Malignant Ovarian Germ Cell Tumors: Clinical Characteristics, Treatment and Outcome. The Experience in a Tertiary Government Institution*

Victorino C. Garcia Jr., MD; Jean Anne B. Toral, MD and Ma. Lilibeth L. Siasu, MD

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

Objective: This retrospective study aims to present the clinicopathologic profile, prognostic factors, treatment methods and outcome of cases of germ cell tumors of the ovary seen at a tertiary government institution. **Methods**: From 1996 to 2005, a total of 130 cases with newly diagnosed malignant germ cell tumors were registered at the hospital. Only 59 cases were included and available for review. The clinical characteristics such as age, gravidity, parity, histology, stage, and treatment such as surgery, and adjuvant chemotherapy were assessed for each available patient. The adjuvant chemotherapy treatment was classified into 3 groups, namely VAC (vincristine, actinomycin D, cyclophosphamide) regimen (n=13), PVB (cisplatin, vinblastine, bleomycin) regimen (n=2) and BEP (bleomycin, etoposide, cisplatin) regimen (n=17). Retrospectively, the correlation between these clinical features and outcomes were analyzed. **Results**: Of the 59 patients included in the study, 13 had dysgerminoma, 16 had immature teratoma, 18 had endodermal sinus tumor, and 12 had mixed germ cell tumor. Age of diagnosis (p=0.78), gravidity (p=0.47), parity (p=0.5), tumor size (p= 0.09) were not significantly different between those with no evidence of disease compared with those with disease or died. Based on tumor type, although dysgerminoma (61.5%) showed a trend toward no evidence of disease and yolk sac tumor (72.2%) showed a trend to disease or death, these differences were not statistically significant (p=0.16). Furthermore, based on stage, although Stage I (53.3%) showed a trend towards no evidence of disease and Stage III-IV (65%) showed a trend toward disease or death, these were not statistically significant (p=0.43). According to the institution where the initial surgery was done, this was not significantly different between the two groups (p=0.59). Surgery alone showed significant increased risk for treatment failure compared to surgery plus chemotherapy (p=0.03). **Conclusion**: Survival is significantly better when adjuvant chemotherapy is given after initial surgery.

Key words: Germ cell tumor, ovarian neoplasm, surgery, chemotherapy

* Second placer, 2007 Philippine Society of Medical Oncology (PSMO) Research Contest.

Germ cell tumors of the ovary comprise a relatively small proportion, approximately 20-25 percent of all ovarian neoplasms[1], and only about 5 percent of these are malignant.[3] Most of these neoplasms occur in young women, and disease eradication involves decisions concerning childbearing and probabilities of recurrence.[1] Before the evolution of new chemotherapeutic regimens, the prognosis for these aggressive tumors was poor. Over the past decade, advances in these chemotherapeutic regimens have made germ cell tumors among the most highly curable diseases.[2] A comprehensive surgical staging with contralateral ovary and uterus preservation is advocated. Postoperative chemotherapy with platinum and etoposide-based regimens except those with stage IA dysgerminoma or Stage IA, grade 1 immature teratoma has been accepted as standard management. Second-look operation is generally unnecessary in completely resected or tumor marker positive ovarian germ cell tumors except advanced-stage immature teratoma.[3]

Studies have shown that this conservative approach is equally effective, in terms of survival, when compared to radical surgery.[3,4] The main advantage of this therapy is that patients with malignant germ cell tumors of the ovary could conserve their reproductive function after effective treatment.

Despite the histological and biological similarities of germ cell tumors from other sites of origin namely ovary, testis, mediastinum, or central nervous system; there are differences in clinical features. It is therefore imperative to mark down their clinical behaviors separately. Considering the extreme rarity of the ovarian germ cell malignancies and their anatomic location from that testicular/extragonadal germ cell malignancies and predilection of intraperitoneal spread, continued efforts should be made to accumulate clinical findings and update the outcome for ovarian germ cell malignancies. Compared to male germ cell malignancies[5,6], prognostic factors of ovarian germ cell tumors are not well-defined.[7,8]

There have been published retrospective reports about malignant germ cell tumors of the ovary[9-18], however no such documentation in the Philippines exists. This report reviews the experience of ovarian germ cell malignancies from 1996 through 2005 in a tertiary government institution.

Objectives

General Objective

This retrospective study aims to present the clinicopathologic profile of germ cell tumors of the ovary seen at a tertiary government institution.

Specific Objectives

a. To determine the important prognostic factors in patients with malignant germ cell tumors of the ovary.

b. To evaluate the treatment methods and clinical outcome of malignant germ cell tumors of the ovary.

c. To investigate if conservative surgery with adjuvant chemotherapy has made preservation of fertility possible, even in patients with advanced disease.

Materials and Methods

From 1996 to 2005, cases with newly diagnosed malignant germ cell tumors were reviewed. The clinical characteristics such as age, gravidity, parity, histology, stage, and treatment such as surgery, and adjuvant chemotherapy were assessed for each available patient. All patients were treated based on the institution's choice. The adjuvant chemotherapy treatment was classified into groups: VAC (vincristine, actinomycin D, cyclophosphamide) regimen, PVB (cisplatin, vinblastine, bleomycin) regimen, BEP (bleomycin, etoposide, cisplatin) regimen and other regimens. Retrospectively, the correlation between these clinical features and outcomes was analyzed. The patient outcomes were evaluated based on their last follow-up.

Statistical Analysis

The overall survival distributions were estimated by the method of Kaplan and Meier. The survival time was defined as the time from the initial diagnosis to death. The surviving patients were censored at the date of last follow-up. The independent T-test and

Pearson chi-square was used to assess the statistical significance of the prognostic factors with outcome.

Results

A total of 130 newly diagnosed cases between 1996-2005 were registered in the hospital. There were 59 patients available for review and included in the study (Table 1). Analyses of the clinicopathologic factors with their outcomes are presented. Patients were divided into those with no evidence of disease and those with disease or death. Age at diagnosis (22.4 vs 23.1; p=0.78) was not statistically significant. Gravidity (0.9 vs 1.3; p=0.47) and parity (0.8 vs 1.1; p=0.5) were likewise not statistically significant. There was also no statistically significant difference on tumor size (20.7 cm vs 17.9 cm; p= 0.09). Based on tumor type, although dysgerminoma (61.5%) showed a trend toward no evidence of disease and yolk sac tumor (72.2%) showed a trend to disease or death, these were not statistically significant (p=0.16). Furthermore, based on stage, although Stage I (53.3%) showed a trend towards no evidence of disease and Stage III-IV (65%) showed a trend towards disease or death, these were not statistically significant (p=0.43). According to the institution were the initial surgery was done, this was not significantly different between the two groups (p=0.59). Surgery alone showed significantly increased risk for treatment failure compared to surgery plus chemotherapy (70.4% vs 56.3%; p=0.03).

Overall survival rates according to patient and treatment variables are presented in Table 2. Figure 1 shows the survival curve for the different tumor types. Though this was not significantly associated with overall survival (p=0.44), dysgerminoma showed trend to best survival followed by immature teratoma, mixed germ cell tumor and endodermal sinus tumor (56.5%, 47.6%, 30% and 20.3%). Excluding those with Stage unknown (n=3), FIGO stage (p=0.52) was not also associated with overall survival. However, Stage I showed a trend for best survival followed by Stage II and finally Stage III/IV (45.3%, 42.4% and 10.8%). Figure 3 shows survival curves of patients whose initial surgeries were done in our institution compared to those from other institutions (27.2% vs 36.6%; p=0.36). This was not a significant prognostic factor for overall survival. Nevertheless, treatment with compared to without chemotherapy (42.1% vs 21.7%; p<0.001) was a strong predictor of survival (Figure 4).

Table 1. Comparison of demographic and clinical characteristics of patients according to their outcomes.

	No Evidence of Disease	With Disease/Death	p value
Mean age	22.4 (SD 5.5)	23.1 (SD 12.4)	0.78*
Gravidity	0.9 (SD 1.5%)	1.3 (SD 2.2)	0.47*
Parity	0.8 (SD 1.4)	1.1 (SD 1.9)	0.50*
Tumor size	20.7 (SD 5.9)	17.9 (SD 6.3)	0.09*
Tumor type			
Dysgerminoma	8 (61.5%)	5 (38.5%)	
Immature teratoma	9 (56.2%)	7 (43.8%)	
Mixed germ cell	4 (33.3%)	8 (66.7%)	
YST	5 (27.8%)	13 (72.2%)	0.16**
Stage			
Stage I	16 (53.3%)	14 (46.7%)	
Stage II	3 (50.0%)	3 (50.0%)	
Stage III-IV	7 (35.0%)	13 (65.0%)	0.43**
Surgery plus chemotherapy	18 (56.3%)	14 (43.7%)	
Surgery alone	8 (29.6%)	19 (70.4%)	0.03**
Institution			
Our institution	14 (48.3%)	15 (51.7%)	
Other institutions	12 (41.4%)	17 (58.6%)	0.59**

* Independent t-test
** Pearson chi-square

Table 2. Cumulative survival of patients according to their grouping or characteristics.

	Cumulative % Surviving	Mean Survival Time
Tumor type		
Dysgerminoma	56.5	22.7
Immature teratoma	47.6	23.7
Mixed germ cell	30.0	17.2
Yolk sac tumor (YST)	20.3	24.6
Stage		
Stage I	45.3	26.6
Stage II	42.4	27.5
Stage III-IV	10.8	17.5
Surgery plus chemotherapy	42.1	31.5
Surgery alone	21.7	11.7
Institution		
Our institution	27.2	19.7
Other institutions	36.6	25.8

[illegible]

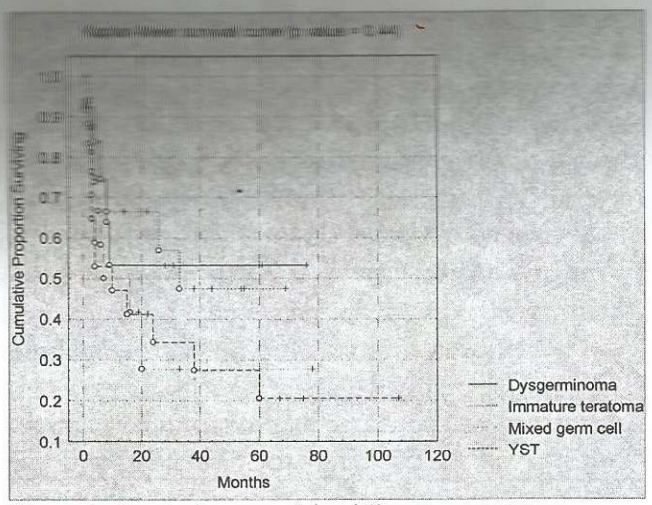

Figure 1. Survival curves of the different tumor types.

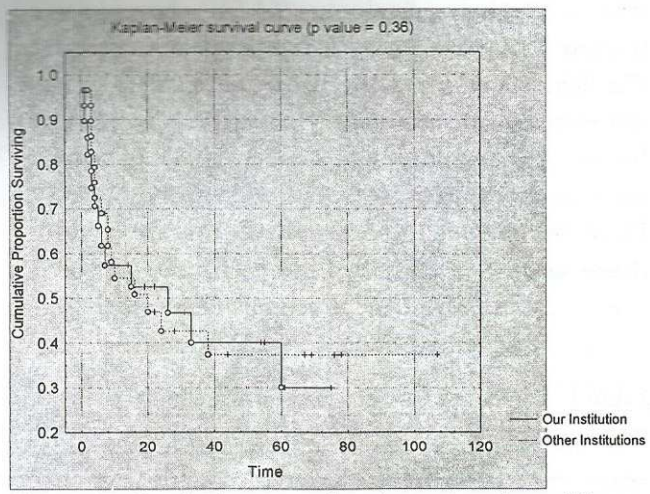

Figure 3. Survival curves of patients seen from different institutions.

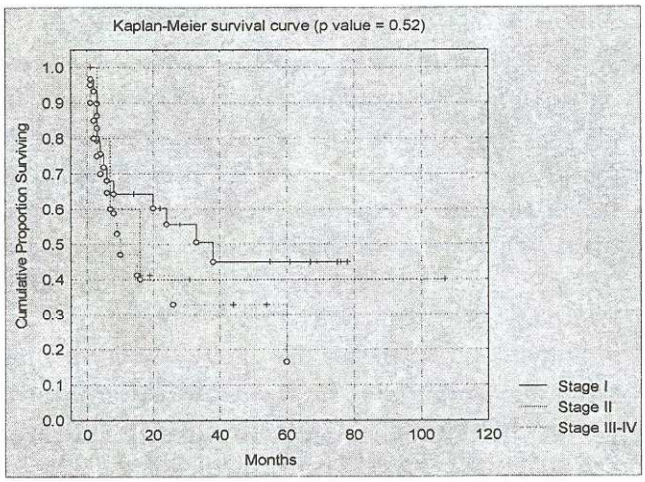

Figure 2. Survival curves of different tumor stages.

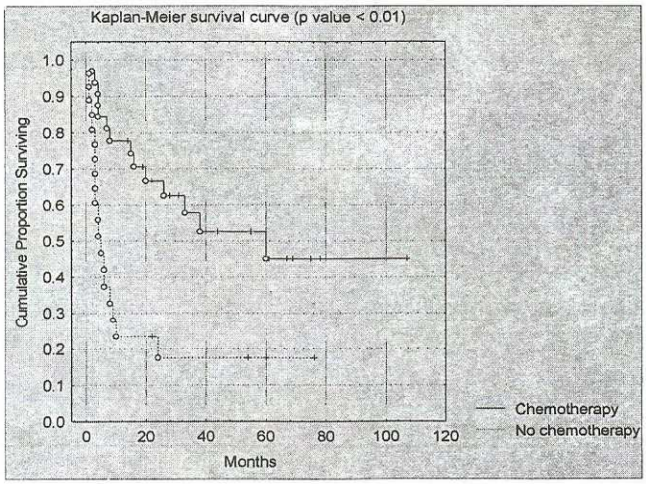

Figure 4. Survival curves of patients with and without chemotherapy.

Of the 59 patients, 45 had fertility sparing surgeries (Table 3). Three of these patients eventually became pregnant. Two had Stage I disease, one received VAC and BEP for the other. The third case was a Stage IIIA for a cul-de-sac implant. Planned chemotherapy was not given because she was lost to follow-up. She eventually got pregnant and currently has no evidence of disease.

Thirty-two patients had their chemotherapy after initial surgery (Table 4). Chemotherapy regimens that were administered are detailed in Table 5.

The summaries of patients' age, stage, histology, surgeries, chemotherapy, current status are in Tables 6-9. Twenty-nine patients had their initial surgery at our institution. Fifteen patients had lymph node assessment which included pelvic lymph node dissection and paraaortic lymph node sampling. This evaluation was not done in surgeries done elsewhere. A second look operation was also done in two Stage I immature teratoma patients after completing chemotherapy. Contralateral cystectomy was done in both cases. One had no evidence of disease while disease progression was noted in the other.

Discussion

Malignant germ cell tumors of the ovary are relatively rare and uncommon. Based on the 2005 Philippine Cancer Facts and Estimates, ovarian cancer is the fifth leading cancer site among females with an incidence rate of 6.0%.[19] In the 1978-1991 review by Siasu and Limson[20] in our institution, a total of 393 ovarian cancer patients were seen during this period. Sixty patients (15.5%) were germ cell tumors. In our report, approximately half of the 59 patients with

Table 3. Details of first surgery.

	USO/UC	BSO/THBSO/Tubal Ligation	Fertility Sparing
Histology			
Dysgerminoma	9	4	9/13 (69%)
Endodermal Sinus Tumor	15	3	15/18 (83%)
Mixed Germ Cell Tumor	7	5	7/12 (58%)
Immature teratoma	14	2	14/16 (87.5%)
Stage			
I	27	3	27/30 (90%)
II	2	4	2/6 (33%)
III	13	6	14/19 (74%)
IV	1	0	1/1 (100%)
Unknown	2	1	2/3 (67%)

USO - unilateral salpingooophorectomy; UC - unilateral ovarian cystectomy; BSO - bilateral salpingooophorectomy; TH - Total abdominal hysterectomy

Table 4. First-line chemotherapy.

Histology	VAC	PVB	BEP	Total Treated
Dysgerminoma	2		3	5
EST	3	2	5	10
Mixed Germ Cell	4		4	8
Immature Teratoma	4		5	9
Total	13	2	17	32

VAC - vincristine, actinomycin D, cyclophosphamide; PVB - cisplatin, vinblastine, bleomycin; BEP - bleomycin, etoposide, cisplatin; EST - endodermal sinus tumor

malignant ovarian germ cell tumors had their initial surgery in our institution, the rest were referrals from elsewhere.

Recent evidence showed that FIGO (International Federation of Gynecology and Obstetrics) staging system (Stage), residual disease, histologic type and elevation of tumor markers appear to be prognostic factors for patients with malignant ovarian germ cell tumors. Lai, et al.[21] illustrated that early FIGO stage and dysgerminoma/immature teratoma histology and low residual disease after salvage surgery were significantly associated with good overall survival. Murugaesu, et al.[22] demonstrated that in addition to FIGO stage, elevation of both hCG and AFP but not when taken alone was a strong predictor of survival. Neither of these studies found age at diagnosis as a prognostic factor. In our, series dysgerminoma and early stage showed trend for favorable outcome. Age was not also a prognostic factor consistent with the above studies.

