulvar cancer. It has been initially used on patients with early stage, small volume vulvar disease.[5,11,12,13] Hacker, et al. in 1984, were the first to report on a series of patients with advanced stage vulvar cancer treated with triple incision technique.[6] Two controlled studies in the literature contained vulvar cancer patients with advanced stage lesions treated with separate incision technique. Survival was similar to that of the matched historical control treated with en bloc incision technique.[14,15]

Hacker, et al. reported one hundred patients who underwent radical vulvectomy and bilateral inguinal lymphadenectomy using separate incision technique. The mean operative blood loss in their series was 620 ml with a range of 150-1900 ml. Blood loss exceeded 1000 ml in 16 patients. Post-operative hospital stay ranged from 1 to 46 days with a mean of 19 days. Thirteen patients required postoperative hospitalization exceeding 4 weeks. In this present study, mean blood loss of patients who underwent separate incision technique was 1018 ml with a range of 600 to 1500 ml. The big difference of this study and that of Hacker in terms of mean blood loss could be the inaccuracy of estimating intraoperative blood loss. The mean hospital stay in this study was 8 days with a range of 5 to 17 days. In addition, mean operating time was 180 minutes with a range of 105 to 240 minutes.

Wound complications continue to be a formidable challenge in the radical surgical treatment of this disease. The triple incision technique allowed skin edges to be approximated without tension, improving wound healing. It has been demonstrated to be effective and has been shown to decrease the local postoperative complication rates, without affecting survival. Notable complications in this study were wound dehiscence, leg edema and cellulitis. There were 5(50%) with wound dehiscence in the en bloc group compared to 2 (25%) in the separate incision group. Two (20%) in en bloc group had leg edema compared to 1(12%) in the separate incision group. No patients had cellulitis in the en bloc group compared to 1(12%) in the separate incision group.

Cavanagh, et al.[16] reported a wound breakdown rate of 70% for the en bloc technique compared with less than 20% for the technique using the separate incision. In

this study, the wound breakdown rate was 50% for patients undergoing en bloc technique and 20% for patients undergoing separate incision technique. Results are similar to that of Cavanagh. However, wound breakdown remains a significant problem even with the separate incision technique. In our experience, the type of vulvectomy probably affected the wound breakdown rate. Similarly, Hopkins, et al.[14] in 1993 reported that complications were more frequent in those patients who had undergone en bloc technique that those with three separate incisions: wound breakdown, 64% versus 38%. respectively (P=0.005); wound infection, 20% versus 12%, respectively (P=0.4); wound cellulites, 21% versus 14%, respectively (P=0.08); and lymphocyst formation, 28% versus 14%, respectively (P=0.08). Other studies have also found decreased complication rates associated with separate incision techniques.[5,13,16]

Surgical sequelae also were less common in the modified radical surgery group. A significant problem in the en bloc group as reported by Cavanagh was persistent lymphedema of the legs that occurred in nearly 9% of their patients.[16] Margina, et al. reported a fourfold reduction in the incidence of lymphedema using the separate surgical incision. In this study, the reported lymphedema in the en bloc group was 20% compared to 12% in the separate incision group.

The median number of months with no evidence of disease between the two groups was not statistically significant: 11 months for the en bloc group and 14.5 months for the separate incision group. However, there were two recurrences in the separate incision group, which could be attributed to the subcutaneous tumor invasion and extracapsular groin node metastasis.

Farias-Eisner, et al.[5] reported that the survival of those treated conservatively was 97% for stage I and 90% for stage II, which was the same as those undergoing a radical vulvectomy which is 100% for stage I and 97% for stage II. Similar results have been reported.[6,13]

In 1981, Hacker, et al.[10] reported 100 patients who had vulvar carcinoma who underwent the triple incision technique. Forty-nine had stage I, 37 stage II and 14 stage III. The 5-year survival for each stage was 97.4%, 86% and 49.2%, respectively. Margina, et al.[4] in 1998 compared radical and modified radical vulvar surgery relative to survival, recurrence, metastasis and complications. The 5-year recurrence rate was 14%. The overall and disease-free survival rates at 5 years were 76.1% and 83.4%, respectively. There were no statistically significant differences between the two procedures regarding overall survival, disease-free survival, or the development of recurrence, even after adjusting for stage (P>0.05). A case controlled study between triple and en bloc radical vulvectomy and inguinal lymphadenectomy in patients with T2/3 vulvar cancer was done by Siller, et al.[16] in 1994. They reported the recurrence rate of 37% in the separate incision group compared to 35% in the en bloc group. There was no difference in the local recurrence rates between the two groups (80% in the separate incision group and 72% in the en bloc group). The 5-year survival rates for the separate incision group and the en bloc group were 65% and 82%, respectively.

The present study, although retrospective and therefore with limited value in its conclusion, validates the actual tenet that reduction of the extent of the operation for patients with primary squamous cell carcinoma of the vulva is associated with fewer complications. Extirpation of the uninvolved vulva and groin skin beyond adequate surgical margin did not decrease recurrences and metastasis and improved survival and it is largely responsible for the higher complication rates associated with radical surgery.[4] Surgical therapy of the vulva should be directed toward obtaining adequate margins in all three tumor dimensions. Groin lymphadenectomy can be accomplished through separate groin incisions, with preservation of the uninvolved overlying groin skin and without compromising results. Due to the significant morbidity that has been associated with en bloc radical vulvectomy and inguinal lymphadenectomy, the separate incision technique has been the preferred method of treatment for most vulvar cancers.

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Accuracy of Frozen Section of the Endometrium: A Preliminary Study

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A prospective study was done to determine the accuracy of frozen section in comparison to the final histopathologic diagnosis. **Methods**: Forty-three patients underwent frozen section within a period of fifteen months. **Results**: All forty-one patients diagnosed with benign endometrial conditions in the final histopathologic reading were correctly diagnosed by frozen section. Two patients were diagnosed with carcinoma by frozen section and verified in the paraffin sections. This study shows a 100% sensitivity, specificity and positive predictive value for frozen section in diagnosing benign and malignant conditions of the endometrium. **Conclusion**: Frozen section diagnosis of the endometrium is extremely accurate, therefore, patients were not subjected to unwarranted prolonged, extensive and more costly surgery on the basis of false positive results.

Key words: frozen section, endometrium

When frozen section was first introduced by William M. Welsh in 1891, it was hardly practiced as a result of its poor accuracy and time-consuming procedure.[1] Gradually, with technical advancement and improvement of interpretation, frozen section diagnosis became a readily available diagnostic procedure in the surgical field.

Intraoperative consultation is widely used in gynecologic surgical practice to make intraoperative diagnosis, primarily to aid the surgeon to plan the extent of surgery.[2,3] An intraoperative histologic diagnosis of endometrial malignancy has important bearings on the choice and extent of surgery. Frozen section is utilized to ascertain the microscopic diagnosis of a neoplasm prior to performing definitive surgery to prevent under and overtreatment of patients.

In gynecology, frozen section has been used intraoperatively mainly for the ovarian tumor and rarely in tissues obtained from endometrial ablation, cervical cone biopsy and suspicious vaginal and vulvar lesions. In a study by Wang,[4] which included 56 uterine/endometrial lesions out of 792 subjects, it has been found to be sufficiently accurate for clinical use, with a low false negative rate and an even lower false positive rate. Most incompatible frozen section diagnoses occurred in ovarian lesions.

Abnormal vaginal bleeding is the most common reason for endometrial sampling.[5] Patients with abnormal uterine bleeding should have an endometrial sample taken for histopathologic examination. Fractional dilatation and curettage (D & C) has been the definitive procedure in ruling out endometrial cancer.[6]

The usual practice in this institution is to do endometrial sampling by fractional dilatation and curettage or sometimes through clinic endometrial biopsy. Results

of endometrial sampling are obtained, usually after two to three days before definitive procedure is planned and the patient is readmitted.

The diagnosis of endometrial carcinoma is usually made pre-operatively before definitive surgical treatment. Thus, intraoperative consultation is most often used to identify the subgroup of patients with features of high risk disease who have an increased likelihood of metastases and who will benefit from formal surgical staging.[2,7] In hysterectomy specimens of endometrial carcinoma, frozen section is also useful to determine prognostic factors.[3]

Frozen section enables the surgeon to identify patients at high risk for pelvic and paraortic nodal metastasis by identifying certain poor prognostic factors including deep myometrial invasion, poorly differentiated tumor, cervical invasion, adnexal involvement and poor histologic type.[8]

Several studies have been done to determine the accuracy of frozen section using different variables. The overall accuracy rate of frozen section diagnosis of myometrial invasion and tumor grade was 80 to 84 percent in a review of studies by Kucera.[9] Their own study with 624 patients showed an overall accuracy rate for myometrial invasion and tumor grade of 88 and 84 percent, respectively. All patients who required surgical staging were accurately identified.

Similar results were demonstrated in the study of Quinlivan.[7] Tumor grade and myometrial invasion were accurately reported in 88.6% and 94% of cases, respectively. Errors were predominantly attributable to difficulties with respect to interpretation of tumor grade.

Only when frozen section diagnosis reaches the accuracy of paraffin sections can the surgeon minimize the risk of over and undertreatment and unnecessary two-stage operations.

Objective

This study attempted to determine quantitatively the accuracy of frozen sections in the differentiation between benign and malignant endometrial pathologies.

This study proposed an alternative to the usual practice of endometrial sampling, either by fractional D & C or clinic endometrial biopsy and waiting for several days for the histopathologic diagnosis.

The gynecologist may:

(1) do endometrial curettage or endometrial biopsy, the frozen section
   a. if results are benign, discharge patient if with no other gynecologic pathology or proceed with conservative procedure (myomectomy, unilateral salpingo-oophorectomy, etc.) for the specific gynecologic pathology (myoma, ovarian cysts, etc).
   b. if results are with atypia or malignancy proceed with definitive procedure (hysterectomy with/without bilateral salpingo-oophorectomy with/without peritoneal fluid sampling and bilateral lymph node sampling (BLND)).

(2) proceed with hysterectomy given that the patient has other indications for hysterectomy like myoma, adenomyosis, procidentia, etc, then submit the entire uterus for frozen section of the endometrium.
   a. if results are benign, end the procedure
   b. if results are malignant, complete surgical staging with peritoneal fluid sampling and BLND

Materials and Methods

A prospective study was done including patients who would have frozen section of the endometrium and comparison with the final histopathologic diagnosis done.

Inadequate specimens sent for frozen section were not included in this study. Patients with a previous endometrial sampling diagnosis from a prior procedure or admission were also not included.

An examination comparing the results of 43 frozen sections performed on endometrial samples from January 1, 2003 to March 31, 2004 with the final diagnosis from paraffin sections of the whole specimen was conducted.

Patients who underwent frozen section of the endometrium were included in the study. These patients included those who had endometrial tissue sampling via fractional, diagnostic or endometrial biopsy. If the result of the frozen section was malignant or with atypia, hysterectomy was performed. Patients with other pathologies (ex. myoma uteri, adenomyosis, etc.) for which a hysterectomy was indicated as well as possible endometrial pathology needing endometrial tissue diagnosis were also included. Hysterectomy was done and the entire uterus sent to pathology for frozen section

of the endometrium. If the frozen section diagnosis was malignant, complete staging was done by doing peritoneal fluid sampling and bilateral lymph node dissection.