Table 5. Chemotherapy regimens.

		Dose/ Day	Treatment Cycles
VAC	Vincristine	1.5 mg/m² per day Days 1,15	6
	Actinomycin D	0.5 mg per day Days 1-5	3
	Cyclophosphamide	150 mg/m² per day Days 1-5	3
PVB	Cisplatin	20 mg/m² per day Days 1-5	4
	Vinblastine	0.15 mg/kg per day Days 1-2	
	Bleomycin	10U/m² per day Days 1,8,15	
BEP	Bleomycin	10U/m² per day Days 1,8,15	3-4
	Etoposide	100mg/m² per day Days 1-5	
	Cisplatin	20mg/m² per day Days 1-5	

Table 6. Summary of patients with dysgerminoma of the ovary.

Patient	Age (Years)	Stage	Surgery	Further Management	Current Status	Follow-up (months)
1	30	IA	THBSO, Om, BLND, PALS USO, CC, Om	-	NED	1
2	29	IA	THUSO, Om, BLND[a] USO, Om	-	NED	76
3	21	IA	THUSO, Om, Deb[a]	VAC VI	NED	61
4	14	IA	USO	BEP IV	NED	28
5	26	IIC	THBSO, Om, BLND	VAC VI	NED	31
6	19	IIIA	USO, Om	-	NED	60
7	11	IIIB	USO, Om	-	PD	9
8	40	IIIB	THBSO	BEP IV	NED	7
9	24	IIIC	USO, Om	BEP IV	NED	4
10	18	IIIC	USO, Om, Deb, App	-	PD	4
11	34	IIIC	USO, CTL, Om, BLND	-	Lost to follow-up	6
12	29	IIIC	USO, Om, BLND, PALS	-	Lost to follow-up	1
13	24	IV	USO, Om	-	Lost to follow-up	8

USO - unilateral salpingooophorectomy; CC - contralateral cystectomy; TH - Total abdominal hysterectomy; Om - omentectomy; BSO - Bilateral salpingooophorectomy; App - appendectomy; Deb - debulking operation; CTL - Contralateral tubal ligation; BLND - Bilateral pelvic lymph node dissection; PALS - paraaortic lymph node sampling; VAC - vincristine/doxorubicin/cyclophosphamide; BEP - bleomycin/etoposide/cisplatin; NED - no evidence of disease; PD - Progressive disease

[a]Repeated operation

Table 7. Summary of patients with dysgerminoma of the ovary.

Patient	Age (Years)	Stage	Surgery	Further Management	Current Status	Follow-up (months)
14	17	IA	USO, Om, BLND, PALS	-	Lost to follow-up	3
15	21	IA	USO, Om Classical CS, USO	-	PD	24
16	22	IC	CS, THUSO[a]	BEP III	NED	67
17	61	IC	THBSO, Om	VAC I	PD	38
18	26	IC	USO	-	PD	2
19	20	IC	UC	BEP IV	NED	22
20	18	IC	USO, Om	-	PD	3
21	24	IC	USO, Om	BEP III	NED	75
22	19	IC	USO, Om	-	PD	4
23	22	IC	CS, UO	-	Lost to follow-up	3
24	31	IIA	USO, THUSO, Om, App[a]	PVB VI	NED	107
25	18	IIC	USO, Om	-	Lost to follow-up	1
26	17	IIC	THBSO, Om, BLND	BEP I	Lost to follow-up	3
27	20	IIIA	USO, Om	VAC II	Lost to follow-up	2
28	19	IIIA	USO, Om, BLND	VAC IV	PD	15
29	19	IIIC	UC, THUSO[a]	-	PD	10
30	10	IIIC	UC	PVB III	PD	60
31	19	Unknown	BSO	BEP I	PD	4

USO - unilateral salpingooophorectomy; CS- cesarean section; UC - unilateral cystectomy; UO - unilateral oophorectomy; TH - total abdominal hysterectomy; Om - omentectomy; BSO - bilateral salpingooophorectomy; App - appendectomy; BLND - bilateral pelvic lymph node dissection; PALS - paraaortic lymph node sampling; VAC - vincristine/doxorubicin/cyclophosphamide; BEP - bleomycin/etoposide/cisplatin; PVB - cisplatin/vinblastine/bleomycin; NED - no evidence of disease; PD - progressive disease
[a]Repeated operation

Table 8. Summary of patients with immature teratoma of the ovary.

Patient	Age (Years)	Stage	Grade	Surgery	Further Management	Current Status	Follow-up (months)
32	18	IA	G1	USO	-	NED	3
33	24	IA	G1	USO, App	VAC VI	NED	69
34	7	IA	G1	USO	-	Lost to follow-up	1
35	18	IA	G1	USO, Om, BLND, PALS	-	NED	22
36	18	IA	G1	USO, CC, Om	VAC VI	NED	55
37	19	IA	G1	USO, Om, BLND, PALS	-	NED	3
38	24	IA	G2	USO	BEP I	NED	14
39	18	IA	G3	USO, Om, BLND, PALS, CC[a]	BEP III	PD	33
40	14	IC	G2	USO, CC	-	Lost to follow-up	3
41	22	IC	G2	USO, Om, CC[a]	VAC VI	NED	38
42	19	IC	G3	USO	VAC II	PD	8
43	14	IIIA	G2	BSO, biopsy of implants, App	BEP VI	NED	44
44	13	IIIA	G3	USO, Om, BLND, PALS	BEP V	PD	26
45	20	IIIB	G1	USO, CC, Om	-	Lost to follow-up	3
46	19	IIIC	G1	THBSO, Om, Deb	-	NED	54
47	12	Unknown	G2	USO, Om	BEP I	Lost to follow-up	4

USO - unilateral salpingooophorectomy; CC - contralateral cystectomy; TH - total abdominal hysterectomy; Om - omentectomy; BSO - bilateral salpingooophorectomy; App - appendectomy; BLND - bilateral pelvic lymph node dissection; PALS - paraaortic lymph node sampling; VAC - vincristine/doxorubicin/cyclophosphamide; BEP - bleomycin/etoposide/cisplatin; NED - no evidence of disease; PD - progressive disease
[a] Repeated operation

Table 9. Summary of patients with mixed germ cell tumor of the ovary.

Patient	Age (Years)	Stage	Surgery	Further Management	Current Status	Follow-up (months)
48	16	IA	USO	-	PD	6
49	21	IA	USO, CC, App	VAC III	NED	33
50	22	IA	BSO, Om, App	VAC V	PD	20
51	23	IA	USO, Om	BEP III	NED	78
52	13	IC	USO, Om, BLND, PALP	-	PD	5
53	35	IIC	THBSO, Om, LNS	BEP IV	DOD	16
54	42	IIC	THBSO, Om	VAC III	DOD	7
55	22	IIIC	USO, Om	BEP III	NED	16
56	22	IIIC	USO, Om, BLND, PALS	BEP IV	NED	19
57	59	IIIC	THBSO, Om, App	-	PD	1
58	35	IIIC	THBSO, biopsy of implants	-	DOD	2
59	34	Unknown	USO	VAC I	PD	4

USO - unilateral salpingooophorectomy; CC - contralateral cystectomy; TH - total abdominal hysterectomy; Om - omentectomy; BSO - bilateral salpingooophorectomy; App - appendectomy; BLND - bilateral pelvic lymph node dissection; PALS - paraaortic lymph node sampling; PALP- paraaortic lymph node palpation; LNS - lymph node sampling; VAC - vincristine/doxorubicin/cyclophosphamide; BEP - bleomycin/etoposide/cisplatin; NED - no evidence of disease; PD - progressive disease; DOD - dead of disease
[a] Repeated operation

It has been established that fertility-sparing surgery has a role in early stage disease (Stages I or II) regardless of histology.[23] Kurman and Norris[24] observed that there was no worsening prognosis associated with fertility-sparing surgery in 182 patients who had limited disease, which has been the standard. Tangir, et al.[25] in his series of 38 patients showed a 76% success rate of getting pregnant. Low, et al.[26] demonstrated that in 74 patients with malignant germ cell tumor of the ovaries, 64% of these had adjuvant chemotherapy. Of the 20 patients who attempted to get pregnant, 19 (95%) were successful. Zanetta, et al.[27] in their study showed that conservative surgery in 81 patients with germ cell malignancy of the ovary and given adjuvant chemotherapy, 16 out of the 20 (80%) patients who attempted to conceive were successful in getting pregnant. In our series, fertility-sparing surgery was performed for preservation of reproductive capacity with the subsequent goal of becoming pregnant even with advanced stage. Of the 45 patients who had conservative surgery, only 3 got pregnant (6.67%). No documentation, however, was made on how many attempted conception.

The SGOP (Society of Gynecologic Oncologists of the Philippines) treatment guidelines revised in 2005[28] ascribes to complete surgical staging in patients with early stage malignant germ cell tumor of the ovary. These include peritoneal fluid cytology, random peritoneal biopsies, omentectomy, lymph node assessment including bilateral pelvic lymph node dissection and paraaortic lymph node sampling. This is based on the experience with epithelial ovarian cancers but is not well studied in malignant ovarian germ cell tumors. The rationale for doing this is that the full extent of disease should be recognized which could serve as guide as to prognosis and need for postoperative management.[29] Our series showed that out of the 29 patients who had their initial surgery in our institution, 15 had lymph node dissection. This was not observed in patients operated elsewhere.

Based on the findings from of the Pediatric Oncology Group and the Children's Cancer Group Intergroup Study[30], a modification from the comprehensive surgical staging guideline did not negatively affect survival. In their study, the following were adapted: collection of ascites with cytologic washings, examination of the peritoneal surfaces with biopsy or excision of any nodule, examination and palpation of retroperitoneal lymph nodes and sampling of any firm or large nodes, inspection and palpation of the omentum with removal of any adherent or abnormal areas, biopsy of any abnormal areas, and complete excision of tumor-containing ovary with sparing of the fallopian tube if not involved. Would

this be the explanation why survival between operations done in our institution was not significantly different from other institutions? This modified guideline, however, warrants further study.

As a general rule, once the diagnosis of advanced malignant ovarian germ cell tumor is observed, resection of all visible tumors is advocated with morbidity and safety precautions. This is of course due to the fact that the tumor is very chemosensitive.[29] Peccatori, et al.[31] further elucidated that cisplatin-based chemotherapy is very effective even with extensive disease and large residual tumor and cytoreductive surgery is not imperative. In our series, there were no second operations performed for inadequately staged operations done in other institutions before the administration of chemotherapy. The benefit of prompt administration of chemotherapy generally outweighs the risks of morbidity from aggressively mutilating first surgeries, as experienced in the more common testicular germ cell tumors.[32]

Second look surgery is not generally recommended in malignant germ cell tumor of the ovary. In the study at the MD Anderson Cancer Center[33], 52 of 53 patients had negative second-look surgery. Williams, et al.[34], in a Gynecologic Oncology Group Study, expressed that second look does not show benefit in patients with completely resected tumor or those with advanced stage but does not contain elements of teratoma. The procedure is however recommended for patients with incompletely resected tumor containing elements of teratoma. There were two cases of second look operation in our series. Both were Stage I immature teratoma cases. One had no evidence of disease while the other had tumor progression on second look surgery.

Before the 1940's, treatment of ovarian germ cell tumors consisted of primary surgery alone and survival was dismal. The introduction of radioisotopes and radiation therapy for women with dysgerminoma provided survival advantage during the 1940's. This however is not duplicated in non-dysgerminomatous lesions since they are radioresistant.[35]

By the 1970's, Vincristine, actinomycin D, cyclophosphamide (VAC) became the standard chemotherapy for malignant germ cell tumor of the ovary demonstrating 75% remission rates in early stage disease and more than 50 percent in advanced disease.[36,37]

With the introduction of platinum-based chemotherapy for testicular cancer by Einhorn and Donahue[38], Vinblastine, bleomycin and cisplatin (PVB) regimen was made available during the early 1980's for women with germ cell tumor of the ovary.[34,39] During that same period, based on the activity of single agent etoposide in refractory testicular cancer, a randomized trial showed that PVB had comparable efficacy with BEP (bleomycin, etoposide, cisplatin) with less toxicity.[40] It is then that BEP became the standard in malignant germ cell tumor of the ovary up to the present. In our series of the 32 patients given chemotherapy, 13 had VAC, 17 had BEP and 2 had PVB.

Limitations of this report include the following: the retrospective nature of the study showed inherent selection bias. Patients who were lost to follow-up posed a limitation on their actual current status. Because of the rarity of the tumor, the number of patients is relatively small. This may explain why no significant difference was seen in some variables. Lack of data on residual disease, tumor markers, attempts on restaging, whether surgically or radiologically, hampered investigation of these additional prognostic factors. Attempts at conception for those who underwent conservative surgery should have been recorded.

Efforts should be made to adequately stage this rare tumor during initial surgery. Attempts to conserve reproductive function should also be considered. Survival is significantly better when adjuvant chemotherapy is given after initial surgery.

References

1. Di Saia and Creasman. Germ cell, stromal and other ovarian tumors. In Clinical Gynecologic Oncology, 6th ed. Mosby Inc., 2002.
2. Benedet JL, Pecorelli S, Ngan HYS, Hacker NF, et al. Staging classifications and clinical practice guidelines of gynecologic cancers by FIGO Committee on Gynecologic Oncology and IGCS Committee, Third edition, November 2006.
3. Gershenson DM. Management of early ovarian cancer: germ cell and sex-cord stromal tumors. Gynecol Oncol 1994; 55: S62-72.
4. Schwartz P, Chambers S, Chambers J, Kohorn E, McIntoch S. Ovarian germ cell malignancies: The Yale University experience. Gynecol Oncol 1992; 45: 26-31.

5. Sonneveld DJA, Hockstra HJ, van der Graaf WTA, et al. Improved long term survival of patients with metastatic nonseminomatous testicular germ cell carcinoma in relation to prognostic classification systems during the cisplatin era. Cancer 2001;91:1304-1315.
6. Beyer J, Kramar A, Mandanas R, et al. High dose chemotherapy as salvage treatment in germ cell tumors: a multivariate analysis of prognostic variable. J Clin Oncol 1996;14:2638-2645.
7. Mitchell PL, Al-Nasiri N, A'Hern R, et al. Treatment of nondysgerminomatous ovarian germ cell tumors. An analysis of 69 cases. Cancer 1999; 85: 2232-2244.
8. Nawa A, Obata N, Kikkawa F, et al. Prognostic factors of patients with yolk sac tumors of the ovary. Am J Obstet Gynecol 2001; 184: 1182-1188.
9. Cuita S, Shono K, Tajiri T, et al. Malignant germ cell tumors: Clinical characteristics, treatment, and outcome. A report from the Study Group for Pediatric Solid Malignant Tumors in Kyushu Area, Japan. J Pediatr Surg 2002; 37 (12): 1703-1706.
10. Sah SP, Uprety D, Rani S. Germ cell tumors of the ovary: a clinicopathologic study of 121 cases from Nepal. J Obstet Gynecol Res 2004; 30(4): 303-308.
11. Li H, Hong W, Zhang R, Wu L, Liu L, Zhang W. Retrospective analysis of 67 consecutive cases of pure ovarian immature teratoma. Chin Med J (Engl) 2002; 115(10): 1496-1500.
12. Zhang R, Hong W, Liu L. Treatment of malignant germ cell tumors of the ovary: a clinical analysis of 233 cases. Zhonghua Zhong Liu Za Zhi 1998; 20(2): 155-157.
13. Hong W, Zhang R, Liu L. Treatment of 129 patients with advanced and recurrent malignant ovarian germ cell tumor. Zhonghua Fu Chan Ke Za Zhi 1998; 33(1): 35-37.
14. Tewari K, Cappuccini F, Disaia PJ, Berman ML, Manetta A, Kohler MF. Malignant germ cell tumors of the ovary. Obstet Gynecol 2000; 95(1): 128-133.
15. Piura B, Dgani R, Zalel Y, Nemet D, Yanai-Inbar I, Cohen Y, Glezerman M. Malignant germ cell tumors of the ovary: a study of 20 cases. J Surg Oncol 1995; 59(3): 155-161.
16. Ayhan A, Tuncer ZS, Yanik F, Bukulmez O, Yanik A, Kucukali T. Malignant germ cell tumors of the ovary: Hacettepe hospital experience. Acta Obstet Gynecol Scand 1995; 74(5): 384-390.
17. Chang FH, Lai CH, Chu KK, Chang TC, Hsueh S, Hung IJ. Treatment of malignant germ cell tumors of the ovary. J Formos Med Assoc 1994; 93(5): 411-416.
18. Germa JR, Izquierdo MA, Segui MA, Climent MA, Ojeda B, Alonso C. Malignant ovarian germ cell tumors: the experience at the Hospital de la Santa Creu i Sant Pau. Gynecol Oncol 1992; 45(2): 153-159.
19. Laudico A, Esteban D, Redaniel MTM, Mapua C, Reyes L. 2005 Philippine Cancer Facts and Estimates. Manila: Philippine Cancer Society 2004.
20. Siasu MLL, Limson G. Clinical profile of patients with ovarian carcinoma at the Philippine General Hospital- a thirteen year review. Acta Medica Philippina 1993; 29(1): 12-17.
21. Lai CH, Chang TC, Hsueh S, Wu T, Chao A, Chou H, Wang P. Outcome and prognostic factors in ovarian germ cell malignancies. Gynecol Oncol 2004; 93: 381-384.
22. Murugaesu N, Schmid P, Dancey G, et al. Malignant ovarian germ cell tumors: Identification of novel prognostic markers and long-term outcome after multimodality treatment. J Clin Oncol 2006; 24: 4862-4866.
23. Gershenson DM. Update on malignant ovarian germ cell tumors. Cancer 1993; 71(suppl): 1581-1590.
24. Kurman RJ, Norris HJ. Malignant germ cell tumors of the ovary. Hum Pathol 1977; 8: 551-564.
25. Tangir J, Zelterman D, Ma W, Schwartz P. Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. Obstet Gynecol 2003; 101: 251-257.
26. Low JJH, Lewis CP, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors. Cancer 2000; 89: 391-398.
27. Zanetta G, Bonazzi C, Cantu MG, Binidagger S, Locatelli A, Bratina G, et al. Survival and reproductive function after treatment of malignant germ cell ovarian tumors. J Clin Oncol 2001; 19: 1015-1020.
28. Society of Gynecologic Oncologists of the Philippines, Inc. Clinical Practice Guidelines, Fourth Edition published August 2005.
29. Gershenson DM. Management of ovarian germ cell tumors. J Clin Oncol 2007; 25: 2938-2943.
30. Billmire D, Vincour C, Rescoria F, et al. Outcome and staging evaluation in malignant germ cell tumor of the ovary in children and adolescents: An intergroup study. J Pediatr Surg 2004; 39: 424-429.
31. Peccatori P, Bonazzi C, Chiari S, Landoni F, Colombo N, Mangioni C. Surgical management of malignant ovarian-germ-cell tumors: 10 years' experience of 129 patients. Obstet Gynecol 1995; 86: 367-372.
32. Javadpour N, Ozols RF, Anderson T, Barlock AB, Wesley R, Young RC. A randomized trial of cytoreductive surgery followed by chemotherapy versus chemotherapy alone in bulky stage III testicular cancer with poor prognostic features. Cancer 1982; 50: 2004-2010.
33. Gershenson DM, Copeland LJ, del Junco G, et al. Second-look laparotomy in the management of malignant germ cell tumors of the ovary. Obstet Gynecol 1986; 67: 789-793.
34. Williams SD, Blessing JA, DiSaia PJ, et al. Second-look laparotomy in ovarian germ cell tumors: The Gynecologic Oncology Group experience. Gynecol Oncol 1994; 52: 287-291.
35. Williams SD, Gershenson DM, Horowitz CJ, Scully RE. Ovarian germ-cell tumors. In Hoskins WJ, Perez CA, Young RC (eds): Principles and Practice of Gynecologic Oncology. 2nd ed. Pennsylvania: Lippincott-Raven 1997; 987-1002.
36. Slayton RE, Park RC, Silverberg SC, et al. Vincristine, dactinomyin, and cyclophosphamide in the treatment of malignant germ cell tumors of the ovary: A Gynecologic Oncology Group Study (a final report). Cancer 1985;56:243-248.
37. Gershenson DM, Copeland LJ, Kavanagh JJ, et al. Treatment of malignant non-dysgerminatous germ cell tumors of the ovary with vincristine, dactinomycin, and cyclophosphamide. Cancer 1986; 56: 2756-2761.

38. Einhorn LH, Donohue J. Cis-diaminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 1977; 87: 293-298.
39. Gershenson DM, Copeland LJ, Kavanagh JJ, et al. Treatment of malignant non-dysgerminatous germ cell tumors of the ovary with vinblastine, bleomycin, and cisplatin. Cancer 1986; 57: 1731-1737.
40. Williams S, Birch R, Einhorn LH, et al. Treatment of disseminated germ cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 1987; 316: 1435-1440.

Acute Toxicity of Radiotherapy Concurrent with Weekly Chemotherapy in the Treatment of Cervical Cancer

Scheryll B. Pua, MD and Lilli May Teodoro-Cole, MD

Section of Gynecologic Oncology and Trophoblastic Disease,
Jose R. Reyes Memorial Medical Center

Ciplatin-based chemotherapy concurrent with radiation has been widely accepted as the standard of care for patients with cervical cancer. Review of literature showed that combined treatment increases toxicity as compared to radiation treatment alone. **Objective**: This study was intended to evaluate the tolerance of patients diagnosed with Stage IIa to IIIb cervical cancer to radiotherapy concurrent with weekly cisplatin chemotherapy. **Methods**: Patients with histologically confirmed cervical cancer regardless of the histologic type were included in the study. Out of the forty five (45) patients evaluated, thirty seven (37) patients met the eligibility criteria. Thirty patients were treated with pelvic external beam radiotherapy, intracavitary brachytherapy and weekly cisplatin. Acute toxicities were evaluated during their weekly follow-up using the Gynecologic Oncology Group criteria. **Results**: The most common adverse effects were gastrointestinal symptoms (GI) manifested as diarrhea and nausea but they are self-limited and reversible. Seventeen (56.67%) of patients exhibited G1 diarrhea, 8 (26.67 %) and 2 (6.67 %) developed G2 and G3 toxicity, respectively. G2 vomiting were also common at 13 (43.33%) while 18 (60%) of patients had G1 nausea. Majority of these GI symptoms were seen on the second to third week of treatment. Another common toxicity was hematologic mostly anemia with 15 (50%) manifesting with G1, 6 (20%) with G2 and 3 (10%) with G3 toxicity. Eleven patients (36.67%) developed G1 leukopenia and 10 patients (33.33%) had G2 leukopenia. Majority of the hematologic toxicities were manifested on the fourth to the sixth week of treatment. **Conclusion**: The combined treatment of weekly cisplatin and radiation for cervical cancer are commonly met with early GI toxicities however, they were found to be generally acceptable. Further follow-up and a larger sample size are needed in order to accurately assess if these toxicities have impact on treatment outcome.

Key words: concurrent chemotherapy and radiotherapy, acute toxicity, cervical cancer

Invasive carcinoma of the cervix is a major cause of death from gynecologic malignancy worldwide. Almost half a million cases are diagnosed each year. It ranks fourth and accounts for about 2.5 percent of all malignancies that afflict women in the United States.[1,2] In the Philippines, it is the second most common female cancer with the incidence reported at 13.3%.[10]

Treatment of invasive cancer involves appropriate management for both the primary lesion and potential sites of metastatic disease. Both surgery and radiotherapy (RT) may be used for the primary treatment of cervical cancer, however, the treatment is individualized based on the extent of the disease and patient characteristics. Chemotherapy and radiotherapy were found to have a synergistic effect, wherein chemotherapy is said to increase the sensitivity of the tumor to radiation. Concurrent chemotherapy inhibits the repair of sublethal damage from radiation, synchronizes cells to a particularly radiosensitive phase of the cell cycle and is cytotoxic in vitro.[6]

In 1999, the National Cancer Institute (NCI) in the United States recommended adding Chemotherapy to Radiotherapy (ChemoRad) in the treatment of cervical cancer. The recommendation was issued in advance of the publication of the 5 randomized phase III trials showing an overall survival advantage of the cisplatin-based therapy given concurrently with RT. The risk of death from cervical cancer was decreased by 30-50% with concurrent ChemoRad.[2]

Although studies have shown an impressive survival gain in the concurrent ChemoRad, there is concern about the toxicities of the said treatment, particularly the acute toxicities that would lead to delay in the RT or in the treatment that the patient will receive. A large study in the U.S. has shown that concurrent ChemoRad is well-tolerated by patients.[3] This study is intended to evaluate the acute toxicities of ChemoRad as a treatment for cervical cancer in the local setting.

Objectives

General Objective

The study aimed to evaluate the tolerance of patients to radiotherapy concurrent with weekly cisplatin as the primary treatment for cervical carcinoma.

Specific Objectives

- To assess the toxicity of ChemoRad specifically on the hematologic (bone marrow), gastrointestinal, genitourinary and neurologic systems.
- To evaluate the delay in treatment secondary to the above mentioned toxicities

Materials and Methods

Inclusion Criteria

- Histologically confirmed carcinoma of the uterine cervix regardless of the histologic type
- Patients who will receive ChemoRad as the primary treatment
- International Federation of Gynecology and Obstetrics (FIGO) Stage IIA - IIIB disease
- Age: 20-70
- Performance Status: Eastern Cooperative Oncology Group (ECOG) : 0-2 *(Appendix 1)*
- Adequate bone marrow, hepatic and renal function
- Written informed consent *(Appendix 2)*

Exclusion Criteria

- Patients with concurrent uncontrolled medical illness
- History of prior chemotherapy or radiotherapy
- Patients with history of abdomino-pelvic surgery

Treatment Protocol

All patients received external beam radiation using Cobalt 60 equipment followed by High Dose Rate Intracavitary Brachytherapy (HDR). The pelvic field is usually at the L4-L5 disc space superiorly, 2 cm to the bony pelvis laterally, and at the midpubis or 3 to 4 cm below the most distal disease in the cervix or vagina inferiorly. The dose distribution of intracavitary brachytherapy was based on the Manchester system, in which Point A is 2 cm lateral and 2 cm superior to the external cervical os in the plane of the implant and Point B which is 3 cm lateral to Point A. The dose that each patient received was based on the calculated

dosing. The EBRT was given at 2 Gy fractions for five consecutive days a week for 25 days while the brachytherapy was given when the tumor volume has decreased to 4 cm in size. The total dose that each patient received to Point A ranged from 72 - 78 Gy (7,200 - 7,800 cGy). However, patients with nodular parametria at the time of brachytherapy were given additional parametrial boosts of 10 Gy. The brachytherapy dose was given at 5-7 Gy per fraction for 4 weeks.

The chemotherapy regimen consists of cisplatin at 40 mg/m^2 given within the first week of pelvic EBRT on an out-patient basis. All patients had adequate renal function before starting the chemotherapy. The chemotherapy was given for 6 hours with 1 liter intravenous hydration prior to cisplatin drip followed by another 500 cc of 0.9 NaCl after chemotherapy. All patients were given premedications with intravenous ramosetron, dexamethasone and furosemide. Post-chemotherapy, patients were given an oral anti-emetic drug taken as needed.

Toxicity Grading

Treatment-related toxicities were graded at weekly intervals using the Gynecologic Oncology Group (GOG) Common Toxicity Criteria *(Appendix 3)* during the course of treatment and monthly thereafter. Treatment was withheld in cases of G2 toxicity for hematologic and G3 for non-hematologic toxicity and resumed until the toxicity resolved and patient can tolerate continuation of treatment. The interruption in the institution of treatment and the interval duration prior to continuation of the treatment were recorded.

Results

Forty-five patients were enrolled in the study, however, 8 patients did not meet the eligibility criteria because of co-existing uncontrolled medical illness and poor patient compliance. Thirty-seven patients met the eligibility criteria. Patient characteristics assessed include the age, performance status, stage and histologic type. The median age of the patients was 48 with a mean age of 49.57 (range: 34 - 68). All patients had ECOG performance status of 0-1. Based on histologic type, 21 (56.76%) were squamous cell carcinoma 13 (35.13%) were adenocarcinomas. Twenty four (64.86%) patients were noted to be at Stage IIIB and only 10 (27.02%) were Stage IIB.

Table 1. Patient characteristics.

	No. of Patients	%
Age		
≤ 50	22	59.46%
> 50	15	40.54%
Gravidity		
0-3	10	27.03%
4-6	21	56.57%
7-9	2	5.40%
≥ 10	1	10.81 %
Stage		
II A	3	8.11%
II B	10	27.03%
III A	0	0
III B	24	64.86%
Histologic Type		
Squamous cell		
LCNK	17	45.94%
LCK	3	8.11%
Small cell	1	2.70%
Adenocarcinoma		
Endocervical	5	13.51%
Clear cell	5	13.51%
Endometrioid	2	5.40%
Mucin	1	2.70%
Adenosquamous	3	8.11 %

Thirty patients received complete radiotherapy and 6 courses of weekly chemotherapy. Six patients were dropped from the study due to discontinuation of the treatment and one patient shifted to PVB chemotherapy due to disease progression. Two patients were given parametrial boost due to persistent parametrial nodularites noted at the start of brachytherapy.

Adverse effects were described based on the GOG toxicity criteria and the delay in treatment was noted when it was manifested.

The most common adverse effects were gastrointestinal symptoms (GI) manifested as diarrhea

Table 2. Toxicity during treatment.

	Toxicity Grading				
	0	1	2	3	4
Hematologic					
Hgb	6	15	6	3	0
WBC	9	11	10	0	0
Plt Ct.	28	2	0	0	0
GI					
Diarrhea	4	17	8	2	0
Nausea	7	18	5	0	0
Vomiting	17	0	13	0	0
Liver					
Transaminases	24	6	0	0	0
ALP	30	0	0	0	0
Kidney/Bladder					
Creatinine	30	0	0	0	0
Hematuria	25	5	0	0	0
Infection	15	0	15	0	0
Neurologic					
Neuromotor	13	17	0	0	0
Neurosensory	29	1	0	0	0

and nausea. Seventeen (56.67%) patients exhibited G1 diarrhea, 8 (26.67%) and 2 (6.67%) patients developed G2 and G3 toxicity, respectively. G2 vomiting was also common in 13 (43.33%) while 18 (60%) patients had G1 nausea. Majority of these GI symptoms were seen during the second to third week of treatment.

The most common hematologic toxicity noted was anemia with 15 (50%) manifesting with G1, 6 (20%) with G2 and 3 (10%) with G3 toxicity. Eleven patients (36.67%) developed G1 leukopenia and 10 patients (33.33%) had G2 leukopenia. Six patients who developed leukopenia had concomitant G2 anemia. Majority of the hematologic toxicities were manifested on the fourth to the sixth week of treatment.

On seventeen patients (56.67%), G1 neuromotor toxicities were noted. Interestingly, the neurologic symptoms were manifested at almost the same time that the GI symptoms were noted. Six patients had G1 liver toxicity as documented by the elevated liver enzymes specifically SGPT. There was no episode of renal failure nor any other condition directly related with the treatment that required hospitalization except for anemia that required blood transfusion.

Treatment delay was seen in 24 patients (80%) and this was broken down as follows: 19 patients with G2-3 hematologic toxicity and 2 patients with G3 gastrointestinal toxicity (Tables 3 & 4). The delay in treatment was recorded at 1- 4 weeks interval. However, for patients who were delayed due to brachytherapy schedule, it was noted at 8-16 weeks interval. Overall treatment duration was recorded at a mean of 85.16 days (range: 44 -183 days).

Table 3. Number of patients who developed toxicity during the course of treatment.

	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10
Hematologic										
Hgb	0	0	1	4	5	8	1	2	2	1
WBC	0	0	0	4	7	3	1	5	1	0
Platelet Count	0	0	0	0	1	1	0	0	0	0
GI										
Diarrhea	1	6	13	5	2	0	0	0	0	0
Nausea	0	5	7	7	3	1	0	0	0	0
Vomiting	0	5	3	4	1	0	0	0	0	0
Liver	0	0	3	0	0	1	1	0	1	0
Kidney/bladder	0	0	1	2	7	6	3	1	0	0
Neurologic	0	6	4	7	1	0	0	0	0	0

Table 4. Cause of delay in treatment.

	No. of Patients	%
Anemia	9	30 %
Leukopenia	10	33.33%
GI (Diarrhea)	2	6.67%
Brachy therapy scheduling	4	13.33%

Table 5. Duration of treatment.

	No. of Patients	%
≤ 56 days	6	20%
> 56 days	24	80%

Discussion

The recent publication of five prospective randomized trials showing the superiority of cisplatin-based chemoradiotherapy over RT alone in cervical cancer has resulted in the common introduction of the combined modality approach into practice. Combined treatment seems to offer substantial benefit for women with cervical cancer. However, acute toxicity was increased with chemoradiation.

It was in 1999 that five landmark studies demonstrated that concurrent chemotherapy and radiation has a proven benefit in locally advanced cervical cancer over radiation alone.[1,8]

In **Gynecologic Oncology Group Protocol 85,** 386 patients with cervical cancer stages IIB-IVA were randomized to external beam (pelvis) and intracavitary radiation therapy with 5-FU infusion and cisplatin or external beam (pelvis) and intracavitary radiation therapy with hydroxyurea. The three-year survival rate for women on the cisplatin-based chemotherapy is 67 percent compared to 57 percent for women on the hydroxyurea arm.

In **Radiation Therapy Oncology Group (RTOG) Protocol 9001,** 389 patients with stages IIB -IVA were randomized to external beam (pelvis) and intracavitary radiation therapy with 5-FU infusion and cisplatin or extended-field external beam (pelvis and para-aortic) and intracavitary radiation therapy. The three-year survival rate for women on the cisplatin-based chemotherapy is superior at 75 percent compared to 63 percent for women on the extended-field radiation treatment.

In **Gynecologic Oncology Group Protocol 120,** 526 patients with cervical cancer stages IIB-IVA were randomized to external beam (pelvis) and intracavitary radiation with weekly cisplatin or external beam (pelvis) and intracavitary radiation with 5-FU, cisplatin, and hydroxyurea or external beam (pelvis) and intracavitary radiation with hydroxyurea. The three-year survival rate for women on the cisplatin-based treatment arm is superior to hydroxyurea/radiaton arm at 65 percent and 47 percent, respectively.