The decision whether a curettage and frozen section prior to definitive procedure or a hysterectomy with frozen section of the endometrium was dependent on the attending physicians and with the patient's consent.

Every frozen section was performed by a qualified pathologist duly accredited by the Philippine Society of Pathologists.

Specimens from the endometrium were either from endometrial scrapings obtained by the gynecologist via endometrial curettage or from the hysterectomy specimen taken by the pathologist.

For the purpose of this study, the paraffin section diagnosis was taken as definitive. The pathologists who gave the frozen section diagnosis made the final histologic diagnosis.

To facilitate comparison, frozen section diagnosis and paraffin section diagnosis were categorized as benign and malignant. The frozen section diagnosis was considered to be correct if it was categorically identical to the paraffin section diagnosis.

After comparison in a 2 x 2 table, the sensitivity, specificity and predictive values for frozen section diagnoses of the endometrium were computed.

Results

During the period between January 1, 2003 and March 31, 2004, there were 43 cases where frozen section of the endometrium was performed.

Fourteen patients had endometrial sampling, one via endometrial biopsy and thirteen via endometrial curettage and specimen sent for frozen section. All fourteen had benign frozen section diagnosis. Four of the fourteen were read as benign and proceeded with conservative surgery for other gynecologic pathologies (three myomectomies and one oophorectomy). Hysterectomy was done in ten other subjects for other indications such as myoma uteri, adenomyosis or ovarian cysts.

The remaining 29 subjects had a hysterectomy for other indications like myoma uteri, adenomyosis or ovarian cysts. Two of these had frozen section diagnosis that were malignant, so staging was completed with peritoneal fluid cytology and bilateral lymph node dissection.

The final histopathologic diagnoses were benign in 41 out of 43 (96.3%) cases and malignant in 2 of 43 (4.7%) cases.

Agreement between the frozen section and permanent section diagnosis is shown in Table 1. Overall, frozen section with permanent section diagnosis in 100 percent of cases.

Table 1. Correlation of histologic diagnosis between frozen section and paraffin section diagnoses.

	Final Diagnosis	
Frozen Section Diagnosis	Benign	Malignant
Benign	41	0
Malignant	0	2

The benign conditions are listed in Table 2. Thirty-one of the benign frozen section diagnoses were exactly the same as the paraffin section diagnoses. The other nine had minor differences as shown in Table 3.

Table 2. Benign diagnoses.

simple hyperplasia with or without atypia
proliferative endometrium
secretory endometrium
endometrial polyp
inactive endometrium
benign endometrium

Three out of the nine (33%) were read from endometrial samples via curettage and biopsy prior to hysterectomy, while six out of nine (66%) were from hysterectomy specimens. It may show that there were more discrepancies with frozen sections of endometrial samples from curettings or biopsy.

There were only two malignant readings in the frozen section confirmed as such by the paraffin section reading shown in Table 4.

The sensitivity of frozen section diagnosis, which represents the probability that a frozen section will be positive in a patient with a malignancy, in this study was 100 percent.

The specificity of frozen section, which represents the probability that the test will yield a negative result in a

patient who does not have a malignancy, was 100 percent in our study.

Table 3. Differences in the frozen section diagnoses and paraffin section diagnoses.

Frozen Section Diagnoses	Final Diagnoses
Endometrial polyp, Secretory endometrium	Endometrial polyp
Endometrial polyp, proliferative endometrium	Proliferative endometrium
Endometrial polyp,	Secretory endometrium
Endometrial polyp, simple hyperplasia	Simple hyperplasia with atypia
Secretory endometrium	Proliferative endometrium
Simple hyperplasia without atypia	Simple hyperplasia with atypia, endometrial polyp
Simple hyperplasia without atypia, endometrial polyp	Endometrial polyp
Simple hyperplasia	Simple hyperplasia without atypia

Table 4. Malignant diagnoses.

Endometrial adenocarcinoma
Poorly differentiated endometrioid adenocarcinoma with focal squamous differentiation

The positive predictive value of a positive frozen section was 100% and the negative predictive value of 100% for malignancy.

Discussion

The value of frozen section in the diagnosis of endometrial pathology has not been extensively examined in the literature. The goal of frozen section of the endometrium is to differentiate between benign and malignant conditions of the endometrium because the diagnosis affects the extent of operation.

There was 100% correlation between frozen section diagnosis and paraffin section diagnosis of benign and malignant conditions of the endometrium. Malignancy with the histologic type was accurately identified. Minor discrepancies were found in the benign readings but none that adversely affected management of the patient. It was shown that there were more discrepancies with frozen sections of endometrial samples from curettings or biopsy than those from hysterectomy specimens.

Four of our subjects who had either myoma uteri or ovarian cysts were not subjected to unnecessary hysterectomy given a benign frozen section diagnosis. They were given the benefit of having an endometrial sampling and results within minutes so that definitive but conservative surgery was done within one admission and a single administration of anesthesia.

The other case where endometrial sampling was done and endometrial tissue sent for frozen section prior to hysterectomy could have saved one step by proceeding with hysterectomy given other gynecologic pathologies requiring management with the guide of the frozen section diagnosis. Only hysterectomy with or without salpingo-ooophorectomy was done given the benign frozen section diagnosis.

The two subjects correctly diagnosed with malignancy by frozen section were given the benefit of complete surgical staging. Again, frozen section saves the patient from waiting for several days for paraffin section diagnosis and prevents patients from being lost to follow-up which may be crucial for cancer patients.

This study shows a 100% correlation between frozen section diagnoses and paraffin section diagnosis with regards to being benign or malignant.

The sensitivity of frozen section diagnosis, which represents the probability that a frozen section result will be positive in a patient with a malignancy, in this study was 100%.

The specificity of frozen section, which represents the probability that the test will yield a negative result in a patient who does not have a malignancy was 100% in our study.

The positive predictive value of a positive frozen section was 100% and the negative predictive value was also 100% for malignancy.

We, therefore, concluded that frozen section diagnosis is extremely accurate. Of great importance is the fact that there are no false positive results. Therefore, the patients were not subjected to unwarranted, prolonged, extensive and more costly surgery on the basis of false positive results.

Intraoperative frozen section diagnosis depends on correct technique when doing endometrial sampling and on careful gross evaluation of the endometrium for selection of tissue for frozen section. The decision ought

to be made within minutes, otherwise, the purpose of the rapid diagnostic procedure will be the time the specimen is obtained. The final histopathologic diagnosis has the advantage of extensive sampling of the entire specimen, which increases the chances of identifying microscopic foci of malignancy in a predominantly benign endometrium.

Reasons for disagreement between frozen section diagnoses and final paraffin section diagnoses were considered to be mainly due to sampling errors. The limitation of the size or site of tissue taken for frozen section precludes extensive tissue sampling especially when endometrial curettage or biopsy is the method done for endometrial sampling.

Recommendations

This study was limited to 43 patients and the results may have improved reliability if more subjects had been included in the study. Given the 100% specificity and sensitivity of frozen section in our setting, we still have the confidence to do frozen section and use it to guide us in managing our patients.

It may also be useful to compare the reliability of frozen section diagnosis of endometrial curettings against frozen section of the endometrium in hysterectomy specimens. Despite the documented reliability of tumor detection of office and operating room curettage, a 15-20 percent upgrade in the final histopathology suggests that frozen section confirmation of grade and depth of invasion in the hysterectomy specimens may be necessary if future surgical staging is not already planned.[10] In another study by Obermair,[11] 78 percent of all cases diagnosed with well-differentiated tumor diagnosed by D & C were confirmed, whereas 20.4 percent had to be upgraded as moderately differentiated tumors after evaluation of the hysterectomy specimens. They recommended intraoperative frozen examination to avoid false findings.

This study is also limited to categorical comparison, whether benign or malignant of frozen section diagnosis against the final histopathologic diagnosis. Further studies comparing the tumor grade and myometrial invasion may also be done.

Although the same pathologist made the frozen section diagnosis and gave the final diagnosis, several pathologists were involved. Future studies can be done involving only one pathologist to minimize interobserver differences in histologic readings.

This procedure may be done in other institutions to give the patients the benefits of doing frozen section. Frozen section may aid surgeons in the management of their patients and to establish the reliability of frozen sections in their particular institutions. However, these institutions should also establish the reliability of frozen sections in their own setting by doing similar studies.

Frozen sections in obviously benign conditions are found to be unnecessary. Frozen sections are also contraindicated when only a small amount of crucial material is available as the paraffin diagnosis may be compromised.

Conclusion

Frozen section of the endometrium can be used to establish histopathologic diagnosis and guide the surgeon to perform the appropriate surgical procedure. This study shows a 100% sensitivity, specificity and positive predictive value for frozen section in diagnosing benign and malignant conditions of the endometrium.

We therefore conclude that frozen section diagnosis is extremely accurate. Of great importance is the fact that there are no false positive results. Therefore, the patients are not subjected to unwarranted prolonged, extensive and more costly surgery on the basis of false positive results.

Despite its restrictions, frozen section diagnosis is an important and reliable tool in the clinical management of patients with endometrial pathologies. The sensitivity of the method in experienced hands is high and the sensitivity is sufficient.

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Mullerian Adenosarcoma with Sarcomatous Overgrowth

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Mullerian adenosarcomas are rare neoplasms characterized by an intimate admixture of benign epithelial and malignant stromal components. They are generally regarded as tumors having a low malignant potential. When characterized by a focal overgrowth of sarcomatous elements that comprise at least one-fourth of the entire tumor, the behavior becomes entirely different. These neoplasms, termed mullerian adenosarcomas with sarcomatous overgrowth (MASO), were found to exhibit a highly malignant course characterized by local recurrences, metastases and death.

A rare case of MASO, the third of its kind to be reported in the Philippines, is herein presented and discussed.

Key words: mullerian adenosarcoma with focal sarcomatous overgrowth, MASO

Mullerian adenosarcoma with sarcomatous overgrowth (MASO) was first reported in literature in 1989, constituting about 0.012% of all uterine malignancies. It refers to a rare neoplasm characterized by a mixture of a benign epithelium and a malignant stroma the exhibits a focal overgrowth of a pure sarcoma comprising at least 25 percent of the tumor.

Patients may present at any age, with non-specific signs and symptoms that can be attributable to any uterine pathology. MASO is a histopathologic diagnosis that can only be arrived at through examination of the hysterectomy specimen.

Surgery is still the primary mode of treatment. Post-operative radiotherapy has been advocated to reduce the frequency of tumor recurrences. The use of adjuvant chemotherapy is controversial.

Majority of patients present with local recurrences, usually within the pelvis or vaginal apex. Metastasis is also common. Survival rates, however, have not been established, due to the paucity of cases that have been reported. An accumulation of experience therefore is necessary to better understand this rare disease.

The Case

A 34 year-old nulligravid from Cavite was admitted for the second time because of abdominal enlargement. Her history started 4 months prior to admission when she experienced profuse vaginal bleeding, consuming about 8-10 pads per day. She self-medicated with Tranexamic acid 500 mg TID. Persistence of

menorrhagia prompted consult at our institution where internal examination revealed a 6 x 6 cm firm, smooth, non-necrotic, nontender mass protruding from the cervical os. The corpus was enlarged to approximately 18-20 weeks' size. She was subsequently admitted with a diagnosis of a prolapsed submucous myoma. Ultrasound showed an endometrial mass with cystic spaces (Figures 1 & 2). Doppler studies revealed the mass to be vascular (Figure 3). Impression was an endometrial mass to consider GTT versus polyp. Pregnancy test was negative. Punch biopsy only showed granulation tissue. Patient underwent exploratory laparotomy and intraoperatively, there was note of a 6 x 5 cm submucous mass attached to the mid-fundal posterior portion of the uterus by a 5 cm pedicle. Myomectomy with chromotubation was then performed. Histopathology of the mass revealed adenomyoma.

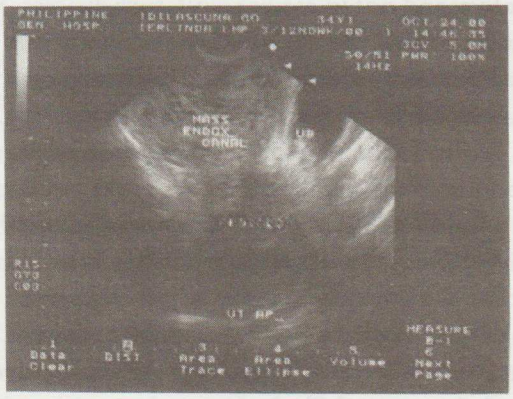

Figure 1. Transvaginal/transabdominal ultrasound revealing a heterogenous mass within the endocervical canal and extending to the endometrial cavity. The mass contained cystic spaces.

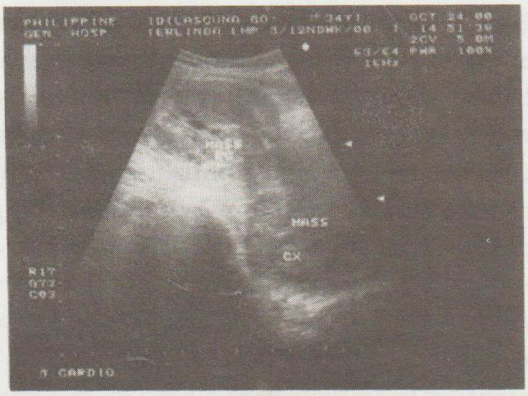

Figure 2. Another transvaginal/transabdominal ultrasound picture revealing the same heterogenous mass within the endocervical canal extending to the endometrial cavity. The mass contained cystic spaces.

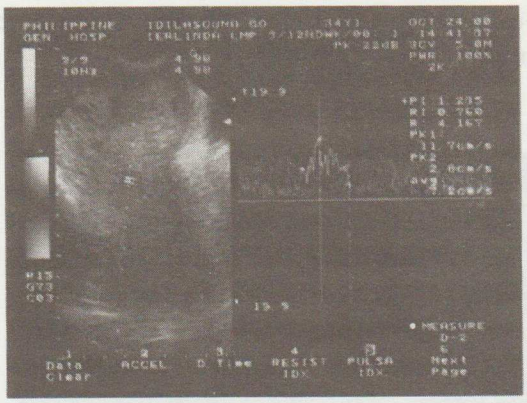

Figure 3. Doppler studies show a vascular mass with PI = 1.235, Ri = 0.760.

The patient was on regular monthly follow-up at the outpatient department. She was asymptomatic until seven weeks prior to admission when she experienced intermittent, bearable, dull lower quadrant pain. There was no consult done or any medications taken. Three weeks after, the patient noted abdominal enlargement accompanied by bilateral inguinal pain and intermittent low-grade fever. She consulted a private physician and was diagnosed to have constipation. She was given stool softeners and Mefenamic acid 500 mg for the pain with no relief of symptoms. Two weeks prior to admission, there was an increase in severity of the abdominal pain, this time radiating to the hypogastric area, associated with hesitancy. She experienced no dysuria or abnormal vaginal bleeding. She consulted at our institution where direct tenderness was noted over the left lower quadrant. Corpus was enlarged to about 20 weeks' size. She was diagnosed to have adenomyoma with concomitant urinary tract infection secondary to urinary stasis secondary to compression by the mass. Again, she was given Mefenamic acid 500 mg for the pain and was subsequently sent home. She was advised to have an ultrasound done. On follow-up at the outpatient department on the day of admission, ultrasound revealed complex masses superior to the uterus composed of several lobules separated by thick echogenic septation forming muscle-like bundles (Figure 4). The uterine cavity was filled with heterogenous hyperechoic fluid (Figure 5). Both the uterus and left ovary were surrounded by dense adhesions (Figure 6). The cul de sac was filled with fluid with septations forming a pseudocyst (Figure 7). Impressions were as follows pelvic abscess with pyometra, rule out hematometra with hematosalpinx, cannot entirely rule out uterine sarcoma,

corpus luteum, left ovary. She was subsequently admitted.

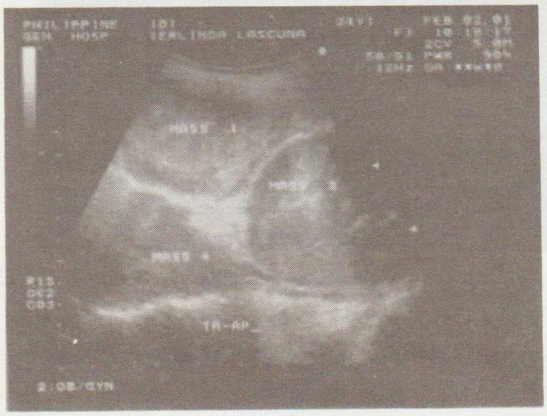

Figure 4. Transvaginal ultrasound illustrating complex masses (M1 - most distal mass, 8.6 x 8.4 x 5.7 cm; M2 - midportion, 7.7x6.8x8.5 cm) superior to the uterus composed of several lobules separated by thick echogenic septation forming muscle-like bundles.

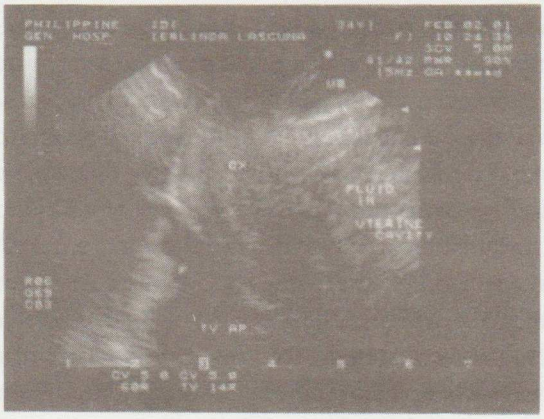

Figure 5. Another transvaginal ultrasound picture demonstrating heterogenous hyperechoic fluid filling the endometrial cavity.

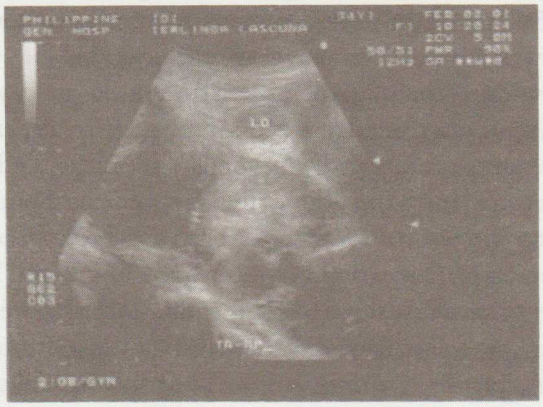

Figure 6. Transvaginal ultrasound revealing dense adhesions surrounding both the uterus and left ovary.

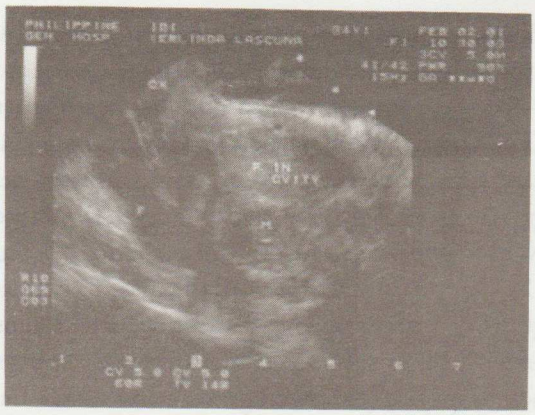

Figure 7. Transvaginal ultrasound showing low-level echo fluid in the cul de sac area, with septations forming a pseudocyst.

On review of systems, the patient had no fever, no anorexia, but with unqualified weight loss. No changes in bowel or bladder habits were noted.

On physical examination, she was conscious, coherent, ambulatory and not in cardiorespiratory distress. Vital signs were as follows: BP 140/100 mm Hg, heart rate 100 beats per minute, respiratory rate 16 cycles per minute. She was febrile at 38.8°C. Body mass index was 20.9 kg/m^2. Heart and lung findings were essentially normal. Her abdomen was slightly globular, with normoactive bowel sounds and was soft. There was 22 x 20 cm abdominopelvic mass, which was cystic, tender and slightly movable. The superior margin of the said mass was palpable 3 cm above the umbilicus, more to the left. The borders were irregular. There was no fluid wave or shifting dullness noted. She had normal external genitalia. On internal examination, the patient had nulliparous vagina and the cervix was firm, smooth, closed, with no note of wriggling tenderness. There were two palpable round masses, one located at the left fundal and the other at the right lateral area, both of which seemed to be adherent to the uterus. Corpus was enlarged to approximately 20-22 weeks' size. The adnexa were difficult to assess. Rectovaginal examination revealed good sphincter tone. There were palpable masses at the right fornix and at the cul de sac area, more to the left, which seemed to be part of the uterus. The rectovaginal septum was smooth with no nodulations noted. Admitting impression was abdominopelvic abscess, s/p myomectomy with chromotubation, October 2000.

Pregnancy test yielded negative results. Hemogram revealed anemia at 93 g/L. One unit pRBC was transfused. WBC was elevated at 18.6 x 10^9/L with predominance

of segmenters. Urinalysis was normal. She was started on intravenous antibiotics. Culture studies yielded no growth. CA 125 levels were elevated at 145.2 U/mL. An endometrial biopsy was attempted but failed due to technical difficulties.

Patient underwent exploratory laparotomy on her 4th hospital day. On exploratory laparotomy, there was note of 500 cc hemoperitoneum. The liver, spleen and kidneys were all grossly normal. There was a 20 x 18 cm solid friable pelvic mass extending up to the supraumbilical area, purplish red in color and with dilated blood vessels over the superior surface, adherent to the omentum, left anterior abdominal wall, lateral abdominal and posterior abdominal walls. Biopsy samples were taken and were sent for frozen section, which showed malignant tumor. Intraoperative diagnosis was abdominopelvic mass, malignant by frozen section, uterine vs ovarian in origin. Additional biopsies from the surface of the uterus were taken and the abdomen closed using retention sutures. The patient underwent an exploratory laparotomy, biopsy and frozen section of tumor.