In **Southwest Oncology Group Protocol 8797,** included were high-risk patients with involvement of lymph nodes or surgical margins who had undergone radical hysterectomy with stages IA2 - IIA. Two hundred forty-three patients were randomized to external beam (pelvis) radiation therapy with cisplatin and 5-FU infusion or external beam (pelvis) radiation therapy. The three-year survival rate for women on the adjuvant cisplatin/5-FU plus radiation arm is 87 percent compared to 77 percent for women on the adjuvant radiation alone arm.

In **Gynecologic Oncology Group Protocol 123** is another study which included bulky stage IB. Three hundred sixty-eight patients were randomized to external beam (pelvis) and intracavitary radiation with weekly cisplatin, followed by extrafascial hysterectomy or external beam (pelvis) and intracavitary radiation followed by extrafascial hysterectomy. The survival rate for women treated with cisplatin chemotherapy is 83% compared to 74% of those treated with radiotherapy alone.

These five randomized phase III trials demonstrated that platinum-based chemotherapy, when given concurrently with radiotherapy, prolongs survival in women with locally advanced cervical cancer.

Although the trials differed with regards to the stage of disease, dose of radiation, and schedule of cisplatin and radiation, they all demonstrated significant survival benefit for this combined approach. The risk

of death from cervical cancer was decreased by 30 percent to 50 percent with concurrent chemoradiation. The results of these studies have changed the standard method by which cervical cancer has traditionally been managed.

The rationale for concurrent chemotherapy and RT include the potential of cytotoxic agents to increase killing of tumor cells, inhibiting repair of radiation damage, inducing cell synchronization, recruiting non-proliferating cells into the cell cycle and the sensitization of hypoxic cells. The augmented effect on tumor cells may also affect normal tissue resulting in potential damage to two diverse cell populations. First, damage to the rapidly proliferating cells such as neutrophils may result in acute toxicity, while damage to more slowly proliferating stromal cells is the major factor contributing to chronic symptoms. Theoretical disadvantages of concurrent chemoradiation include increased acute toxicity that might limit or delay the delivery of definitive irradiation or allow time for tumor repopulation.

Pelvic irradiation can have a significant effect on the bone marrow included in the radiation field, thus causing hematological toxicity. On the other hand, acute gastrointestinal side effects such as diarrhea and fecal incontinence may become chronic symptoms, and any increase may be an indicator for long-term bowel disorders. Overall, however, the effect of irradiation on the small and large bowel probably accounts for the majority of non-hematological toxicity.

Long-term toxicity data are incomplete on some of these trials, but to date all these regimens appear tolerable. Acute toxicities vary among the regimens, as do the doses and schedule of drugs and radiation. Acute toxicities are those appearing during treatment, generally of short duration, resolve with medical management and usually reversible while late effects are often permanent and affect quality of life.

A recent meta-analysis on toxicity following radiation alone or in combination with chemotherapy for locally advanced cervical cancer confirmed that concurrent chemotherapy increases toxicity as compared to radiation alone.[4] Maduro, et al. 2003, reported that adding chemotherapy to radiotherapy increases acute hematological toxicity from 5 to 37 percent of the patients and nausea and vomiting from 12 to 14 percent.

In the Addenbrooke study, concurrent chemo-radiotherapy using weekly cisplatin-based chemotherapy was found to be well-tolerated. Among 74 patients, only 2 (2.8%) patients were found to have G3 or G4 hematological toxicity and only one (1.4%) patient had G3 gastrointestinal toxicity. In another published meta-analysis of cisplatin-based chemotherapy, the reported rates of acute G3 or G4 toxicity ranged from 4-47 percent for hematological toxicity, 0-15 percent for gastrointestinal toxicity and 1-8 percent for genitourinary toxicity. However, these trials have different treatment regimens.[3]

In a systematic review by Kirwan, et al. 2003, there was a two-fold increase in white cell count, a three-fold increase in platelet toxicity and a two-fold increase in gastrointestinal toxicity for patients who were given concomitant chemoradiation.[13] In a study by Serkies, et al., 44 percent experienced G1 or G2 leukopenia, 5 percent had G3 or G4 leukopenia and 38 percent had gastrointestinal toxicity.[14] In our study, 3 (10 %) patients had G3 hematological toxicity and 16 patients (53.33%) had G2. Twenty patients (86.66%) and 2 patients (6.67%) had G2 and G3 gastrointestinal toxicity, respectively. Only mild neurological toxicities were noted.

Rose and Whitney in 1995 reported that prolongation of radiotherapy may result in inferior local control rates. In 2000, the American Brachytherapy Society (ABS) recommended keeping the total duration of radiation treatment (EBRT and HDR) to less than 8 weeks because the prolongation of the treatment was found to adversely affect local control and survival.

As the overall treatment time of RT is believed to be an important prognostic factor in cervical cancer patients, the avoidance of treatment prolongation seems to be of particular importance. The treatment duration was shorter in a study by Serkies, et al. demonstrated at 42 days.[14] Other randomized trials, however, showed a longer duration. In the study by Rose, et al., the median duration was 63 days; in the study by Keys, et al., it was 50 days; and in the NCI CTG study, it was 48 days.[14]

In this study, the overall treatment duration was recorded at a mean of 85.16 days (range: 44 -183 days). Twenty four patients (80%) had delay in the treatment and only 6 (20%) were noted to be within the

recommended treatment duration of 6-8 weeks (42-56 days). Additionally, the cause of the delay in the treatment in some patients was not related to toxicity.

Thirty patients (81.08 %) completed the desired treatment of pelvic EBRT, brachytherapy and six cycles of weekly cisplatin chemotherapy even though the treatment was withheld temporarily in 80 percent of patients. This is in contrast to a study by Serkies in which only 42 percent of patients received five cycles of cisplatin concurrent with radiotherapy.[14] In the published Addenbrooke study on toxicity with chemoradiation, the completion rate for radiation is 90-97 percent and only 70-80 percent for chemotherapy.[3]

Although 80 percent of our patients experienced delay in treatment because of the toxicities cited, the acute toxicities manifested by our patients were self-limited and resolved promptly with medical management. The satisfactory treatment results in this study were attributed to good patient compliance in spite of the complications they experienced with the combined treatment.

Conclusion

Cisplatin-based ChemoRad was found to be well tolerated by patients included in this study. This study was found to be consistent with the published reports on toxicities of the current treatment of cervical cancer. A larger sample size, however, is needed to further evaluate these adverse effects and to find out whether they have an impact on the treatment outcome of these patients.

References

1. Chi DS, Lanciano RM and Kudelka A. Cervical Cancer; Cancer Mangement: A Multidiscplinary Approach, Sixth edition, 2005; 419-447.
2. National Cancer Institute, Guideline on Cervical Cancer, 2005.
3. Tan LT, Russel S and Burgess L. Acute toxicity of chemo-radiotherapy for cervical cancer: The Addenbrooke's experience. Clin Oncol (Royal College of Radiologists) 2004; 16(4): 255-260.
4. U.S. Cancer Facts and Figures 2006.
5. Cetina L, et al. Routine management of locally advanced cervical cancer with concurrent radiation and cisplatin. Five year results. BMC Women Health Journal 2006; 6: 3.
6. Vrdoljak E, Hamm W. Current state-of-the-art of concomitant chemoradiation in cervical carcinomas. Eur J Gynaecol Oncol 2003; 6: 475-479.
7. Rose PG, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. The New Engl J Med 1999; 340: 1144-1153.
8. Maduro JH, Pras E, Willmese PH, de Vries EG. Acute and long term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. Int J Rad Oncol Biol Phys 2003; 57(4): 1010-1018.
9. Grigsby PW and Herzog TJ. Current management of patients with invasive cervical carcinoma. Clin Obstet Gynecol 2001; 44 (3): 531-535.
10. Laudico AV, et al. Philipiine Cancer Facts and Estimates 2005.
11. Sottlo LSJ, Manalo AM, Limson GM. Gynecologic Oncology for the Clinician, 99-143.
12. Ngelangel CA, et al. Delineation of an appropriate and replicable cervical cancer screening program for Filipino women, 2001.
13. Kirwan JM, Symonds P, Green JA, et al. A systematic review of acute and late toxicity of concomitant chemoradiation for cervical cancer. Radiother Oncol J 2003; 68: 217-226.
14. Serkies K and Jacek JM. Concurrent weekly cisplatin and radiotherapy in routine management of cervical cancer: A report on patient compliance and acute toxicity. Int J Rad Oncol Biol Phys 2004; 60 (3): 814-821.

Appendix 1. Eastern Cooperative Oncology Group (ECOG) performance scale.

Score	Activity Level
0	fully active; unrestricted activity of daily living
1	ambulatory but restricted in strenuous activity
2	ambulatory but capable of self-care; unable to work; out of bed greater than 50% of waking hours
3	limited self-care; confined to bed or chair 50% of waking hours; needs special assistance
4	completely disabled; no self-care
5	dead

Appendix 2

CONSENT FOR INCLUSION IN THE STUDY OF ACUTE TOXICITY OF RADIOTHERAPY CONCURRENT WITH WEEKLY CHEMOTHERAPY FOR CERVICAL CANCER PATIENTS

I, _____ hereby authorized the medical staff to take charges in the care of _____ to perform the treatment and procedures deemed necessary in the interest of the patient. I shall not hold any member of the medical staff and or his/her assistants responsible for untoward effects/complications or death beyond their scientific control, which has been explained to me fully and I understand very well.

_____ _____

Patient Nearest kin/relative

_____ _____

Date Witness

Appendix 3. Gynecologic Oncology Group Toxicity Criteria.

Toxicity	0	1	2	3	4
Hematologic					
WBC	≥ 4.0	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
Plt	WNL	75.0-Normal	50.0-74.9	25.0-49.9	<25.0
Hgb	WNL	10.0-Normal	8.0-10.0	6.5-7.9	<6.5
GI					
Nausea	None	Able to eat Reasonable intake	Intake significantly decreased but can eat	No significant intake	-
Vomiting	None	1 episode in 24 hr	2-5 episodes in 24 hr	6-10 episodes in 24 hr	> 10 episodes in 24 hr or requiring parenteral support
Diarrhea	None	Increase of 2-3 stools/day over pre-Rx	Increase of 4-6 stools/day, or nocturnal stools or moderate cramping	Increase of 7-9 stools/day, or incontinence or severe cramping	Increase of 10 stools/day or grossly bloody diarrhea or Need for parenteral support
Liver					
Transaminases	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
ALP	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
Kidney/Bladder					
Creatinine	WNL	≤ 1.5 x N	1.5-3.0 x N	3.1-6.0 x N	>6.0 x N
Hematuria	negative	microscopic only	gross hematuria, no clots	gross and clots requires transfusion	---
Neurologic					
Neurosensory	none or no change	mild paresthesia, loss of DTR	mild or moderate objective sensory loss; moderate paresthesias	severe objective sensory loss or paresthesia that interferes with function	---
Neuromotor	none or no change	subjective weakness no objective findings	mild objective weakness without significant impairment	objective weakness with impairment	paralysis

Etoposide, Cisplatin/ Etoposide, Methotrexate, and Actinomycin D (EP/EMA) in Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine (EMACO) Resistant Gestational Trophoblastic Neoplasia: A Retrospective Study

Quennie G. Salcedo-Quiño, MD and Agnes Soriano-Estrella, MD

Section of Trophoblastic Disease, Department of Obstetrics and Gynecology,
Philippine General Hospital, University of the Philippines Manila

Objective: To evaluate the efficacy of Etoposide,Cisplatin/Etoposide,Methotrexate and Actinomycin D (EP/EMA) in the treatment of high risk gestational trophoblastic neoplasia patients who were refractory to the Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine (EMACO) regimen.

Methods: From January 1999 to December 2005, 21 patients with high risk gestational trophoblastic neoplasia were treated with EP/EMA after showing apparent drug resistance and/or recurrence after EMACO treatment. Clinical response, electrolyte imbalance, hematologic, renal and hepatic toxicities were analyzed retrospectively. The profile of patients in the remission group and non-remission group were also analyzed and compared.

Results: The medical records of 19 patients were available for analysis and review. The overall survival rate for 1 year was 32%(6/19). Six patients (32%) went into primary remission with EP/EMA giving a primary remission rate of 31.6%. An additional 3 patients achieved remission using Paclitaxel-Carboplatin. All of these patients were alive a year following treatment giving an overall one-year survival rate of 47.4%. There were 8 patients (42%) who went home against medical advice while 2 (11%) died during treatment due to tumor bleed. Clinical complete response to EP/EMA was significantly influenced by the patient's age, duration and stage of disease and use of concomitant brain radiation. The use of EP/EMA caused grade 3-4 toxicity in both the remission group and non-remission group. Sixty three percent had grade 3 anemia, 37% had grade 4 leukocytopenia, 47% had grade 4 neutropenia, 47% had grade 3 hypomagnesemia, 21% and 26% with grade 2 elevated transaminases (SGPT and SGOT).

Conclusion: The EP/EMA regimen is an acceptable second line treatment for EMACO resistant GTN despite its moderately toxic effect.

Key words: Gestational trophoblastic neoplasia

Gestational Trophoblastic Neoplasia (GTN) is one of the most curable human malignancies with an overall cure rate of more than 90%.[1,2] This is mainly because of its sensitivity to chemotherapy and the availability of a sensitive tumor marker (serum ßhCG) that allows accurate monitoring of the disease. At present, cure is anticipated in all patients with non-metastatic and low risk metastatic disease treated by single agent chemotherapy. Methotrexate and Dactinomycin have been widely accepted as the first line treatment for such cases. On the other hand, high risk GTN are best treated using multiple agent chemotherapy. The first multidrug regimen for high risk trophoblastic tumors to be extensively evaluated was MAC consisting of Methotrexate, Actinomycin D and Cyclophosphamide which achieved a remission rate of 63-73%.[3,4] The CHAMOCA regimen consisting of cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, vincristine and doxorubicin was also employed for high risk patients with sustained remissions reported in 56 to 83 percent of patients. Despite its higher remission rate, the toxicities associated with it prevented widespread use of the regimen. Currently, EMACO (Etoposide, Methotrexate, Actinomycin, Cyclophosphamide and Vincristine) has emerged as the treatment of choice for patients with high risk metastatic disease (Table 1).

Since the introduction of EMACO by Newlands, et al. in 1979, the overall survival of high risk patients has improved dramatically.[5] Complete response rates and long term survival rates of over 80% have been reported by several groups.[6,7,8] Given the high response and survival rates as well as acceptable patient tolerance with regards to acute and long term toxicity, EMACO is now considered as the most effective first line treatment for metastatic high risk GTN patients.

Despite the excellent prognosis of GTN, around 10-25 percent of high risk patients still fail treatment using the EMACO regimen. [1,3,9,10] It is in this subgroup of patients that several platinum-based treatment regimens combined with surgery and radiotherapy have been used in an attempt to improve survival rate, with the least possible toxicity.

The successful use of cisplatin was first reported in 1977 in patients with disseminated testicular carcinoma including testicular choriocarcinoma.[11] In 1979, Newlands used the EP/EMA regimen (Table 2), for patients exhibiting resistance to the EMACO regimen or among those with recurrence after achieving remission with EMACO.[12] He achieved a remission in 21 of 22 patients (95%). However, the toxicity from EP/EMA was significant with grade 3 and 4 toxicity in hemoglobin, white blood cell and platelets.

Table 1. The EMACO regimen.

Regimen	Schedule
EMA	
Day 1	
ETOPOSIDE	100mg/m² in 200cc PNSS over 30 minutes
METHOTREXATE	100 mg/m² iv push and 200 mg/m² iv infusion in 1000cc of PNSS over 12 h
ACTINOMYCIN	0.5 mg iv push
Day 2	
ETOPOSIDE	100mg/m² iv infusion over 30 min
ACTINOMYCIN D	0.5 mg/iv push
FOLINIC ACID	15 mg im every 12 h for four doses beginning 24 h after start of methotrexate
Day 8	
CYCLOPHOSPHAMIDE	600mg/m² iv infusion
VINCRISTINE	1.0 mg/m² iv push

Table 2. The EP/EMA regimen.

Regimen	Schedule
EP	
Day 1	
ETOPOSIDE	100mg/m² in 200cc PNSS over 30 minutes
CISPLATIN	80mg/m² x 6 hours
Day 7	
ETOPOSIDE	100mg/m² in 200cc PNSS over 30 minutes
METHOTREXATE	100mg/m² IV bolus then 200mg/m² IV in 1 liter PNSS over 12 hours
ACTINOMYCIN D	500 ug IV bolus
Day 8	
ETOPOSIDE	100mg/m² in 200cc PNSS over 30 minutes
ACTINOMYCIN D	500 ug IV bolus
FOLINIC ACID	15 mg IM q 12h x 4 doses beginning 24 hrs from giving of MTX bolus

In the Trophoblastic Disease Section of the Philippine General Hospital, the use of EP/EMA as second line treatment was started in 1999. This study was undertaken to present our experience with EP/EMA, in terms of its efficacy and toxicity profile.

Objectives

General Objective

To review the efficacy of EP/EMA in the treatment of high risk GTN refractory to the EMACO regimen among patients who were admitted at the Philippine General Hospital from January 1999 to December 2005.

Specific Objectives

1. To describe the clinical profile of EMACO resistant GTN patients in terms of age, gravidity, parity, antecedent pregnancy, interval from last pregnancy, largest tumor size, site of metastases, serum BhCG levels, stage of disease amd FIGO risk scoring.

2. To determine the primary remission rate as well as overall one year survival rate of patients treated with EP/EMA.

3. To determine the mortality rate associated with the use of EP/EMA.

4. To compare the profile of patients who achieved remission versus those who did not achieve remission.

5. To evaluate the electrolyte imbalance, hematologic, renal and hepatic toxicities resulting from the administration of EP/EMA.

Materials and Methods

Study Design

This is a retrospective, descriptive study done to analyze the safety and efficacy of EP/EMA regimen in the treatment of EMACO resistant GTN.

Study Population

All high risk GTN patients who were treated with the EP/EMA regimen at the Section of Trophoblastic Disease of the Philippine General Hospital from January 1999 to December 2005 were included in the study. Patients with histologic diagnosis of Placental Site Trophoblastic Tumor were excluded from the study.

Methods

The weekly ward reports as well as annual reports of the Section of Trophoblastic Disease of the Philippine General Hospital from 1999-2005 were reviewed to obtain the name and case number of patients who were treated with the EP/EMA regimen. The medical records of these patients were then retrieved and reviewed. The demographic and clinical data of each patient were recorded using the patient data extraction form. The hematologic, renal and hepatic toxicities were recorded based on the WHO Toxicity Scoring System. (Table 3).

Outcome Measures

Response to treatment was monitored by serial determination of the beta hCG titer using the radioimmunoassay. Complete remission was achieved after three consecutive normal beta hCG titers. Persistent radiological or sonologic abnormalities during or after treatment are not considered evidence of disease as long as the βhCG concentration is normal. Resistance to EP/EMA, on the other hand, was diagnosed in the presence of an increase or a plateau in the hCG titers.

The efficacy of EP/EMA was assessed using the following parameters:

1. **Primary Remission Rate**, defined as the number of all EMACO resistant GTN patients who achieved remission using the EP/EMA over the total number of patients included in the study.
2. **Overall 1 year Survival Rate**, defined as the percentage of all EMACO resistant GTN patients who are alive after 1 year of treatment.

Table 3. WHO common toxicity criteria grade.

Toxicity	0	1	2	3	4
BONE MARROW					
WBC (cells/mm3)	>4	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
Platelet	WNL	75.0-normal	50-74.9	25-49.9	<25.0
Hb (g/dl)	WNL	10-normal	8.0-10.0	6.5-7.9	<6.5
Granulocytes/bands (cells/mm^3)	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Lymphocytes(cells/mm^3)	>2.0	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
GASTROINTESTINAL					
Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat	6-10 episodes in 24hr	>10 episodes in 24hr
			2-5 episodes in 24hr		
Stomatitis	None	Painless ulcers, erythema or mild soreness	Painful erythema, edema or ulcers, but can eat	Painful erythema, edema or ulcers, and cannot eat	Requires parenteral or enteral support
LIVER					
Transaminase (SGOT, SGPT)	WNL	<2.5 x N	2.5 - 5.0 x N	5.1 - 20 x N	>20 x N
KIDNEY					
Creatinine	WNL	<1.5 X N	1.5 - 3.0 x N	3.1 - 6.0 x N	>6.0 x N
ALOPECIA	No Loss	Mild hair loss	Pronounced or total hair loss	---------	----------
METABOLIC					
Hypomagnesemia(mg/dl)	>1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	<0.5
SKIN	None	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Generalized symptomatic macular, papular or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis

3. **Toxicity Grade** is a composite score of the following laboratory examination: CBC with differential count and platelet count, serum creatinine, liver enzymes (SGPT/SGOT) and serum magnesium. A rise in SGPT/ SGOT and creatinine above 2.5 x N is rated a score of 2 and onwards while values for hematologic indices and serum magnesium is reversely scored in reverse.
4. **Mortality Rate** is defined as the total number of deaths from patients treated with EP/EMA over the total number of patients included in the study.

Statistical Analysis

Descriptive statistics including medians and range were computed for continuous variables while the qualitative variables were summarized as proportions. To determine the comparability of the group who achieved remission versus those who did not achieve remission, 2-tailed Fisher exact test were employed. Association of clinical variables and outcomes were determined using chi-square test or Fisher exact test. Crude rates for remission and mortality were computed. All tests of significance were pegged at .05 alpha level of significance, 95% confidence interval using STATA version 7 software.

Results

A total of 21 patients received EP/EMA from January 1999-December 2005. However, only the records of 19 cases were retrieved. These formed the patient population of the study.

Table 4 shows the clinical characteristics of the patients included in the study. The youngest patient was a 20-year old nullipara with stage IV disease who achieved remission after another salvage platinum-based chemotherapy (paclitaxel-carboplatin) while the oldest was a 44-year old multipara also with stage IV disease but went home against advice. The median age of the sample was 28 years (range 20-44 years). Most were multigravid, while three subjects were nulliparous (10%).

In 16 subjects (84%), the antecedent pregnancy was a hydatidiform mole while in three subjects (16%), the antecedent pregnancy was a term pregnancy. The interval of disease occurrence from the last recognized pregnancy was more than 12 months in 58% of cases while in 42% the interval was from 4 to 12 months.

Majority were in the stage III and stage IV of disease (42% each respectively).

Thirteen patients (68%) had tumors more than 5 centimeters in size while 6 patients (32%) had tumors 3 to 5 centimeters in size.

The lung was the most common site of distant metastasis. In 12 cases, the lung was the only site of metastasis (56%), followed by both lungs and brain (8 cases or 30%), lungs and vagina (3 cases or 11%) ; both lungs and liver (1 case or 4%). The median serum beta-HCG level prior to start of any chemotherapeutic agent was 123,000 U/L (Range 596 – 852,000U/L). As an inclusion criteria, all had a FIGO risk score of more than 7 (high risk).

Table 4. Demographic profile of patients with EMACO-resistant gestational trophoblastic neoplasia treated with EP-EMA, UP-PGH, Jan.1999-Dec.2005.

Characteristic	Frequency (N= 19)*	Percentage (%)
Age (Years)		
Median	30.5	--
Range	20 - 44	
Gravidity		
1	2	10
2	6	32
3	3	16
>4	8	42
Antecedent pregnancy		
Hydatidiform mole	16	84
Term	3	16
Interval from last pregnancy		
4 - 12 months	8	42
> 12 months	11	58
Stage of Disease		
I	3	16
II	0	--
III	8	42
IV	8	42
Largest tumor size (cm)		
3 - 5	6	32
> 5	13	68
Sites of Metastasis*		
Lungs	15	56
Lungs & brain	8	30
Lungs & vagina	3	11
Lungs & liver	1	4
FIGO Risk Scoring		
< 7 (Low Risk)	0	--
> 7 (High Risk)	19	100
β- HCG Levels (U/L)		
Median	123,000	--
Range	596 - 852,000	

*Profile includes the two deaths
*Total organ-sites of metastasis

Clinical Outcomes of Patients

Table 5 shows the clinical outcome of patients treated with EP/EMA. Of the nineteen patients included in the study, a total of six patients achieved remission using the EP/EMA regimen giving a primary remission rate of 31.6%. An additional three patients achieved remission using a third line chemotherapeutic regimen in the form of Paclitaxel combined with Carboplatin. All patients received an additional three courses as consolidation therapy following the first normal beta hCG titer. All patients who achieved remission were alive at least one year following treatment giving an overall survival rate of 47.4%. Two patients (11%) died while on EP/EMA treatment, while eight patients (42%) went home against medical advice and were subsequently categorized as "no remission" in the study.

A total of 71 cycles of EP/EMA were given to the 19 patients included n the study. The number of EP/EMA cycles administered varied per patient. An average of 5 to 6 cycles of EP/EMA were needed to achieve remission.

Table 5. Clinical outcomes in EMACO-resistant gestational trophoblastic neoplasia treated with EP-MA, UP-PGH, Jan.1999-Dec.2005.

Outcomes	Frequency (N= 19)	Percentage (%)
Remission with EPEMA	6	32
Remission with second line agents	3	15
Home against advice*	8	42
Died during EP-MA	2	11

*Categorized as "no remission"

Toxicity Ratings

Table 6 shows the toxicity grading encountered by all the patients. Hematologic toxicities were usually encountered in these patients. Anemia was common wherein 63 percent had grade 3, 32 percent had grade 2 while 5 percent had grade 4 anemia. There were 11 percent of patients who developed grade 3 and 4 thrombocytopenia while 26 percent had grade 3 and 47 percent had grade 4 neutropenia. Grade 4 leukopenia occurred in 37 percent of patients. The most common electrolyte imbalance, hypomagnesemia, which is secondary to cisplatin occurred in all 19 patients, where 42 percent (8) had grade 3 and 16 percent (3) had grade 4. Elevated transaminases were seen in 21 percent (SGPT –grade 4) and 26 percent (SGOT- grade 2). Elevated creatinine was seen in 27 percent (7) of patients with grade 2 toxicity.

Comparison of the Remission Group and the No-remission Group

Table 7 shows the comparison between the remission group and the no remission group. The remission group consisted of those who achieved remission with EP/EMA while the no remission group consisted of those who went home against advice and those who showed resistance to EP/EMA and shifted to another salvage regimen. The two deaths were excluded.

A statistically higher median age was seen with those who achieved remission than those who did not (median = 35 years versus 26 years old, p=.021). All patients in the non-remission group had the disease a year after the last pregnancy when compared to those with remission (p=.03). There was also a statistically significant difference in terms of the distribution of the stage of the disease (p=.037) and brain radiation (p=.009).

Table 6. Toxicity grading with EP-EMA among EMACO-resistant gestational trophoblastic neoplasia, UP-PGH, Jan.1999-Dec.2005.

Toxicity Criteria		No. of Events N= 19*	(%)
Hemoglobin (g/dL)			
8 - 10	(grade 2)	6	32
6.5 - 7.9	(grade 3)	12	63
<6.5	(grade 4)	1	5
White blood cell (per mm^3)			
> 4	(grade 0)	2	11
3 -3.9	(grade 1)	1	5
2 - 2.9	(grade 2)	5	26
1 - 1.9	(grade 3)	4	21
< 1	(grade 4)	7	37
Platelet count			
Normal	(grade 0)	4	21
75 - Normal	(grade 1)	7	36
50 -74.9	(grade 2)	4	21
25-49.9	(grade 3)	2	11
< 25	(grade 4)	2	11
Absolute neutrophil count			
1.5-1.9	(grade 1)	2	11
1.0-1.4	(grade 2)	3	16
0.5-0.9	(grade 3)	5	26
< 0.5	(grade 4)	9	47
Serum magnesium			
>1.4	(grade 0)	2	11
1.4 - 1.2	(grade 1)	1	5
1.1 - 0.9	(grade 2)	5	26
0.8 - 0.6	(grade 3)	8	42
<0.5	(grade 4)	3	16
SGPT			
Within normal	(grade 0)	5	26
< 2.5 the normal	(grade 1)	10	53
2.5 - 5x the normal	(grade 2)	4	21
SGOT			
Within normal	(grade 0)	2	11
< 2.5 the normal	(grade 1)	12	63
2.5 - 5x the normal	(grade 2)	5	26
Creatinine			
< 1.5 x the normal	(grade 1)	12	63
1.5 - 3x the normal	(grade 2)	7	27

*Includes the two deaths

Table 7. Comparison of the remission group and no remission group in 17 patients with EMACO- resistant gestational trophoblastic neoplasia treated with EP-EMA, UP-PGH, Jan.1999-Dec.2005.

Characteristic	Remission		No Remission		p-value*
	N = 6	%	N = 11	%	
Age (Years)					
Median	35.5		26		.021*
Range	(25-44)		(20-36)		
Gravidity					
1	0	--	2	18.2	.32 (NS)**
2	1	16.7	5	45.4	
3	1	16.7	2	18.2	
≥ 4	4	66.6	2	18.2	
Antecedent pregnancy					
Hydatidiform mole	5	83.3	10	91	.64 (NS)**
Term	1	16.7	11	9	
Interval from last pregnancy					
4 - 12 months	5	83	2	18	.03**
> 12 months	1	17	9	82	
Largest tumor size (cm)					
3 - 5	3	50	3	27	.35 (NS)**
> 5	3	50	8	73	
Stage of Disease					
I	2	33	1	9.1	.037**
II	0	--	0	--	
III	4	67	3	27.3	
IV	0	--	7	63.6	
Timing of Hysterectomy					
After EMACO	4	66	4	36.4	.54 (NS)**
Before EMACO	1	17	4	36.4	
After EP/EMA	0	--	1	9.1	
Before MAC	0	--	2	18	
After MAC	1	17	0	--	
Brain Radiation					
Yes	0	--	8	73	.009**
No	6	100	3	27	
β - HCG prior to EP/EMA					
< 50	2		4		.46 (NS)**
100 - 500	3		3		
1000 - 5,000	1		1		
10,000 - 15,000	--		1		
20,000 - 25,000	--		0		
30,000 - 35,000	--		1		
50,000 - 60,000	--		1		
Trend of β-HCG					
Increasing	2	33	3	27	.61 (NS)**
Plateauing	4	67	8	73	
Salvage Chemotherapy					
Paclitaxel-carboplatin	0		3	27.3	.17 (NS)**
Bleomycin-Etoposide-Cisplatin	0	--	2	18.2	
MEA plus cisplatin	0	--	1	9.1	
None	6	100	5	45.5	
With treatment delay †					
1st Cycle	0	--	4	38	.03**
2nd Cycle	1	17	7	75	
3rd Cycle	4	100	1	4	
4th Cycle	0	--	2	100	
5th Cycle	0	--	1	100	
6th Cycle	--	--	1	100	
7th Cycle	--	--	1	100	

* Significant difference if p-value is <.05, Mann Whitney U Test, ** Fisher-Exact Test/Chi-square
NS- Not significant, HAA= 8, Deaths=2 † -adjusted for total cycles per patient

Table 8. Comparison of toxicity grading with EP-EMA among EMACO-resistant gestational trophoblastic neoplasia, UP-PGH, Jan.1999-Dec.2005.

Characteristic	Remission N = 6	%	No Remission N = 13	%	p-value*
Hemoglobin (g/dL)					
8 - 10 (grade 2)	3	50	3	23	.37 (NS)**
6.5 - 7.9 (grade 3)	3	50	9	69	
<6.5 (grade 4)	0	--	1	8	
White blood cell (per mm^3)					
> 4 (grade 0)	1	17	1	8	.44 (NS)**
3 -3.9 (grade 1)	1	17	0	--	
2 - 2.9 (grade 2)	2	32	3	23	
1 - 1.9 (grade 3)	1	17	3	23	
< 1 (grade 4)	1	17	6	46	
Platelet count					
Normal (grade 0)	1	17	3	23	.44 (NS)**
75 - Normal (grade 1)	1	17	6	46	
50 -74.9 (grade 2)	2	32	2	15	
25-49.9 (grade 3)	1	17	1	8	
< 25 (grade 4)	1	17	1	8	
Absolute neutrophil count					
1.5-1.9 (grade 1)	1	18	1	8	.41 (NS)**
1.0-1.4 (grade 2)	2	32	1	8	
0.5-0.9 (grade 3)	1	18	4	30	
< 0.5 (grade 4)	2	32	7	54	
Serum magnesium					
>1.4 (grade 0)	0	--	4	31	.66 (NS)**
1.4 -1.2 (grade 1)	0	--	1	8	
1.1 - 0.9 (grade 2)	0	--	4	31	
0.8 - 0.6 (grade 3)	4	67	3	23	
<0.5 (grade 4)	2	33	1	8	
SGPT					
Within Normal (grade 0)	2	33	2	25	.45 (NS)**
< 2.5 the normal (grade 1)	3	50	6	75	
2.5 - 5x the normal (grade 2)	1	17	0	--	
SGOT					
Within Normal (grade 0)	0	--	2	15	.54 (NS)**
< 2.5 the normal (grade 1)	4	67	10	77	
2.5 - 5x the normal (grade 2)	2	33	1	8	
Creatinine					
< 1.5 x the normal (grade 1)	5	63	6	46	.64 (NS)**
1.5 - 3x the normal (grade2)	1	17	7	54	

* Significant difference if p-value is <.05, Mann Whitney U Test, ** Fisher-Exact Test
NS - Not significant

No observable significant difference exists in terms of gravidity (p=.32), parity (p=.32), antecedent pregnancy (p=.64), largest tumor size (p=.35), third line salvage chemotherapy (p=.17) and timing of hysterectomy (p=.54).

The serum βhCG level prior to EP/EMA varied. In the remission group, 2 (33%) had levels below 50mIU/ml, 3 (50%) had levels below 500 mIU/ml while 1 (17%) had level below 5000.However, no significant difference was seen between the remission group and no remission group (p=0.46).