Postoperative course was unremarkable. Patient, however, decided to go home against medical advice on her 10th hospital day, 6th postoperative day.

A review of slides of the previous myomectomy specimen was requested. The mass was signed out this time as an adenosarcoma. After the second exploratory, laparatomy the final histopathologic diagnosis of the tumor biopsy specimen was mullerian adenosarcoma with sarcomatous overgrowth.

Discussion

Definition

Mullerian adenosarcoma was first recognized as a distinct clinicopathologic type of mullerian tumor in 1974.[1] It is characterized by a mixture of malignant stromal and benign epithelial elements and is generally considered as a low-grade malignancy manifested by local recurrence but exceptionally by metastases.

The term "sarcomatous overgrowth" was first used and reported by Clement in 1989 to define a mullerian adenosarcoma with focal overgrowth of pure sarcoma occupying at least 25 percent of the tumor.

Incidence

Uterine sarcomas represent 30 percent of all uterine malignancies.[3] Among the sarcomas, mullerian adenosarcoma comprises 5 percent of cases,[4] only 8% of which has been reported to exhibit an overgrowth of sarcomatous elements.[2] MASOs therefore constitute 0.012 percent of all uterine malignancies.

In the Philippines, only two cases of MASO have been previously reported, both of which were from the Philippine General Hospital.[5,6] The first was in 1987, antedating Clement's report by 2 years. This case, however, was initially labeled as mullerian adenosarcoma of the uterus. When MASO was recognized as a distinct disease entity two years later, slides from this case were reviewed and subsequently relabeled as such.[5]

MASO can occur at any age, with reported cases ranging from 32 to 90 years old.

Majority of cases of adenosarcoma with a focal sarcomatous overgrowth arose from the endometrium.[2,7] The first case of extrauterine adenosarcoma with sarcomatous overgrowth was reported in 2001. This was a primary peritoneal tumor that developed within the perisplenic area.[8] Subsequent cases of extrauterine tumors were reported in the ovary.[9]

Our patient is 34 years old. The presence of an adenosarcoma in a previous myomectomy specimen could lead us to surmise that the tumor is also of endometrial origin.

Signs and Symptoms

Majority of cases presents with an abnormal or postmenopausal vaginal bleeding which may be associated with abdominal pain in some instances. A small proportion of patients manifests with increasing abdominal girth, ascites or a pelvic mass. On internal examination, the uterus is usually enlarged and a mass may be palpated or seen protruding from the cervical os.[2,7]

Our patient initially presented with abnormal uterine bleeding four months prior to admission. Internal examination revealed a corpus comparable to 18-20 weeks age of gestation, with note of a 6 x 6 cm mass protruding from the external os. She underwent myomectomy and no further therapy was instituted. Initial histopathologic diagnosis was adenomyoma. Review of slides revealed adenosarcoma. Two months after, the

patient experienced abdominal pain and noticed rapid abdominal enlargement. Discomfort may have been secondary to the peritoneal irritation caused by the enlarging uterus. Urinary symptom such as hesitancy may also be attributed to the pressure exerted by the pelvic mass on the urinary bladder. No gross bladder involvement was noted intraoperatively.

Diagnosis

Signs and symptoms of mullerian adenosarcoma with sarcomatous overgrowth are similar to any other neoplasms of the uterus. Use of imaging modalities such as ultrasound and a magnetic resonance imaging would only confirm the presence of a uterine mass, or identify sites of metastasis if there are any.

The role of CA 125 in uterine sarcomas has also been questioned. A study by Peter, et al. (1986) revealed that levels of this tumor marker appear to follow the clinical course of mixed mesodermal tumors of the female genital tract. In fact, in two of the patients they reported, elevated levels have been documented as early as one month before clinical signs of recurrence have become apparent. Although the study did not include patients with MASO, a role of CA 125 in this disease entity of similar embryologic origin as those previously reported, is still a possibility.

Tissue biopsies that yield small or scanty specimens, as in punch biopsies and fractional curettages, are at times insufficient to demonstrate the features necessary for a correct diagnosis.[11] Adenosarcomas, particularly those with sarcomatous overgrowths, can be accurately diagnosed only in a hysterectomy specimen.[7]

Gross Features

Mullerian adenosarcoma with sarcomatous overgrowth is mainly a pathologic diagnosis. Grossly, the tumors vary in size, ranging from 3 to 17 cm[27] and are generally larger than neoplasms with no sarcomatous overgrowth.[7] They are usually broad-based, occurring as single or multiple polypoid masses that fill the endometrial cavity. On cut section, the neoplastic tissues are soft, fleshly and gelatinous. Cystic spaces may be seen and focal areas of hemorrhage and necrosis may be present. More than half (60%) of tumors with sarcomatous overgrowth show invasion into the subjacent myometrium. Among those with myometrial involvement, 50% of MASO cases illustrate deep invasion, with the tumor cells extending up to the outer one third of the myometrial wall.[2]

Intraoperatively, the specimen obtained from the previous myomectomy revealed a 6 x 5 cm mass located at the submucous area attached to the mid-fundal portion of the uterus by a 5 cm pedicle. Preoperative ultrasound showed this heterogenous mass containing cystic spaces. The tumor was also noted to be very vascular.

On the other hand, the sonographic examination done prior to the second laparotomy revealed complex multilobulated masses superior to the uterus, with septations formed by muscle-like bundles which could have represented the sarcoma invading into the myometrial wall. However, this is difficult to conclude since no hysterectomy was ever performed and the myometrium was never examined microscopically.

Microscopic Features

Histologic examination reveals features representing a typical mullerian adenosarcoma characterized by an intimate admixture of a bland or atypical but benign glandular component and a sarcomatous stromal component.

The glands may vary in size and usually exhibit a proliferative phase pattern. Other types of benign mullerian epithelia may be seen lining the glands, including endocervical, tubal, stratified squamous and secretory endometrioid with subnuclear vacuoles. The scanning view of a section taken from the submucous mass of the first laparotomy shows numerous glandular structures set within a hypercellular stroma that may be mistaken for an adenofibroma. (Figure 8) Low power magnification (Figure 9) of the same area shows that the glands appear benign and are surrounded by irregularly shaped stromal cells disposed in a haphazard fashion. Note the absence of proliferation of stromal cells around the glandular structures in this area. Although nuclear atypia may be observed among the columnar cells lining the endometrial glands, mitotic figures are rare. Futhermore, no focus of adenocarcinoma can be seen within the glandular component.

The stromal component, on the other hand, is composed of loosely dispersed round to oval or spindle-shaped cells arranged in whorls that show varying degrees of nuclear pleimorphism (Figures 10, 11 & 12). The cytoplasm is usually scant and indistinct. Mitotic figures

may vary, but in general, number 2 or more per 10 high power fields (Figure 13). Focal fibrosis with hyalinization may also be noted occasionally.

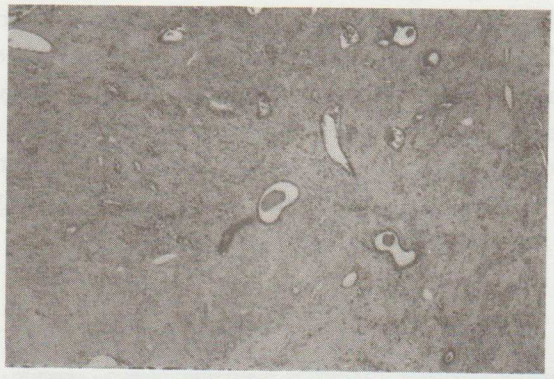

Figure 8. Scanning view (x4) of a section taken from the submucous mass showing numerous glandular structures set within a hypercellular stroma that may be mistaken for an adenofibroma.

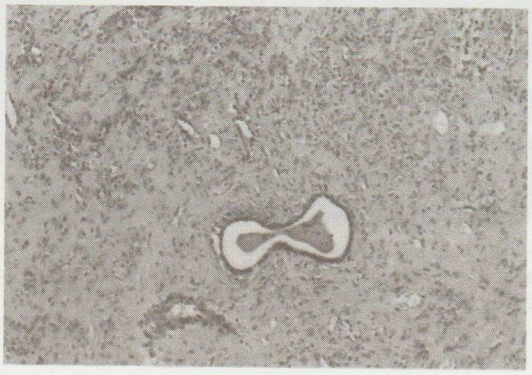

Figure 9. Low power magnification (x10) shows that the glands appear benign and are surrounded by irregularly shaped stromal cells disposed in a haphazard fashion. Note the absence of proliferation of stromal cells around the glandular structures.

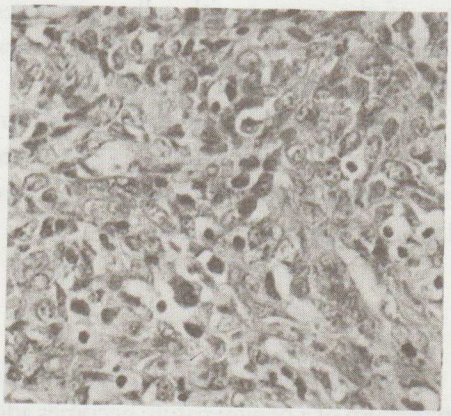

Figure 10. High power magnification (x40) reveals the stromal cells to be pleiomorphic with hyperchromatic nuclei and prominent nucleoli.

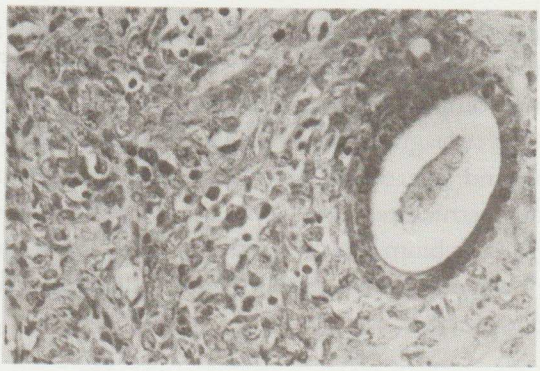

Figure 11. High power magnification (x40) illustrates the glands lined by bland low columnar cells resembling endometrial glands, admixed with a sarcomatous stromal component that is characterized by cellular pleiomorphism and nuclear hyperchromatism.

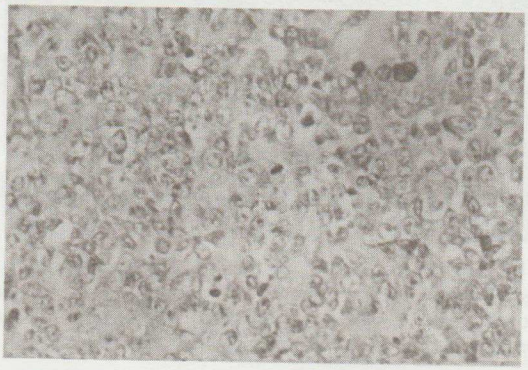

Figure 12. High power view (x40) from the tumor biopsy specimen shows the stroma composed of round to ovoid irregularly shaped cells with vesicular nuclei, prominent nucleoli figures.