A statistically higher percentage of patients in those who did not achieve remission had treatment delays in the chemotherapy sessions during the first, second, fourth and fifth cycles (p=.03). However, no significant difference in the actual number of days of delay was seen in both groups. (p= .34). Causes of treatment delay varied and included blood transfusion in 45 percent (18 out 40 reasons), neutropenia in 20 percent (8 out of 40), financial burden in 15 percent (6 out of 40) and hypomagnesemia in 13 percent (5 out of 40 reasons).

Toxicity Ratings

Table 8 shows the toxicity grading among the remission group and the no remission group. No significant difference exists in terms of the distribution of low hemoglobin (p=.37), white blood cell count (p=.44), platelet count (p=.44), the absolute neutrophil count (p=.41), serum magnesium (p=.66), elevation in SGPT (p=.45) , SGOT (p=.54) and elevation in serum creatinine (p=.64).

Discussion

Since the introduction of chemotherapy as the primary modality for the treatment of gestational trophoblastic neoplasia, this disease has become one of the most curable malignancies in the world today. High-risk GTN patients are now treated with the EMACO regimen with around 80 percent of cases entering remission. However, despite proper and timely administration of treatment, around 10-25 percent of these patients still exhibit poor response to first line chemotherapy. Nevertheless, a good proportion of these patients could still be salvaged by second- and third-line combination chemotherapy with or without surgery and/or radiotherapy. Newlands, et al. included cisplatinum in the treatment of patients who failed the EMACO regimen. Using the EP/EMA along with salvage surgery, they reported a 65% remission rate.[12] In 2000, Newlands, et al.[13] updated their results showing an overall remission rate of 84% (30/34). However, Newlands emphasized that EP/EMA was a moderately toxic treatment regimen. In a study by Lurain, et al. in 2005[14], 26 patients failed primary treatment. Of these, 3 received EP/EMA and all went in remission. A retrospective local study by Cagayan showed EP/EMA used as salvage chemotherapy for EMACO resistant GTN with a complete remission rate of 17.6% and a mortality rate of 5.8%[15] In a recently published study by Mao Y, et al. 66.7% of patients achieved complete remission with EP/EMA.[16] The EP-EMA schedule that they used followed a weekly interval for EP and EMA. The EP is given on Day 1 followed a week after by EMA with an interval of 14 days in each cycle. This is the same treatment schedule being used in our institution.

Unlike the reported high remission rate, our study only showed a 31.6% remission rate. The low remission rate can be attributed to the late stage of the disease when the patient sought medical attention. Most of them belonged to the poor sector in the society with little knowledge of the magnitude of their disease and with limited means to seek early medical consult. Thus, most of them have extensive metastases to the lungs, liver and brain upon admission. The low remission rate can also be attributed to the high number of patients who opted to go home without completing their treatment. Approximately, 42 percent of the patients included in the study went home against medical advice. Prolonged hospital stay as well as the financial burden caused by multiple administration of chemotherapy caused these patients not to complete treatment. In this group of patients, we were unable to fully evaluate the efficacy of the EP/EMA regimen nor assess whether or not they would still respond to a third line treatment regimen. However, since these patients had either rising or plateauing ßhCG titers at the time of leaving the hospital, we could only assume that these patients succumbed to the disease upon withdrawal of treatment. With the exclusion of those

who went home against advice in the analysis of data, primary remission rate would have been 54 percent (6/11) with an overall survival rate of 81.8%.

Clinical complete response was seen in patients classified under stage I, (33%) and stage III (67%) thus no brain radiation was given to these patients. Interval from last pregnancy was also a factor for complete response as seen in patients with < 12 months interval as well as term antecedent pregnancy. It is known that the clinical variables related to survival included brain and liver metastases, interval from antecedent pregnancy greater than 12 months and antecedent term delivery. In our study, all the patients were categorized as high risk GTN, presenting with metastases to any of the following organs: the lungs, vagina, liver and brain. Clearly, the risk for resistance to chemotherapy was higher among patients with a higher stage. Patients presenting with metastatic disease whose interval from last antecedent pregnancy was more than 2 years responded poorly as observed in their serum ßhCG levels which either plateaued or increased. Even with a small study population, it was clear that remission was achieved in patients with less than 2 years interval from antecedent pregnancy and if the antecedent pregnancy was a hydatidiform mole. The higher the level of serum ßhCG prior to EP/EMA, the poorer the response to further chemotherapy as observed in the remission group. Thus, we can only overemphasize the importance of early diagnosis and prompt institution of proper treatment.

Chemotherapy can be successful if given in short intervals as tolerated by the patient. In several studies reviewed, the use of EP/EMA presented with toxicities and treatment delays. The common side effects encountered during the regimen included hematologic, electrolyte and gastrointestinal toxicities such as nausea, vomiting and stomatitis. In our study, only the electrolyte imbalance, hematologic, renal and hepatic toxicities were analyzed retrospectively. Neutropenia, thrombocytopenia and anemia caused delay in the treatment for a maximum of 7 days. In order to avoid treatment delays, several authors suggested the use of Granulocyte-Colony Stimulating Factor (G-CSF).[6,17,18] Less neutropenia, fewer infections, fewer treatment delays and fewer hospitalization days were among the several beneficial effects of G-CSF. In a case report by Hartenbach[19], the use of G-CSF given at 5 ug/kg/day subcutaneously on day 3-6 and 9-14 of each cycle of EMACO avoided treatment delays and dose reduction. However, G-CSF was not routinely used among the neutropenic patients in our study mainly because of the cost. Unlike other studies reviewed, no dose reduction was done in the treatment regimen used for the patients included in the study. These patients were managed by isolating them from other patients, performing septic work-up, providing antibiotic prophylaxis when indicated, adequate hydration with monitoring of laboratory parameters and transfusion of appropriate blood products when warranted. Most of the treatment delays were encountered in the interval within the treatment cycle, that is, in between EP (day 1 and 2) and EMA (day 7 and 8). After completing the whole cycle, the main reason for the delay of the next cycle was unavailability of chemotherapeutic drugs due to lack of funds to procure the drugs. The toxicities encountered in the study are comparable with the other studies. Toxicity grade of 3 to 4 were encountered in hemoglobin, WBC, neutrophil, platelets and grade 2 hypomagnesemia. Thus, we can say that EP/EMA is a moderately toxic treatment regimen.

The two deaths in this study had lung and brain metastases for mortality rate of 11%. They were due to hemorrhage in the lungs and brain respectively. The patient with lung metastasis received 2 doses of EP/EMA after an initial treatment with 2 cycles of MAC and 2 cycles of EMACO as well as hysterectomy. The patient with brain metastasis was initially treated with EMACO and brain radiation as well as hysterectomy however, after 2 cycles of EP/EMA succumbed to the disease. Both deaths occurred while under going treatment with EP/EMA.

Adjuvant surgery in the form of hysterectomy and/or thoracotomy, may be useful in decreasing the total number of chemotherapeutic cycles as well as removing known foci of chemotherapy-resistant disease with persistent and recurrent high risk gestational trophoblastic neoplasia. At the Brewer Center, surgery, including hysterectomy, pulmonary resection, splenectomy, craniotomy and cornual resection of the uterus, has played an important part in the management of most of these patients.[14,17] In

our study, only one patient had hysterectomy during the EP/EMA regimen since most of the patients already had the procedure earlier on in their treatment.

A number of newer anticancer agents have not been fully evaluated including taxanes (paclitaxel, docetaxel), gemcitabine and temozolomide. In this review, 3 patients had resistance to EP/EMA thus paclitaxel-carboplatin combination was used with associated good response however, outpatient follow-up on these patients was not assessed. The BEP (Bleomycin-Etoposide-Cisplatin) protocol was used as the first chemotherapy of choice for patients who had relapse or who were refractory to EP/EMA in some centers.[20] Two of our patients who showed resistance to EP/EMA were given BEP however, these patients went home against advice. Other trophoblastic disease centers have reported an occasional success in treating these patients with high dose ifosfamide and carboplatin with or without etoposide along with autologous bone marrow transplantation or peripheral stem cell support.[20] Therefore, high success rates have been encountered with the use of intensive multimodality therapy with adjuvant radiotherapy and surgery.

Conclusion

The treatment of gestational trophoblastic neoplasia represents one of the success stories in modern cancer medicine. Early diagnosis, sensitivity to chemotherapy, availability of a sensitive tumor marker and provision of care in a specialty center have all contributed to this success. Continued awareness and education is therefore required, so that GTN is detected as early as possible, thereby reducing the mortality rate. The early diagnosis in patients can reduce the occurrence of brain and/or liver metastases and in turn reduce the poor prognosis of these patients.Time interval between antecedent pregnancy and onset of chemotherapy is crucial to the prognosis of this disease.

The use of EP/EMA as a second line treatment for EMACO resistant GTN can be very promising provided there is correct timing of chemotherapy and prevention of possible toxicities. Adjuvant surgery and radiotherapy have also played an important role in the management of these patients. Despite its moderately toxic effect as compared to EMACO, dose reduction or addition of preventive measures can be done to reduce toxicity.

Recommendations

Further efficacy analyses can be performed using a higher sample size in a comparative trial design. Furthermore, provision of treatment in a controlled setting where measures can be undertaken to avoid delays due to toxicities or unavailability of drugs should be taken into consideration.

References

1. Hammond CB, Borchert LG, Tyrey L, Creasman W, Parker L. Treatment of metastatic trophoblastic disease: Good and poor prognosis. Am J Obstet Gynecol 1973; 451-457.
2. Lurain JR, Brewer JI, Torok EE, Halpern B. Gestational trophoblastic disease center. Obstet Gynecol 1982; 60: 354-360.
3. Berkowitz RS, Goldstein DP, Bernstein MR. Modified triple chemotherapy in the management of high risk gestational trophoblastic tumors. Gynecol Oncol 1984; 19: 173-181.
4. Hammond CB, Borchert LG, et al. Treatment of metastatic gestational trophoblastic disease: good and poor prognosis.Am J Obstet Gynecol 1973; 115: 451-457.
5. Newlands ES, Bagshawe KD, Begent RHJ, et al. Development in chemotherapy for medium and high risk patients with gestational trophoblastic tumors,1979-1984. Br J Obstet Gynecol 1986; 93; 63.
6. Newlands ES, Bagshawe KD, Begent RHJ, et al. Results of EMACO regimen in high risk GTT, 1979-1989. Br J Obstet Gynecol 1991; 98: 550-557.
7. Schink JC, Singh DK,Rademaker AW, et al. EMACO for treatment of metastatic high risk GTD. Obstet Gynecol 1992; 50: 817-820.
8. Escobar P, Lurain J, Singh D. Treatment of high risk GTN with EMACO. Gynecol Oncol 2003; 91: 552-557.
9. Surwit EA, Alberts DS, Christian CD, Graham VE. Poor prognosis gestational trophoblastic disease: an update. Obstet Gynecol 1984; 64: 21-26.
10. Lewis JL Jr. Current status of treatment of gestational trophoblastic disease. Cancer 1976; 38: 620-626.
11. Higby DJ, Wallace HJ, et al. Diamminedichloro-platinum in the chemotherapy of testicular tumors. J Urol 1974; 112: 100-104.
12. Newlands ES, Bower M, Holden L, et al. Management of resistant GTT.J Reprod Med 1998; 43: 111-118.
13. Newlands ES, Mulholland PJ, Holden L, et al. EP/EMA for patients with high risk GTT refractory to EMACO and patients presenting with metastatic PSTT. J Clin Oncol 2000; 18: 854-859.
14. Lurain J, Nejad B. Secondary chemotherapy for high risk GTN. Gynecol Oncol 2005; 97: 618-623.

15. Cagayan MS, Gacoba MC. Chemotherapy regimens used in the treatment of gestational trophoblastic neoplasia at Philippine General Hospital. Treatment outcomes and toxicity. J Reprod Med 2006; 51(11).
16. Mao Y, Wan X, Lu W,Xie X. Relapsed or refractory GTN treated with the EP/EMA regimen. Int J Gynecol Obstet 2007.
17. Lurain, JR. High risk metastatic GTT. Current management. J Reprod Med 1994; 39: 217-222.
18. Neidhart JA. Hematopoeitic colony-stimulating factors: uses in combination with standard chemotherapeutic regimens and in support of dose intensification. Cancer 1992; 70: 913-920.
19. Hartenbach E, Saltzman A, et al. A novel strategy using G-CSF to support EMACO for high risk GTD. Gynecol Oncol 1995; 56: 105-108.
20. Lurain JR. Advances in management of high risk gestational trophoblastic tumors. J Reprod Med 2002; 47: 451-459.

Synchronous Squamous Cell Carcinoma of the Cervix and Ovarian Germ Cell Tumor: A Case Report

Mary Evangeline A. Villa-Mercado, MD and Maria Julieta M. Victoriano-Germar, MD

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

We are presenting the case of a 41 year old, G3P2 (2012) who was diagnosed to have squamous cell carcinoma, large cell non-keratinizing cervix, stage IIIB. She underwent exploratory laparotomy, bilateral salpingo-oophorectomy, infracolic omentectomy, lymph node assessment because of large bilateral adnexal masses. Histopathology showed dysgerminoma on the right ovary and mixed germ cell tumor on the left ovary: dysgerminoma 80%, yolk sac tumor 20%. The patient was subsequently staged as squamous cell carcinoma, cervix, stage IIIB; dysgerminoma, right ovary; mixed germ cell tumor, left ovary, stage IC. Postoperatively, the plan was to give concurrent chemoradiation followed by chemotherapy with bleomycin, etoposide, and cisplatin for 4 cycles. Unfortunately, the patient expired due to renal complications before concurrent chemoradiation could be started. This is the first reported case of synchronous tumor consisting of a squamous cervical neoplasm and ovarian germ cell tumors.

Key words: squamous cell carcinoma of the cervix, dysgerminoma, mixed germ cell tumors, synchronous tumors

Multiple primary gynecologic neoplasm is a relatively uncommon, but a well recognized phenomenon. Since Theodore Billroth first documented such cases in 1889, there has been more than 30,000 reported cases in the literature involving different combinations of gynecologic organ.

This concept of simultaneously occurring tumors is still poorly understood and continues to pose diagnostic and therapeutic dilemma for physicians confronted with such cases. Several questions are usually raised in an attempt to understand such complex disease entity.

1. Are we dealing with 2 separate primary tumors or is this metastatic?
2. Is it just a mere coincidence or is there a common carcinogenic event that led to their development?
3. How are cases of multiple primary tumors staged and managed?

* Second placer, 2007 SGOP Fellows' and Residents' Interesting Case Contest.

4. Is the prognosis altered by multiple malignancies?

We report a simultaneously detected ovarian germ cell carcinoma and a squamous cell carcinoma of the cervix. Related literature was reviewed and it appeared that no similar case has been documented previously.

The Case

The patient is a 41 year old, G3P2 (2012) who presented with a 3 month history of foul-smelling vaginal discharge accompanied by hypogastric pain and abdominal enlargement. Her past medical and family history were both unremarkable. She is married and a housewife. Her first coitus was at 18 years old and had only 1 sexual partner. She had no vices, history of oral contraceptive pill or IUD use and history of Pap smear done.

She had her menarche at 13 years old. Subsequent menses would occur regularly at monthly intervals, lasting for 3 days, soaking 4 pads/day. Her last normal menses was in November 2006.

Three months prior to her admission in November, she noted foul-smelling vaginal discharge associated with hypogastric pain. She consulted a private OB gynecologist who did a cervical punch biopsy which showed a poorly differentiated squamous cell carcinoma. She was referred to our Gynecologic Oncology Clinic for further evaluation and management. A repeat punch biopsy was done which showed possibility of small cell carcinoma. Immunohistochemistry showed positive for cytokeratin (Figure 1) while negative for LCA and chromogranin. Final histopathology showed squamous cell carcinoma, large cell, non-keratinizing. (Figure 2)

On consult at the clinic, she had stable vital signs. Heart and lung findings were essentially normal. Abdominal findings showed a non-tender, movable abdominopelvic cystic mass extending up to the level of the umbilicus. On internal examination, the patient had normal external genitalia, the cervix was converted to a nodular, fungating mass, 8 cm x 8 cm involving the upper half of the anterior and lateral vaginal wall, corpus 14 weeks size, with a cystic, movable mass at the left adnexa ~ 15 cms, both parametria nodular and fixed.

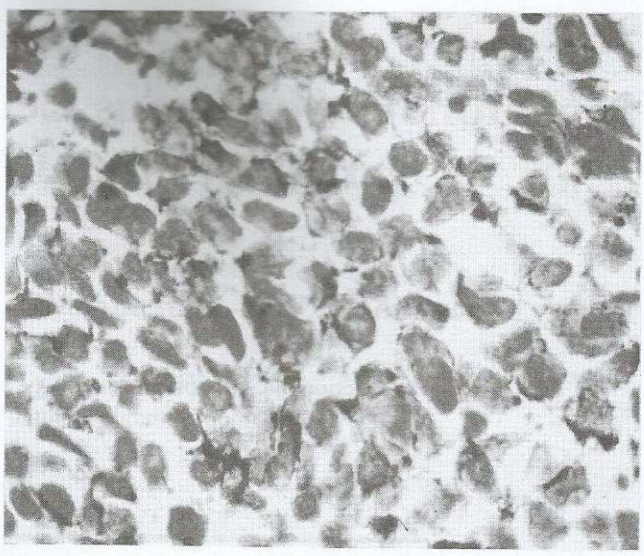

Figure 1. Squamous cell carcinoma, cervix cytokeratin positive.

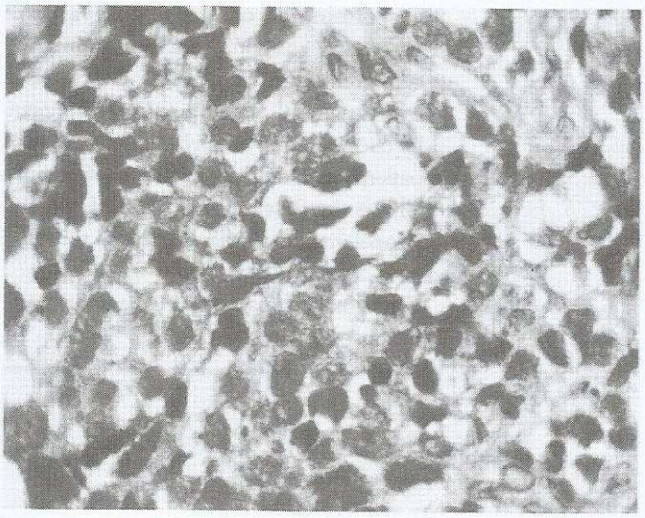

Figure 2. Squamous cell carcinoma, cervix.

The transvaginal ultrasound done showed a normal-sized uterus with minimal endometrial fluid; large cystic masses, both adnexae. Preoperative impression was squamous cell carcinoma, large cell, non-keratinizing, cervix, IIIB; ovarian new growth, probably malignant, metastatic vs. primary. She subsequently underwent exploratory laparotomy, bilateral salpingo-oophorectomy, infracolic omentectomy, lymph node assessment. Intraoperative findings were as follows:

There was 2L of straw colored ascites.

The surfaces of the liver, spleen, stomach, intestines, appendix, subdiaphragmatic area were smooth and grossly normal. There were no palpable pelvic or paraaortic lymph nodes.

The right ovary was converted to a 15 cm x 12 cm x 10 cm multiloculated predominantly cystic mass. The external capsule was smooth (Figure 3). On cut section, there was egress of hemorrhagic fluid. The inner wall of the cystic mass was smooth with no excrescences. There was a 10 cm x 8 cm x 4 cm solid, friable, hemorrhagic area (Figure 4). The left ovary was converted to a 17 cm x 10 cm x 10 cm multiloculated predominantly cystic mass. The external capsule was also smooth (Figure 5). On cut section, there was egress of hemorrhagic fluid. The inner wall of the cystic mass was smooth with no excrescences. There was a 6 cm x 6 cm x 3 cm solid mass within with areas of necrosis and hemorrhage (Figure 6). Both ovaries were free of adhesions. Intraoperatively, both ovaries were inadvertently ruptured. The uterus was slightly enlarged but with smooth, serosal surface. Both superior portions of the parametria were smooth with no note of nodularities. However, nodularities were noted on the inferior aspect lateral to the cervix over the cardinal ligaments. The cervix was bulky and nodular on palpation. The cul de sac was smooth. Both fallopian tubes were normal but were stretched along the ovarian masses. The rest of the pelvic organs were grossly normal.

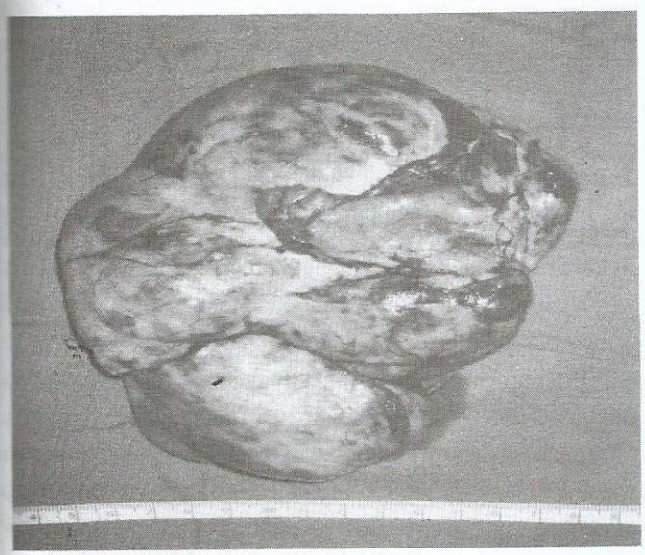

Figure 3. Dysgerminoma, right ovary.

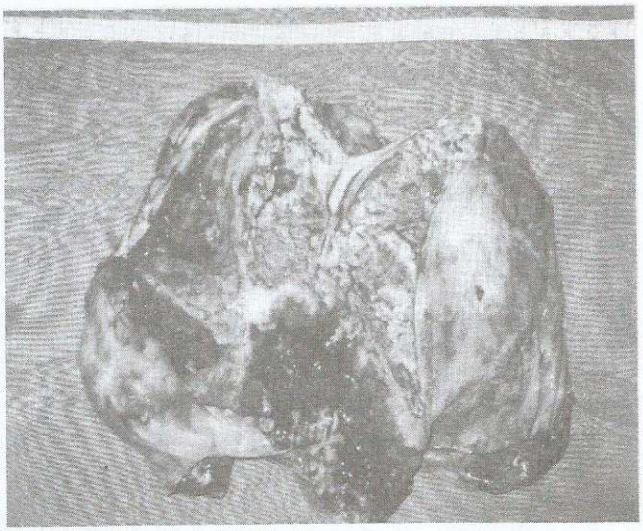

Figure 4. Dysgerminoma, left ovary.

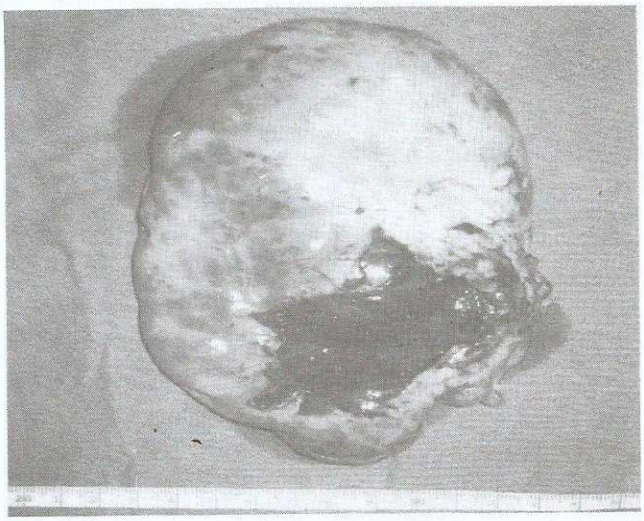

Figure 5. Mixed germ cell tumor, left ovary.

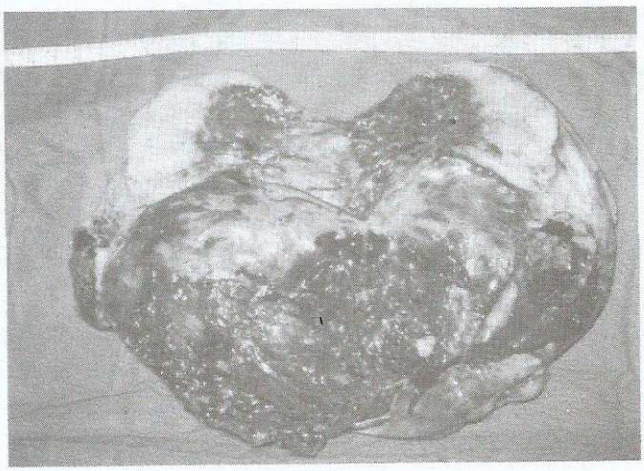

Figure 6. Mixed germ cell tumor, left ovary.

Histopathology showed: A) Dysgerminoma, right ovary. (Figures 7A & 7B) No diagnostic abnormality recognized, right fallopian tube. B) Mixed Germ Cell tumor, left ovary: dysgerminoma 80%, yolk sac tumor 20%. (Figures 8A & 8B) No diagnostic abnormality recognized, left fallopian tube: Negative for tumor, omentum.

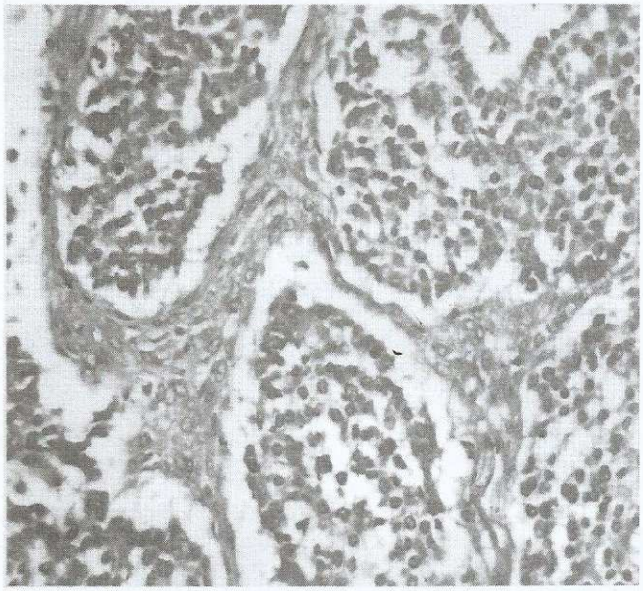

Figure 7A. Dysgerminoma, right ovary. Low power view. Note the presence of large, round, ovoid or polygonal cells with stroma infiltrated by lymphocytes.

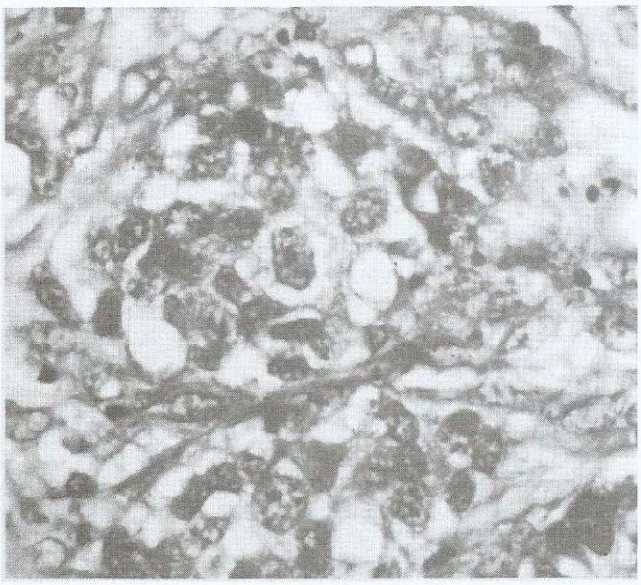

Figure 7B. Dysgerminoma, right ovary. High power view. Note the presence of large, round, ovoid or polygonal cells with stroma infiltrated by lymphocytes.

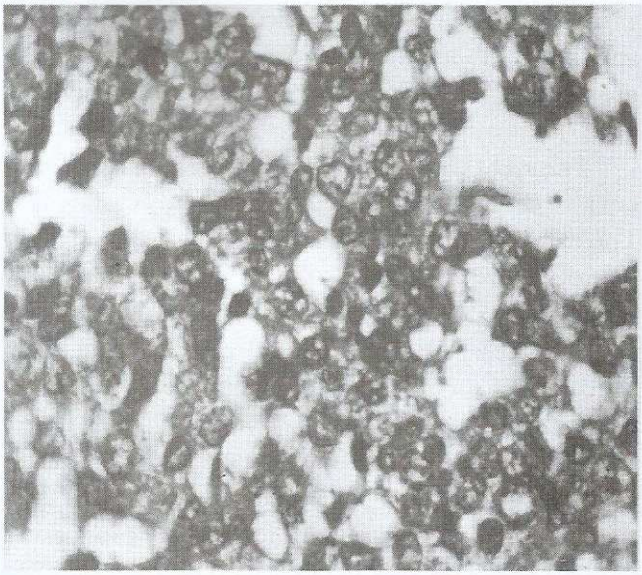

Figure 8A. Dysgerminoma component, left ovary . Note the presence of large, round, ovoid or polygonal cells with stroma infiltrated by lymphocytes.

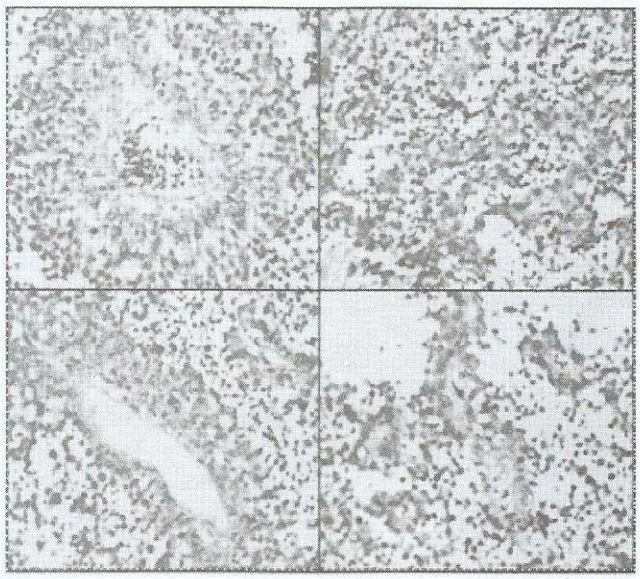

Figure 8B. Yolk sac component, left ovary. Note the papillary projections containing single blood vessel and having peripheral lining of neoplastic cells (Schiller-Duval Body).

Postoperatively, the plan for the patient was to undergo concurrent chemoradiation followed by chemotherapy with bleomycin, etoposide, and cisplatin for 4 cycles. Unfortunately, the patient succumbed to acute renal failure and eventually expired before concurrent chemoradiation could be started.

Discussion

Multiple primary malignancies can either be synchronous or metachronous tumors. Synchronous tumors are defined as tumors that occur, or are diagnosed at the same time, or secondary tumors that occur within 12 months. Metachronous tumors occur at different times usually greater than 1 year after the primary neoplasm.[1]

Ovarian and endometrial cancers are the most common synchronous genital primary tumors.[2,3,4,5] Coexistence of ovarian and cervical tumors have been reported in the past, although, rarely.

In 1961, Moertel, et al. reported 6 cases of cervical and ovarian cancer among 921 cases of double primary tumors derived from multiple tissues of origin.[6] In 1983, LiVolsi reported 4 cases of endocervical adenocarcinoma coexisting with ovarian mucinous adenocarcinoma.[7]

In the Downstate Medical Center Tumor Registry, Axel, et al. in 1984 noted the occurrence rate of synchronous gynecologic malignancies in patients with gynecologic tumor was 1.78% and 3 out of 2362 patients were cases of synchronous invasive cervical and ovarian cancer. In 1989, a single case of synchronous ovarian and cervical tumors (0.025%) out of 26 patients (0.7%) with invasive synchronous female genital malignancies was recorded in the UCLA tumor registry over a 30-year period.[2]

In 1990, Miller, et al. reported a simultaneously occurring small cell carcinoma of the cervix and adenocarcinoma of the ovary.[8] In 1994, Ilesanmi, et al. reported 4 cases of synchronous carcinoma of the cervix and ovary. In all cases the ovarian and cervical tumors were adenocarcinoma.[9]

In 2004, there were 2 cases of synchronous ovarian and cervical cancers in 861 women with gynecologic tumors in Taiwan. One of the cervical cancers was squamous cell carcinoma and the other was adenosquamous carcinoma. The ovarian cancers were both serous cystadenocarcinoma.[6]

In 2006, a case of ovarian endometrioid adenocarcinoma and endocervical mucinous adenocarcinoma was reported.[6] On the same year, Ferchichi, et al. reported another case of ovarian mucinous adenocarcinoma and endometrioid adenocarcinoma of the cervix.[10]

Our patient presented with a rare synchronous primary gynecologic tumors of ovarian germ cell and squamous cell carcinoma of the cervix. This is the first case with such histology yet to be reported.

Determining the nature of the ovarian and cervical tumors for our patient was straightforward because it satisfied the criteria set by Warren and Gates in 1932, namely:

1. Each of the tumors must present a definite picture of malignancy.
2. Each must be distinct.
3. The probability that one is a metastatic lesion from the other must be excluded.

The histologic appearance of the ovarian germ cell tumors is, undoubtedly, completely different from that of a squamous cervical carcinoma and excludes the possibility of metastasis of one tumor to the other.

This case is noteworthy not only because it is the first of its kind. The most common histology reported for the few cases of synchronous ovarian and cervical tumors reported involved mucinous type. The concept of "extended mullerian system" is theorized to partly explain the development of synchronous mucinous ovarian and cervical tumor. This theory is based on the embryonic pathway by which the mullerian ducts are formed. Mullerian ducts arise by the invagination of the coelomic epithelium. They evolve to become the serous (tubal), endometrioid (endometrium), and mucinous (cervix) epithelia. Coelomic epithelium, on the other hand, is incorporated into the ovarian cortex.[11,12] Since both are ultimately derived from coelomic epithelium and subcoelomic mesenchyme, it may not be surprising to find similar histopathologic epithelia at separate foci given a carcinogenic stimuli.[3,11,13] This view cannot be invoked in our case. Germ cell tumors arise from an embryonal defect in the pathway of the development and differentiation of primordial cells which will explain why germ cell tumors are common in younger age groups including adolescents and reproductive age while squamous cell carcinoma of the cervix arose from multiple cervical insults and HPV-related mutation causing tumorigenesis. They are common in women in the premenopausal and menopausal age. Thus, we wonder: How was it that two tumors associated with different histopathogenesis and opposite spectrum of

age range would occur simultaneously? Why did the germ cell tumor of our patient manifested at a relatively late age? Was there a common carcinogenic event that could have triggered the simultaneous development of these 2 entirely distinct disease entity or was it merely coincidental?