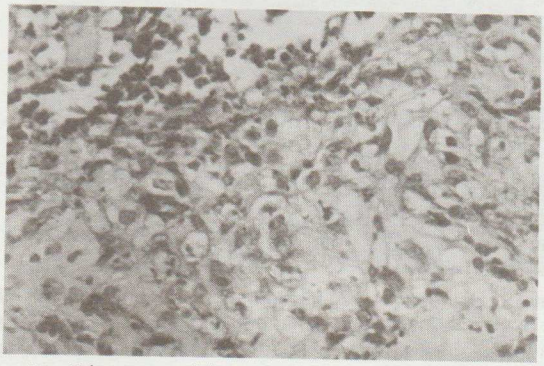

Figure 13. Other areas of the tumor under high power magnification (x40) show prominent mitotic activity.

A characteristic feature of this type of neoplasm is the way in which the stromal cells are concentrated around glandular components, forming a cuff or the so-called "cambium layer" around the glands. In figure 14 is a low power view from the areas of the myomectomy

specimens showing intimate admixture of glandular and stromal elements with characteristic condensation of the stromal component around the glands. In figure 15 is a high power magnification of the biopsy specimen from the second laparotomy illustrating occasional benign glandular structures seen within the neoplastic stroma, with the cambium layer around the gland. This cellular zone is where nuclear atypia is maximal and mitotic activity is pronounced.[7]

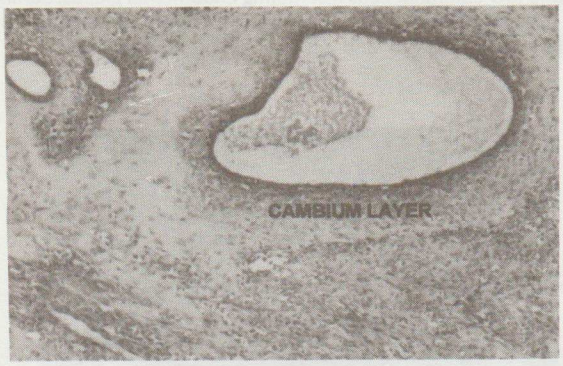

Figure14. Low power view (x10) of the rest of the sections taken from the myomectomy specimen shows intimate admixture of glandular and stromal elements with characteristic condensation of the stromal component around the glands, forming the "cambium layer."

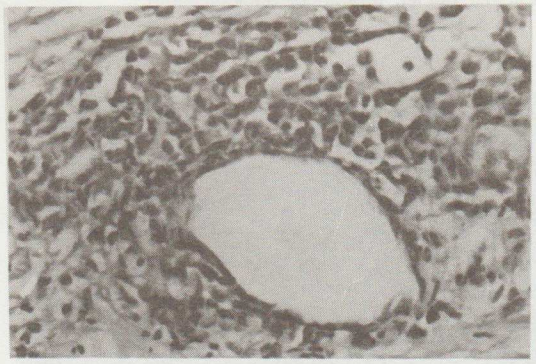

Figure 15. High power magnification (x40) of some portions of the tumor biopsy illustrates occasional benign glandular structures seen within the neoplastic stroma. Note the condensation of the stromal cells around the gland.

The distinctive feature of this disease entity that distinguishes it from a typical mullerian adenosarcoma is the presence of a pure sarcomatous component that comprises at least 25 percent of the tumor.[2] Figure 16 shows a section taken from the biopsy of the uterine surface demonstrating hypercellularity, with the stroma representing 90 percent of the tumor. There is usually a gradual margin of the border between the adenosarcoma and the pure sarcoma. In majority of cases, this area of sarcomatous overgrowth is more poorly differentiated and of a higher grade than the sarcomatous component of the underlying adenosarcoma. Futhermore, a two to twelve-fold increase in mitotic rate has also been demonstrated in this area of the neoplasm.[2] Heterologous elements are also observed to occur more commonly in adenosarcomas with sarcomatous overgrowth, with a rate of 50 percent.[7] Elements such as bone,[6] cartilage[6,7] and rhabdomyoblasts[7] have been noted.

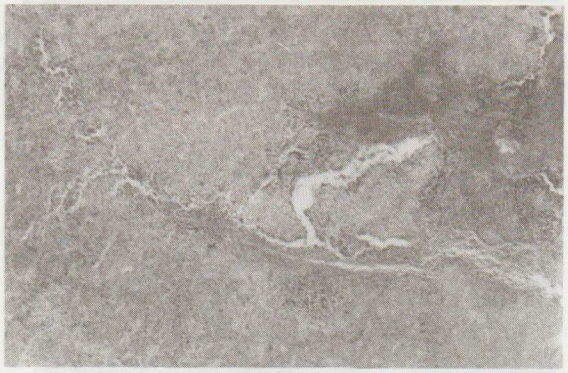

Figure 16. Scanning view (x4) of a section taken from biopsy of the uterine surface demonstrates hypercellularity, with the stroma representing 90% of the tumor.

In contrast, tissues taken from recurrent tumors or metastatic foci usually consisted of poorly differentiated sarcoma resembling the pure sarcomatous component of the primary tumor. In figure 17 is a low power view of a section of the tumor with adherent omentum demonstrating the same sarcomatous cells found within and infiltrating omental adipose tissue.

In the case presented, cut sections of the biopsy specimen showed the typical mullerian adenosarcoma with approximately 90 percent sarcomatous overgrowth. No heterologous elements were seen.

Pathogenesis

There are two possible explanations as to how a glandular epithelium of a benign nature becomes admixed with a stromal component that is unquestionably malignant. The first theory was proposed by Clement

and Scully (1974), suggesting a simultaneous neoplasia of both the glandular and stromal elements. According to Katzenstein, et al. (1977), mullerian adenosarcomas arise from multiple neoplastic cells with fixed potencies. Some stem cells would produce malignant stroma while others would produce benign epithelium. Many authors claim that the proliferation of glands having mitotic activity and focal atypia, together with atrophy of the glands in the uninvolved endometrium seen in most cases, is a strong evidence that the glands within the tumor are clearly neoplastic.[13,14,1] Futhermore, the condensation of sarcomatous stroma around the glands supports the idea that this area is vital in the development of the neoplasm.[14] The observation that recurrent adenosarcomas showed similar histologic characteristics to the primary tumors lends further support to this glandular neoplastic theory.[1]

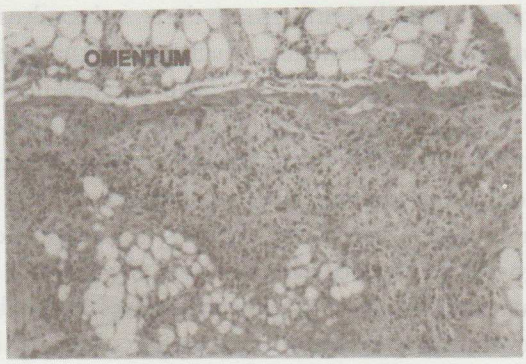

Figure 17. A low power view (x10) of a section of the tumor with adherent omentum demonstrates the same tumor cells found within and infiltrating omental adipose tissue.

On the other hand, Katzenstein, et al. in 1997 suggested that the malignant stroma, which could have arisen either within the endometrium or foci of adenomyosis or endometriosis, entraps normal endometrial glands. These glands are somehow subsequently stimulated to proliferate by the adjacent neoplastic stroma. According to the authors, such theory offers a possible explanation to the occurrence of extrauterine tumors and is further supported by the finding of an abundant hyperplastic stroma containing a few entrapped normal endometrial glands three years before the development of mullerian adenosarcoma seen in one of the cases reported.

Meanwhile, different theories have been suggested to explain how a sarcomatous overgrowth could have arisen from the these tumors, although none of them have been proven.[2] One is the phenomenon of "dedifferentiation" which proposes that the poorly differentiated sarcoma found in the focal overgrowths has actually arisen from an initially well-differentiated sarcoma. This implies that the pure sarcoma represents a secondary tumor that originated from the adenosarcomatous stroma, explaining why the sarcomatous overgrowths are usually more poorly differentiated and of a higher grade than the underlying sarcoma.

This theory however, does not support the finding of a pure sarcoma that resembles the sarcomatous stroma of the associated adenosarcoma as evidenced in our case. In such instances, the underlying stroma has been found to be poorly differentiated and of a high grade, implying that the sarcomatous overgrowth is more likely to occur in malignancies with a high-grade sarcomatous component. Another explanation would be that the high-grade pure sarcoma actually originated from and subsequently totally replaced a previously low-grade adenosarcomatous stroma.

Spread Patterns

Mullerian adenosarcomas with sarcomatous overgrowths differ from those without by its high incidence of myometrial involvement. Almost half of cases demonstrate extension into the outer one-third of the myometrial wall.[2]

Hematogenous spread may also occur in 40 percent of cases.[2] Implants along the liver surfaces, diaphragm and the lungs have been described.

Lymphatic involvement has also been observed, with a rate varying from 10^2 to 17 percent.[7] Spread to retroperitoneal lymph nodes has been mentioned.[7]

In the case presented, it is difficult to make a conclusion as to the manner by which tumor spread occurred, since no histologic examination of the myometrium to document invasion was undertaken. However, because the uterus was diffusely enlarged and because tumor spread by myometrial involvement is more common than the hematogenous spread, then probably, tumor extension into the uterine surfaces occurred through this route.

Differential Diagnosis

Primary consideration in the differential diagnosis of mullerian adenosarcomas with sarcomatous overgrowths is the spectrum of diseases belonging to the mixed epithelial-mesenchymal tumors, from the benign adenofibromas to the highly malignant mixed mullerian tumor. Difficulties may arise in distinguishing one from the other clinically. Treatment is similar and differentiation is mainly pathologic, with a diagnosis of disease arrived at through histologic examination of the hysterectomy specimen.

Perhaps the most important disease entity from which a mullerian adenosarcoma should be distinguished from is adenofibroma. Microscopically, there is note of a considerable overlap in the degree of stromal cellularity and cellular atypia between these two. Zaloudek, et al. (1981) enumerated 4 important features that can be used to distinguish one from the other, namely; (1) degree of mitotic activity, (2) degree of atypia of the mesenchymal cells, (3) a histologically malignant heterologous element and (4) involvement of the myometrium. Among these 4 characteristics, the single most reliable diagnostic criterion was found to be mitotic activity. The presence of a greater degree of mesenchymal cellular atypia, heterologous elements of a malignant nature, and/or myometrial invasion, strengthens the diagnosis of a malignancy. However, these features are not always present in every tumor and the absence of any of them does not exclude a diagnosis of adenosarcoma. It has thus been recommended that tumors with one or more of the abovementioned features be designated as adenosarcoma.[15] Although hysterectomy is the recommended treatment for both neoplasms, a distinction between them should be made, as recurrences and metastases never occur in adenofibromas but may arise in 40 percent of adenosarcomas, thus necessitating adjuvant therapy and long-term clinical observation and follow-up in the latter.[15]

The typical mullerian adenosarcoma has the same microscopic features as MASO, except for the absence of the pure sarcoma component that comprises at least 25 percent of the latter. Ward, et al. (1986) demonstrated that sarcomatous overgrowth is a significant histologic indicator of malignant behavior. A distinction between these two disease entities should therefore be made, because those with sarcomatous overgrowth were found to be more malignant with a more aggressive behavior. Local recurrences, usually within the pelvis or the vaginal apex, occur in 70 percent of cases with overgrowth and only 25 percent of typical adenosarcomas. Moreover, metastases by the hematogenous route have been demonstrated in 40 percent of MASO cases. In contrast, bloodborne metastases have been reported to occur in less than 5 percent of typical adenosarcomas. These recurrent or metastatic tumors have been observed to appear 9 months to 6 years after the initial surgery. Mortality rates from tumor progression also differ significantly between adenosarcomas with sarcomatous overgrowth and those without.[2]

Malignant mixed mullerian tumors should be also be differentiated from adenosarcomas. Although the stromal characteristics of both malignancies may appear similar, careful examination of the epithelial component can distinguish one from the other, since this component of the neoplasm is benign in adenosarcomas and clearly malignant in MMTs. Furthermore, the typical condensation of stromal cells around the epithelial glands characteristic of adenosarcomas is never seen in malignant mixed mullerian tumors.[17] As with adenosarcomas with sarcomatous overgrowth, treatment is primarily surgical. Although radiotherapy given postoperatively has been found to be useful in controlling local recurrence, prognosis is still poor even in patients with early stage disease, indicating that occult metastases are probably present at the time of the initial surgery. A comparison of survival rates between MMTs and MASO cannot be made of the present due to limited number of reported cases of the latter. They only conclusion that can be made so far is that prognosis for patients with sarcomas exhibiting overgrowth parallel those of MMTs. Five-year survival rate for stage I and II MMTs is placed at 40-50 percent as compared to rates of 25-30 percent for those with stage III and IV disease.[3]

Endometrial stromal sarcomas also present in a similar fashion as previously described for mullerian adenosarcomas. Although adenosarcomas are usually characterized by a stromal component that is very much similar to that found in ESS, the main differentiating factor between the two would be the absence of a glandular component in the latter. In cases where occasional endometrial glands become trapped at the margin of the tumor in endometrial stromal sarcomas, a distinction from adenosarcomas becomes difficult to make. In such cases, the absence of the characteristic periglandular stromal cuffing seen in adenosarcomas would clinch a

diagnosis of ESS.[18] However, when a sarcomatous overgrowth occurs and the tumor is composed predominantly of a stromal component very similar to an endometrial stromal sarcoma, a dilemma may arise. A meticulous search for glandular components together with adequate samples taken from the specimen would help in arriving at proper diagnosis. Treatment is similar to malignant mixed mullerian tumors. Prognosis is relatively better, with a 5-year survival rate of 50-80 percent for women with stage I ESS, but is less favorable at 0-50 percent in the presence of advanced disease at the time of clinical presentation.[3]

A summary of histologic features of each of the disease entities mentioned is tabulated (Table 1).

Table 1. A summary of histologic features that will differentiate mullerian adenosarcomas with sarcomatous overgrowth from other tumors.

	Glandular Element	Cambium Layer	Stromal Element	Pure Sarcoma
Adenofibroma	Benign	(–)	Benign	(–)
Mullerian adenosarcoma	Benign	(+)	Malignant	(–)
MASO	Benign	(–)	Malignant	≥25%
MMMT	Malignant	(–)	Malignant	(–)
ESS	(–)	(–)	Malignant	(+)

Management

Management of these cases should be similar to that of highly malignant uterine sarcomas. If a diagnosis of this condition is entertained preoperatively, patient work-up should include a meticulous search for extrauterine spread.[2] Treatment is primarily surgical. A total hysterectomy with bilateral salpingo-oophorectomy is recommended. During laparotomy, other procedures for adequate staging could be performed, which include peritoneal washing, omentectomy and careful inspection and palpation of abdominopelvic organs and peritoneal surfaces.

Postoperative radiotherapy has been advocated for mullerian adenosarcomas confined to the pelvis as a possible means of reducing the frequency of local recurrences.[1] In an ultrastructural study of mullerian adenosarcomas before and after radiation therapy, Damjanov, et al. (1978) has also demonstrated that the undifferentiated cells forming the cambium layer are the potentially most malignant component of the tumor. Under the electron miscroscope, these cells resembled immature mesenchymal elements with no specific features. Post-irradiation, there was disappearance of the cambium layer, suggesting that these tumors are probably radiosensitive. No similar study on MASOs has been done so far, but this finding could have implications for future treatment, particularly since the area of overgrowth has been found to be composed of cells that are more poorly differentiated than the underlying stroma. In the report by Clement (1989), however, no conclusive evidence can be derived from this mode of treatment, since only 1 out of the 10 patients with MASO received adjuvant therapy postoperatively. This patient was alive with no evidence of disease 4 years after hysterectomy. However, when radiotherapy is used to treat local recurrences, no response was observed and patients died of the disease within 3 months to 2.2 years after the initial surgery.

The use of hormone therapy in uterine sarcomas has also been questioned. Both estrogen and progesterone receptors have been demonstrated in this group of tumors, although concentrations were not high enough to reach the threshold for a successful hormonal manipulation.[20] However, the presence of detectable estrogen receptors has been associated with a greater likelihood of survival at one year, but does not appear to influence response to hormonal or cytotoxic therapy. A similar study for mullerian adenosarcomas with sarcomatous overgrowth is yet to be done.

The role of chemotherapy is still controversial. Combination regimens DTIC-doxorubicin-vincristine[2] and cisplatinum-adriamycin[7] have both been cited in literature but no conclusive benefits have been reported.

Prognosis

Identification of mullerian adenosarcoma with sarcomatous overgrowth is important clinically. As mentioned, stromal overgrowth has been found to be a significant histologic indicator of malignant behavior, the presence of which suggests a poor prognosis.[16] Clement (1989) observed that such particular tumors exhibited a more highly malignant course when compared to the typical adenosarcomas. Local recurrences, usually within

the pelvis or the vaginal apex, occur in 70 percent of cases. Metastases by the hematogenous route have been demonstrated in 40 percent of cases. These recurrent or metastatic tumors have been observed to appear 9 months to 6 years after the initial surgery. Seidman, et al. (1999) demonstrated a 60% mortality rate during a follow-up period of less than two years in patients with stage II and III disease. Death can occur in 60% of cases with sarcomatous overgrowth,[2] with patients succumbing to the disease as early as 3 months to as late as 5 years after the appearance of either recurrence or metastases.

Estrogen receptor content has also been implicated as a probable important prognostic factor. The presence of detectable estrogen receptors has been shown to be associated with a greater likelihood of survival at one year.[20]

Long-term follow-up is mandatory.

Summary

We are presented with a rare case of mullerian adenosarcoma with sarcomatous overgrowth in a 34-year old nulligravid complaining of profuse vaginal bleeding. She presented with a prolapsed submucous mass initially diagnosed as adenomyoma. Myomectomy was performed and no adjuvant therapy was given. Patient came back two months later with signs and symptoms attributable to a uterine pathology. An exploratory laparotomy was done and a frozen section was requested intraoperatively. Provisional histopathologic diagnosis of the samples taken showed a malignant tumor. The pelvic mass however, was unresectable. Biopsy of the uterine surface was taken. Final histopathologic diagnosis was mullerian adenosarcoma with sarcomatous overgrowth.

The role of adjuvant therapy in the treatment of this malignancy is still controversial because of the limited number of cases available. Survival rates have not been established as well and accumulation of experience from individual cases such as the one presented is needed. For now, suffice it to say that mullerian adenosarcomas with sarcomatous overgrowths are neoplasms with a definitely more aggressive behavior than their typical counterpart without the overgrowth component. An awareness of the existence of this clinical entity is thus important.

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Pelvic Hemangiopericytoma: Report of a Case and Review of Literature*

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A 27 year old Filipino woman underwent total hysterectomy with bilateral salpingo-oophorectomy for pelvic hemangiopericytoma. This rare tumor affecting the uterus belongs to less than 100 cases reported worldwide, and may be the first reported in the Philippines. Pre-operative diagnosis of hemangiopericytoma is difficult. Diagnosis relies on microscopic examination of the lesion. CD 34 and Factor VIII are among the few immunostains that help in the definitive diagnosis of this tumor. Therapy remains primarily surgical, with varying views regarding the use of adjuvant therapy.

Key words: Hemangiopericytoma, pelvis, uterus

Hemangiopericytoma accounts for less than 1 percent of all vascular tumors, first described by Stout and Murray in 1942. It may arise from any part of the body, but predominantly on the head, neck and extremities.

A case of hemangiopericytoma of the pelvis is presented in a 27 year old Filipino woman who underwent total hysterectomy with bilateral salpingo-oophorectomy, peritoneal fluid cytology, frozen section, tumor debulking, and palpation of retroperitoneal nodes. Review of literature on this rare disease entity is also discussed.

Case History

This is the case of I.G., a 27 year old nulligravid with the chief complaint of abdominal pain. She underwent excision of an endometriotic cyst in 2002, and has no other co-morbid illnesses. Her family medical history non-contributory. The patient is a nurse in London, with no vices. She denies any history of coitus and oral contraceptive pill or intrauterine device use. Menarche was at 10 years of age, with subsequent menses occurring at regular monthly intervals, 7 days duration, 3 pads per day. She had dysmenorrhea but no menorrhagia nor metrorrhagia.

Symptoms started 2 weeks prior to consult, when she noted crampy abdominal pain during menses, not relieved by pain medications. She then consulted a private physician and a transrectal ultrasound showed: Normal sized anteverted uterus with no myometrial lesion. The endometrium is thin and intact. The right ovary is normal in size and echotexture. Normal left ovarian tissue measures 3.4 x 2.8 cm. To the left and posterior to the uterus is a heterogenous mass which seems solid and adherent to the uterus and normal left ovarian tissue measuring 6.1 x 5.0 x 6.0 cm. No free fluid was noted in the cul-de-sac. Impression was: Normal sized anteverted

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uterus; thin endometrium; Normal right ovary; Left, solid adnexal mass, probably myoma, cannot totally rule out solid ovarian new growth. Laboratory examinations revealed hemoglobin of 14.4, hematocrit of 43.7, white blood cell count of 7.1, with normal platelet count and differential count. Prothrombin time, partial thromboplastin time and urinalysis were likewise normal. CA 125 was found to be elevated at 81.71 U/ml (normal < 35U/ml). The patient was subsequently referred to a gynecologic oncologist for further management. On review of systems, patient had no constitutional signs and symptoms.

On examination, the patient was awake, coherent, ambulatory, not in cardio-respiratory distress, with stable vital signs. Her systemic physical examination findings were essentially normal. The abdomen was flat, with normoactive bowel sounds and no tenderness or organomegaly. Rectal examination revealed a good sphincter tone, intact rectal vault, smooth mucosa, with a palpable mass, solid, approximately 8 cms, at the left adnexal area, adherent to the corpus and pelvic side wall. There was no blood or feces per examining finger. Admitting diagnosis was: Ovarian New Growth, probably malignant. The plan was to do exploratory laparotomy, peritoneal fluid cytology, unilateral salpingo-oophorectomy with frozen section, possible infracolic omentectomy, and selective pelvic and periaortic lymphadenectomy.

On laparotomy, there was no ascites. The liver, subdiaphragmatic, peritoneal, and intestinal surfaces, spleen, stomach, omentum, kidneys and appendix were grossly normal and smooth. The uterus measured 8 x 4 x 3 cm with smooth serosal surface. There was a 9 x 8 cm bilobed, solid, friable mass at the left pelvic retroperitoneum. The mass was densely adherent to the pelvic side wall and the left posterolateral uterine wall at the isthmic and cervical portions. The mass was also noted to invade more than 50 percent of the left posterolateral uterine wall at the isthmic and cervical portions. Cut section of the mass revealed hemorrhagic, necrotic, friable material. The uninvolved myometrium measured 3.0 cm anteriorly. The endometrium measured 0.5 cm with spongy consistency. The uterine cavity depth measured 7.5 cm, 3.5 cm of which was the endocervical canal. The endocervix was grossly normal with no gross lesions within the canal. The right ovary and right fallopian tube were grossly normal. The left ovary and left fallopian tube were grossly normal, but with note of brown blebs and dense adhesions to the posterior wall of the uterus and cul-de-sac. Palpation of pelvic nodes was performed with open posterior parietal peritoneum. No palpable pelvic and periaortic nodes.

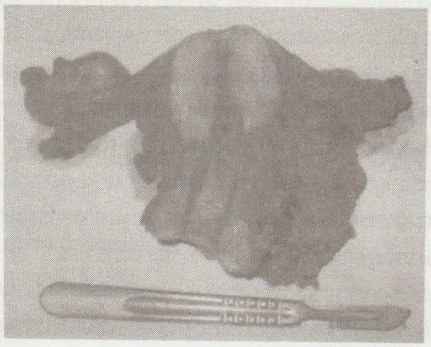
Received for frozen section was a specimen labeled "retroperitoneal mass, L", consisting of a maroon, soft to firm, well circumscribed tissue. Cut section showed maroon to cream cut surface surrounded by 0.1 cm thick fibrous capsule. (Figure 1)

Figure 1 - Cut section of the specimen labeled "retroperitoneal mass, L" showing maroon to cream cut surface surrounded by 0.1 cm thick fibrous capsule.

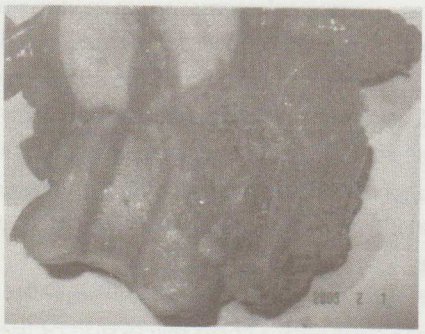
Frozen section of the mass was read as Malignant Round Cell Tumor, to consider: Malignant Mixed Mullerian Tumor, Stromal Sarcoma, or Malignant Neural Tumor. Defer to paraffin was recommended. Intra-operative diagnosis was Uterine Sarcoma Stage IIIA. The patient underwent total hysterectomy with bilateral salpingo-oophorectomy, peritoneal fluid cytology, tumor debulking, and palpation of retroperitoneal nodes under spinal anesthesia. The patient was transfused with 2 units of whole blood. Her post-operative course was unremarkable and she was discharged after 5 days.

Additional 3 specimens were received by the Department of Pathology. It consisted of a previously-opened uterus with attached bilateral adnexae. (Figure 2) The uterus measured 9 x 5 x 3 cm and with tan brown surface. It was soft to firm. There was a tan, ill-defined serosal mass at the left lower uterine segment, involving the isthmus and endocervical area. It measured 4 x 2 x 1 cm. Serial sections showed less than 50 percent stromal infiltration. On opening the uterus, no mass was

noted. The endometrial depth measured 7.5 cm; 3.5 cm of which was the endocervical canal. The myometrium and endometrium measured 0.8 cm and 0.3 cm thick respectively at the fundal area. The endocervix was cream tan and corrugated. The ectocervix was smooth. The 3 x 2 x 1.5 cm left ovary was soft to firm. It had a cream, tan lobulated surface. Cut sections showed multiple lobules ranging from 0.5 cm to 0.3 cm. They contained clear, water fluid. The rest of the parenchyma had cream, homogenous cut surface. The 3.5 x 2 x 1 cm right ovary was soft to firm. It had yellow to brown lobulated surface. Cut sections showed multiple locules ranging from 2 cm to 0.2 cm. They contained clear, watery fluid. The rest of the parenchyma had cream, homogeneous cut surface. The 5.5 x 0.5 x 0.5 cm left fallopian tube and 7 x 0.6 x 0.6 cm right fallopain tube were grossly unremarkable. The specimen labeled "peritoneal fluid" consisted of about 50cc of cloudy, blood tinged fluid. The specimen labeled "uterus, retroperitoneum" consisted of a deformed 6 x 3 x 2.5 cm, tan-brown, soft to firm, irregular tissue. Cut sections showed cream to tan homogenous cut surface.



(A)



(B)

Figure 2 - (A) Anteriorly opened uterus measuring 9 x 5 x 3 cm with attached bilateral adnexa. There was a tan, ill defined serosal mass at the left lower uterine segment, involving the isthmus and endocervical area measuring 4 x 2 x 1 cm. (B) Closer view of the specimen.

This slide is a scanning view of the tumor, showing cellular nodules, separated by less cellular areas of densely collagenous connective tissue with prominent vessels, suggestive of a sclerosing mesothelial tumor. (Figure 3)

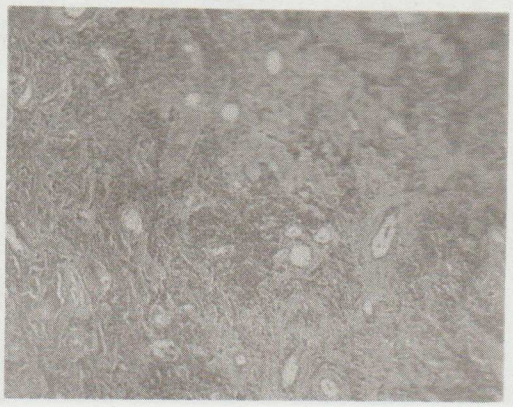


Figure 3 - This is a scanning view of the tumor, showing cellular nodules, separated by less cellular areas of densely collagenous connective tissue with prominent vessels, suggestive of a sclerosing mesothelial tumor.

This scanning view is more cellular, and on high power shows serpentine to spindle shaped nucleus, suggestive of a neural origin. (Figure 4)

(A) (B)

Figure 4 - (A) This is a scanning view of the tumor, showing cellular, and (B) on high power shows serpentine to spindle shaped nucleus, suggestive of neural origin.

This another scanning view of the tumor, showing proliferation of blood vessels with hemorrhagic areas. Tightly packed nests and cords of small epithelioid to fusiform cells that were distributed around an elaborated and rich vasculature is seen. The vessels are varying in sizes and occasionally show an antler-like configuration,

and many of which show perivascular hyalinization in areas extending into the stroma. (Figure 5)

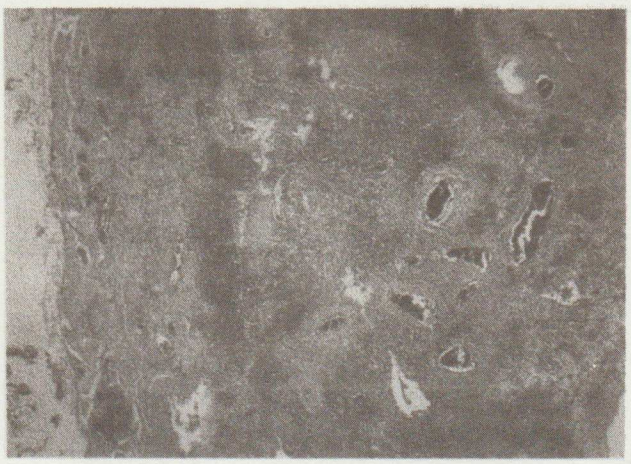


Figure 5 - This is another scanning view of the tumor, showing proliferation of blood vessels with hemorrhagic areas. Vessels are varying in sizes and occasionally show an antler-like configuration, and many of which show perivascular hyalinization in areas extending into the stroma.

Diagnosis

- Malignant tumor, low grade, considerations: 1) neural tumor, 2) vascular tumor, 3) sclerosing mesothelial tumor, with infiltration to the endometrial and endocervical stroma
- Endometriosis
- Proliferative endometrium
- Chronic Cervicitis
- Cystic follicles, both ovaries
- Regressing corpus luteum, ovary, right
- Hydrosalpinx, left
- No diagnostic abnormality recognized, right fallopian tube
- Negative for tumor, specimen labeled "peritoneal fluid"

Immunohistochemical stains for S100, CD34, and calretinin revealed the final diagnosis: Malignant Fusiform Cell Tumor with an elaborate vasculature, suggestive of a hemangiopericytoma.

Discussion

Hemangiopericytomas are rare vascular tumors composed of patent or collapsed capillaries surrounded by peculiar round or spindle-shaped cells known as pericytes, which contain complex processes and smooth muscle type filaments to facilitate contraction. Since the original clinico-pathologic description by Stout and Murray in 1944, several papers have described the histopathologic features, clinical presentation, treatment modalities, and outcome of these tumors.[1] Although uncommon, these tumors have been reported in every location in the body and in all age groups.[2] This tumor most frequently affects the lower extremity (especially the thigh) and the retroperitoneum, 35% and 25% respectively.[3] Less frequently, it affects the pelvis, abdomen and upper extremity. Considered unusual sites are nasal passages and paranasal sinuses, orbit, breast, lung, mediastinum, bone and organs of special interest to us- the ovary, vagina and the uterus.[4]

Hemangiopericytoma was initially reported in the female genital tract in 1954 by Greene and Gerbie, and most have been of uterine origin.[5] Although questioned by many, these authors have stated that uterine hemangiopericytoma should be considered seriously in the differential diagnosis of uterine cellular tumors. Since that time, less than 100 cases have been reported worldwide, and that which was just presented may be the first case encountered in our institution, and maybe the first ever reported ever in our country. No specific age group appears to be at particular risk for development of such neoplasms.[5,6] Ages ranged from 23 to 81 years, although the youngest known patient reported was only 19 years of age.[7] Often times, uterine hemangiopericytomas present in a bizarre manner, making its diagnosis difficult.[8] But the most common presenting symptom of such a tumor is attributable to the existence of an abdominopelvic mass.[6] It may present as a pelvic mass simulating an ovarian tumor, as seen in our patient, or as a uterine enlargement with menometrorrhagia, simulating fibroids in others. In a study conducted by Buscema, et al. other various conditions found associated with it included endometrial cancer, urinary incontinence, primary infertility, and endometriosis. However, lack of data makes a direct correlation with the above mentioned disease entities, and identification of specific risk factors not possible at this time.

What exactly is hemangiopericytoma? Its meaning can be made clear with a short discussion of the pericyte, first described by the Swiss histologist Zimmerman in 1923.[4] Capillaries and venules are both lined by endothelium and peripheral to the endothelium is the basement membrane. The pericyte is also an intrinsic part of the wall of these vessels, abutting against but separated

from the endothelium by a portion of the basement membrane which also surrounds the pericyte. Four types of abnormalities can evolve from these blood vessels. A benign proliferation of all elements results in a capillary hemangioma. If the tumorous element is the endothelium, a hemangioendothelioma results. In a hemangiopericytoma, the endothelium is normal and the proliferating elements are the pericytes. Another tumor containing pericytes is the glomus tumor, hemangiopericytoma lacks neural elements, and the well-defined histologic substructure, the so-called organoid pattern.[9]

It is however unfortunate that correct pre-operative diagnosis of uterine hemangiopericytoma is rare. Even gross appearance is variable and not characteristic.[7] It may vary from a relatively smooth, firm, vascular tumor to a necrotic irregular mass. Most tumors are between 5 and 25 cms in diameter, and color described by different authors vary. Diagnosis thus rest on microscopic examination of the lesion. Distinction of hemangiopericytoma from other neoplasms with prominent vascular patterns may cause considerable difficulty, but with electron microscopy and the benefit of immunohistochemistry, most hemangiopericytomas can be identified by their uniform cellular and vascular pattern and the dense reticulin meshwork that surrounds the individual tumors cells.[4] Endometrial stromal tumor and cellular leiomyoma are the most important lesions to be considered in the differential diagnosis of uterine hemangiopericytoma.[10]

In our patient, frozen section of the mass was read as Malignant Round Cell Tumor, to consider: Malignant Mixed Mullerian Tumor, Stromal Sarcoma, or Malignant Neural Tumor. Defer to paraffin was recommended due to the unusual presentation of the tumor. Intra-operative diagnosis was Uterine Sarcoma Stage IIIA, adapting the FIGO Staging Classification of Endometrial Carcinoma. (Table 1)

After routine paraffin examination, the diagnosis made by the Department of Pathology was malignant tumor, low grade, considerations: 1) neural tumor, 2) vascular tumor, 3) sclerosing mesothelial tumor, with infiltration to the endometrial and endocervical stroma. It was suggested that immunohistochemical stains for S100, CD-34, and calretinin be done for confirmation.

S-100 protein stains the nucleus and cytoplasm and may be used to identify a tumor of CNS origin. In our patient, the tumor cells were negative for S-100, making the diagnosis of a neural tumor likely. (Figure 6) Calretinin also stains the nucleus and cytoplasm. It is a unique and useful marker in identifying epithelial mesotheliomas more than 90 percent of the time, and is negative in carcinoma. Since the tumor cells were also negative for calretinin, a possible sclerosing mesothelial tumor is ruled out. (Figure 7). This then leaves us with the possibility of a vascular tumor.

Table 1. FIGO staging classification of endometrial carcinoma (1988).

Stage		Characteristics
I		Confined to the corpus
	IA G123	Tumor limited to endometrium
	IB G123	Invasion to < 1/2 of myometrium
	IC G123	Invasion to > 1/2 of myometrium
II		Involvement of the corpus and cervix
	IIA G123	Endocervical glandular involvement only
	IIB G123	Cervical stromal invasion
III		Extension outside the uterus but not outside true pelvis
	IIIA G123	Invasion of serosa, and/or adnexae, or/or positive peritoneal fluid cytology
	IIIB G123	Vaginal metastasis
	IIIC G123	Metastasis to pelvic and/or para-aortic lymph nodes
IV		Extension outside the true pelvis or involves mucosa of bladder or rectum
	IVA G123	Tumor invasion of bladder and/or bowel mucosa
	IVB	Distant metastases including intraabdominal and/or inguinal lymph node

Figure 6 - Tumor cells showing negative for S-100.

Figure 7 - Tumor cells showing negative for Calretinin.

CD 34 stains the cytoplasm and membrane, and may be used in identifying endothelial or myofibroblastic differentiation in tumors. Although CD 34 is one of the few immunostains that is positive for hemangiopericytomas, only about 60-70 percent is positive. It may not be specific, but can be very useful if correlated with other features. On review of the patient's slide, a tumor composed of tightly packed nests and cords of small epithelioid to fusiform cells that were distributed around an elaborated and rich vasculature was seen. The vessels were described to be small to large and occasionally showed an antler-like configuration, many of which showed perivascular hyalinization in areas extending into the stroma. CD 34 was found to stain the endothelial cells, and with very focal staining of the epithelioid/fusiform cells present. (Figure 8)

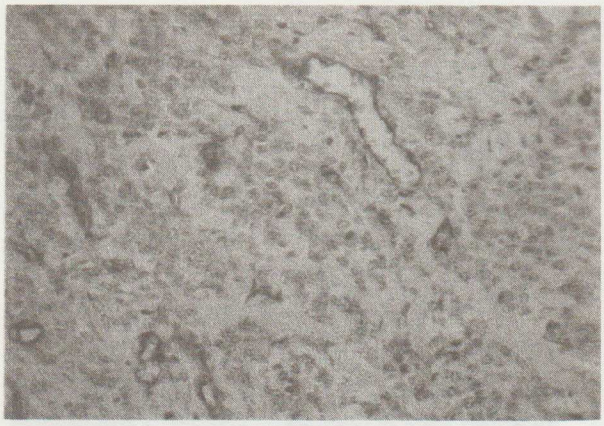


Figure 8 - CD 34 was found to stain the endothelial cells, with very focal staining of the epithelioid/fusiform cells present.

To strengthen the diagnosis, Factor VIII was then used by the institution. Normal pericytes express factor VIII and may be used as a marker of fibrohistiocytic differentiation in hemangiopericytomas. Most tumors with a hemangiopericytoma-like pattern are negative for Factor VIII.[12] Factor VIII was found to focally stain the endothelial cells of the tumor. (Figure 9) Hence, final diagnosis of our patient is Malignant Fusiform Cell Tumor with an elaborate vasculature, suggestive of a Hemangiopericytoma.

Figure 9 - Factor VIII was found to focally stain the endothelial cells of the tumor.

It would then be more prudent to use the staging system of the American Joint Committee on Cancer (AJCC) on soft tissue sarcoma, which would include malignant hemangiopericytomas. (Table 2)[13]

With this classification, staging of the tumor would be T2bN0M0, low grade, equivalent to Stage I. The question now that remains to be answered is whether this pelvic hemangiopericytoma is indeed a primary uterine tumor with extension to the pelvic sidewall or a primary extrauterine tumor with extension to the uterus. Although the low grade of malignancy and the resectability of the tumor would point more to a primary uterine lesion, its appearance and position would indicate otherwise, considering that a greater area of the mass is located outside the uterus. Limited information on the behavior

of this vascular tumor will make it very difficult to commit to an answer at the present time.

Table 2. AJCC classification, 2002 on soft tissue sarcomas.

Stage Grouping

Stage	T	N	M	G	
I	T1a, 1b, 2a, 2b	N0	M0	G1	Low
II	T1a, 1b, 2a	N0	M0	G2-3	High
III	T2b	N0	M0	G2-3	High
IV	Any T	N1	M0	Any G	High or Low
	Any T	N0	N1	Any G	High or Low

Definition of TNM:

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor 5 cm or less in greatest dimension
T1a Superficial tumor (above superficial fascia)
T1b Deep tumor (beneath superficial fascia or retroperitoneal, mediastinal and pelvic sarcomas)
T2 Tumor more than 5 cm in greatest dimension
T2a Superficial tumor
T2b Deep tumor

Regional Lymph Nodes (N)

NX Regional lymph nodes (LN) cannot be assessed
N0 No regional LN metastasis
N1 Regional LN metastasis

Distant Metastasis (M)

MX Distant Metastasis cannot be assessed
M0 No distant metastasis
M1 Distant Metastasis

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated

Hemangiopericytoma is a tumor with variable malignant potential and its biological behavior is difficult to reliably predict.[10] Others have suggested that 50 percent of hemangiopericytomas are "malignant" and that nearly two-thirds recur locally or metastasize.[5] The natural history of HPC is associated with cellularity, mitotic activity, anaplasia, necrosis and hemorrhage.[14] Increased cellular intensity, cytologic pleomorphism, focal calcification, hemorrhage, necrosis and increased number of mitoses are the signs of malignancy.[3] However, in general, uterine hemangiopericytoma is considered to have better prognosis as compared to its extrapelvic counterparts. Nevertheless, subsequent reports have documented various pelvic and intraabdominal recurrences up to 26 years from the initial diagnosis. Metastases to the vagina, ovary and broad ligament have been reported.[8] In addition, numerous fatalities have been attributed to lesions arising in the uterus.[5]

Regardless of whether it is primarily uterine which has extended to the pelvic sidewall or vice versa, management for this malignant hemangiopericytoma will not vary. Radical surgery is usually recommended as the treatment of choice. Total hysterectomy with bilateral salpingo-oophorectomy is said to be the best treatment for hemangiopericytomas affecting the uterus. Incomplete excision invariably leads to local recurrence and metastasis. With regards to adjuvant therapy, different authors have varying views on the matter. Based on an ultrastructural study done by Silverberg, et al. on such tumors, radiation therapy was believed to have no place in the primary treatment of uterine hemangiopericytomas.[18] However, Munoz, et al. in 1990 reported that most unresectable tumors showed a favorable response to radiation therapy, making subsequent resection possible in all cases. They have concluded in the study that radiation therapy, up to 5000cGy, appears to be beneficial both in unresectable pelvic hemangiopericytomas and in the treatment of isolated recurrences if radiation has not been employed previously.[1] Furthermore, a multivariate analysis done by Livi, et al. in 2003 showed that best result were obtained with post-operative radiotherapy, regardless of the stage. Reslova, et al. described radical surgery with pre-or postoperative adjuvant chemotherapy. However, various authors have countered this. In fact, some say that chemotherapy has not been proven useful for the management of resectable hemangiopericytomas.[3] Although it may improve local disease-free survival when given with radiotherapy, it has not been proven to prolong overall survival.[17] However, novel agents and administration are under investigation.

Conclusion

It has been a year since the patient was diagnosed with this unusual and perplexing tumor. She is back in London where she continues to work as a nurse, and is

currently asymptomatic. She is indeed very lucky to have undergone treatment in time. Although she remains well at the moment, long term follow-up is required, especially since very little is known as to the course of this disease. Hemangiopericytomas have been labeled "exasperating tumors" because they are rare, and hard to distinguish from other tumors. However, with this report, it is important that attention has been called to the fact that such a tumor can be encountered in our field, and as good obstetrician-gynecologists, we should be able to recognize it when it is present.

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