The patient was subsequently staged as Squamous cell carcinoma, cervix, stage IIIB; Dysgerminoma, right ovary; Mixed germ cell tumor, left ovary, stage IC. Its implication in the course and prognosis is not certain.

In general, synchronous double primary cancers have a more favorable prognosis than a single metastatic lesion. In the more studied cases of synchronous endometrioid tumors of the ovary and endometrium, they tend to be of low grade and early stage, with excellent prognosis. [15,17] Our patient already presented with an advanced stage of cervical cancer. Prognosis in itself is poor. On the other hand, although still with an early ovarian carcinoma, the yolk sac tumor component is responsible for the very aggressive behavior of mixed germ cell tumor when combined with dysgerminoma. Thus, we can deduce that this is an aggressive combination.

Because of the limited cases of independent ovarian and cervical tumors reported and the different combinations of histology involved, the behavior, aggressiveness and prognosis of these tumors taken together are uncertain. Even the therapeutic options are not conclusive. It is interesting also to note that both dysgerminoma and squamous cell carcinoma of the cervix have predilection for lymphatic spread and are radiosensitive. Thus, concurrent chemoradiation could address both ovarian and cervical tumors. However, because of the yolk sac component of the mixed germ cell tumor, chemotherapy is warranted. Our plan for the patient is for concurrent chemoradiation followed by 4 cycles of bleomycin, etoposide, and cisplatin. Unfortunately, the patient expired due to complications of obstructive uropathy before any postoperative chemoradiation can be started.

Summary and Conclusion

The uncertainty of one tumor's influence over another with regards to its tumorigenesis, behavior, nature, prognosis and treatment make this disease entity unique and complicated. Slowly, molecular advances in technology are making it possible to analyze the nature and behavior of the different tumors.[16,17,18] However, in spite of increasing number of cases of synchronous tumors reported through the years, it is still not enough to gain the necessary knowledge and experience in coming up with the most logical and definite answers to inquiries previously raised. Until such time that this knowledge can be translated to improvement in the prognosis and survival of the patient, it remains to be a diagnostic and therapeutic challenge.

References

1. Rose PG, Herterick EE, Boutselis JG, et al. Multiple primary gynecologic neoplasms. Am J Obstet Gynecol 1987; 261-267.
2. Axelrod J, Fruchter R, Boyce J. Multiple primaries among gynecologic malignancies. Gynecol Oncol 1984; 18: 359-372.
3. Eisner RF, Nieberg R, Berek J. Synchronous primary neoplasm of the female reproductive tract. Gynecol Oncol 1989; 33(3): 335-339.
4. Kucukali T. Synchronous primary malignancies of female genital tract. Eur J Obstet Gynecol Reprod Biol 1992; 45: 63-66.
5. Silverman BB, O'Neill R, Mikuta JJ. Multiple malignant tumors associated with primary carcinoma of the ovary. Surg Gynecol Obstet 1972; 134: 244-248.
6. Huang, et al. Synchronous ovarian endometrioid adenocarcinoma and endocervical mucinous adenocarcinoma. Taiwanese J Obstet Gynecol 2006; 45(3): 264-267.
7. LiVolsi VA, Merino MJ, Schwartz PE. Coexistent endocervical adenocarcinoma and mucinous adenocarcinoma of ovary: a clinicopathologic study of 4 cases. Int J Gynecol Pathol 1983; 1(4): 391-402.
8. Miller B, El-Torky M, Photopulus G. Simultaneous small cell carcinoma of the cervix and adenocarcinoma of the ovary. Gynecol Oncol 1990; 39: 99-102.
9. Ilesanmi AO, Edozien LC, et al. Synchronous carcinoma of cervix and ovary: case reports. Afr J Med Med Sci 1994; 23(4): 397-400.
10. Ferchichi L, Rammeh-Rommani S, Hammouda B, et al. Gynecol Obstet Fert 2006; 34 (5): 410-412.
11. Fausto N, Kumar V, Albao A. Robbin's and Cotran Pathologic Basis of Disease. 7th edition, Philadelphia: Saunder, 2005.
12. Woodruff JD, Solomon D, Sullivant H. Multifocal disease in the upper genital canal. Obstet Gynecol 1985; 65: 695-698.
13. Kaminski, et al. Coexistence of ovarian neoplasms and endocervical adenocarcinoma. Obstet Gynecol 1984; 4: 553-556.
14. Kumar J. Blaustein's Pathology of the Female Genital Tract. 5th edition, New York: Springer, 2002.

15. Falkenberry SS, Steinhoff MM, Gordinier M, et al. Synchronous endometrioid tumors of the ovary and endometrium. J Reprod Med 1996; 41(10): 713-718.
16. Elishev E, Gilks CB, Miller D, Srodon M, Kuman RJ, Ronnett BM. Synchronous and metachronous endocervical and ovarian neoplasms: evidence supporting interpretation of the ovarian neoplasms as metastatic endocervical adenocarcinomas simulating primary ovarian surface epithelial neoplasms. Am J Surg Pathol 2005; 29: 281-294.
17. Matias-Guiu X, Lagarda H, Catasus L, et al. Clonality analysis in synchronous or metachronous tumors of the female genital tract. International Society of Gynecological Pathologists 2002; 21(3):205-211.
18. Smit V, Cornelisse C, De Jong D, et al. Analysis of tumor heterogeneity in a patient with synchronously occurring female genital tract malignancies by DNA flow cytometry, DNA fingerprinting and immunohistochemistry. Cancer 1988; 62: 1146-1152.

Rare Cutaneous Recurrence in Early-Stage Squamous Cell Carcinoma of the Uterine Cervix

Scheryll B. Pua, MD; Rey H. de los Reyes, MD, MHSA and Benjamin D. Cuenca, MD

Section of Gynecologic Oncology and Trophoblastic Disease,
Jose R. Reyes Memorial Medical Center

Disease recurrence is a dreadful event for any seeming cancer survivor. A 52-year old, multipara who was diagnosed with early-stage cervical squamous cell carcinoma underwent radical hysterectomy, bilateral salpingo-oophorectomy, bilateral lymph node dissection and adjuvant pelvic external beam radiation (EBRT) concurrent with three cycles of single-agent cisplatinum chemotherapy. After remaining in remission for 20 months, an umbilical mass and papular lesion over the incision scar at the hypogastrium developed. Histopathology revealed metastatic squamous cell carcinoma. Salvage chemotherapy with Cisplatin-Cyclophosphamide regimen was started for three cycles but was shifted to Cisplatin-Topotecan regimen due to disease progression. Cutaneous recurrence is considered a pre-terminal event. Though there is still no established chemotherapy regimen for recurrent cutaneous cervical carcinoma, cisplatin-based chemotherapy is considered for palliative intent.

Key words: early-stage cervical cancer, squamous cell carcinoma, radical hysterectomy, cutaneous recurrence, salvage chemotherapy

Cervical carcinoma, although largely preventable, is one of the most prevalent cancers worldwide. Early-stage disease can be successfully treated with surgery alone, while locally advanced cases are treated with radiation and concurrent weekly cisplatin chemotherapy.

Disease persistence or recurrence is a stressful experience to the patients and attending physicians alike, since it spells a 1-year survival rate of 10-15%.[4] Recurring cervical cancers are often local although distant metastases can occur and most often seen in the lungs (40.4%), bone 33.3%, peritonitis carcinomatosis (26.7%) and liver (13.3%).[6] Involvement of the skin is quite rare in cervical cancer with a reported incidence of 0.1-2.0 %.[7,9] Among those with cutaneous sites of recurrence, the more commonly reported sites of primary disease in decreasing order are the breast, large intestine, lung, kidney and ovary.[6,7,14] This paper presents an early-stage cancer of the cervix, adequately treated with surgery, which developed a rare cutaneous recurrence.

Treatment is directed toward palliation with systemic chemotherapy. Although platinum-based chemotherapy is most often employed, no standard

* Third placer, 2007 SGOP Fellows' and Residents' Interesting Case Contest.

chemotherapeutic regimen has so far been established for patients with cutaneous pattern of recurrence.

Objectives

General Objective

This study aimed to present a case of an early-stage squamous carcinoma of the cervix with rare cutaneous pattern of recurrence after an adequate primary surgical treatment.

Specifically, it aimed to:

1. Discuss the pathophysiologic mechanisms of cutaneous recurrence and metastasis in cervical cancer,
2. Present the efficacy of various chemotherapeutic agents for cutaneous metastasis, and
3. Review the value of other treatment modalities for such condition.

Case Profile

Fifty-two year old L.R., a G4P3 (3013), was initially seen due to vaginal bleeding of one month duration. Two weeks prior to consult, bleeding became moderate consuming 1-2 pads per day. No consultation was done or medications taken until a few days prior to consult when bleeding became profuse. Consultation was sought in this institution where speculum examination showed a suspicious cervix which easily bled. A cystic, movable, non-tender left adnexal mass measuring 5.0 cm x 5.0 cm was also noted which was probably dermoid on ultrasound. The cervix was described to be eaten-up with an ill-defined stroma and complex echoes suggestive of blood clots. On internal examination, the cervix was firm and smooth measuring 3.0 cm x 3.0 cm, the vaginal walls and fornices were also smooth, the corpus was not enlarged, with no right adnexal mass or tenderness. A movable, non-tender mass was noted on the left adnexa measuring 5.0 cm x 5.0 cm. Rectovaginal examination revealed free and pliable parametria.

Colposcopy showed thick acetowhite epithelium with mosaic pattern at the anterior cervical lip. Biopsy revealed squamous cell carcinoma, large cell non-keratinizing (SCCA, LCNK) type. Diagnosis at this point was Cervical Squamous Cell Carcinoma, Large Cell Non-Keratinizing type, Stage IB1; Ovarian New Growth, left, probably Dermoid cyst.

Radical hysterectomy, bilateral salpingo-oophorectomy, bilateral lymph node dissection (RH BSO BLND) was undertaken. Intra-operatively, all the visceral and parietal surfaces were smooth. There were no palpable para- and peri-aortic lymph node. The corpus was smooth, tan-brown, measuring 5.0 cm x 5.0 cm x 3.0 cm. Cut section showed a smooth cavity with a depth of 3.2 cm, thin and smooth endometrium (2.0 mm). The anterior myometrium measured 2.0 cm while the posterior was 2.2 cm. The ectocervix showed some erosions and ulcerations and measured 3.0 cm x 3.5 cm x 3.5 cm. The endocervical canal measured 3.0 cm containing a yellowish tan, rubbery, friable mass measuring 3.0 cm x 3.0 cm with more than 50% cervical stromal invasion. The vaginal cuff was likewise smooth measuring 4.0 cm. The parametria were not suspicious and measured 5.0 cm x 4.0 cm on each side. The left ovary was cystically enlarged to 5.0 cm x 4.0 cm x 3.0 cm with tan pink, smooth surface cut section of which showed sebaceous material with ball of hair and cartilage. The right adnexa and left fallopian tube were grossly normal. The right obturator lymph nodes showed firm, tan-to-pink nodules with areas of necrosis. The rest of the lymph nodes harvested were not suspicious for tumor involvement.

Final histopathology confirmed squamous cell carcinoma, lung cell non-keratinizing (SSCA, LCNK) cervix, dermoid cyst, left ovary, lymph nodes harvested from the right obturator area were positive for malignant cells (Figures 1-3). Adjuvant external beam radiotherapy (EBRT) of 5000 cGy was given concurrently with 3 courses of cisplatin (at a dose of 75mg/m) chemotherapy every three weeks.

She was, however, lost to follow up for 15 months after the completion of treatment. She only showed up 20 months after, apparently with no clinical evidence of disease. Two months later, however, a weeping nodular mass at the umbilical area measuring 1.0 cm x 1.0 cm and pruritic plaques developed at the inferior

third of the incisional scar at the hypogastrium (Figures 4-5). Pelvic examination was unremarkable. Biopsy of the umbilical mass and skin lesions revealed SCCA (Figure 6).

Whole abdominal CT scan revealed a suspicious solitary hypodense nodule in the liver and the spleen suggestive of metastasis. There was no evidence of abdominal lymphadenopathy (Figures 7-8).

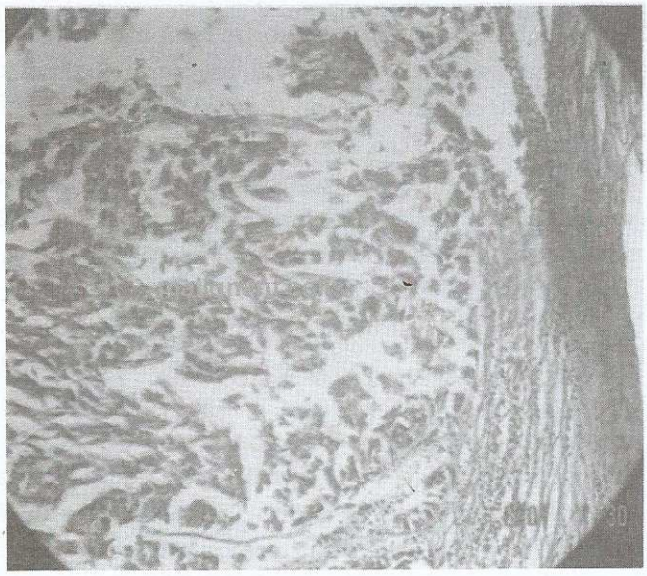

Figure 1. High power view of the cervical tumors.

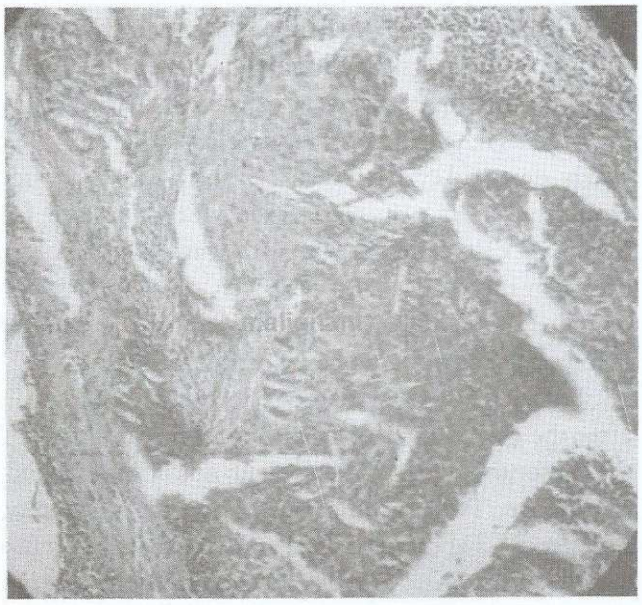

Figure 2. High power view of the lymph node involvement.

Figure 3. High power view of the left ovarian cyst with ectodermal derivative.

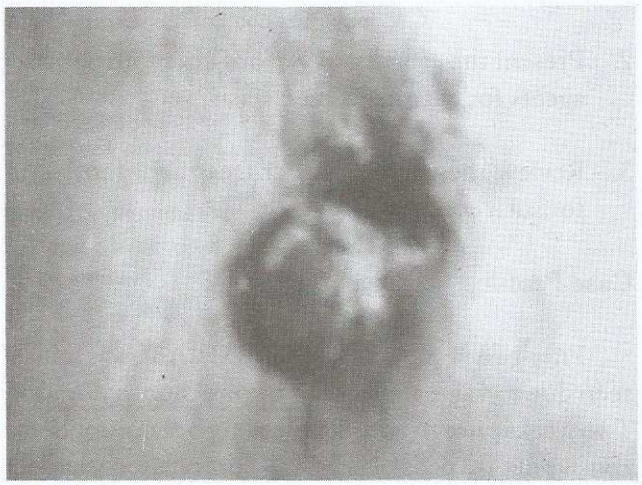

Figure 4. Umbilical mass.

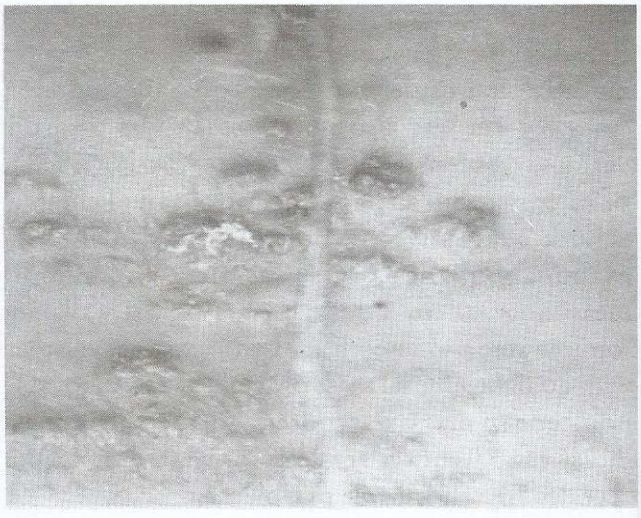

Figure 5. Hypogastric lesions.

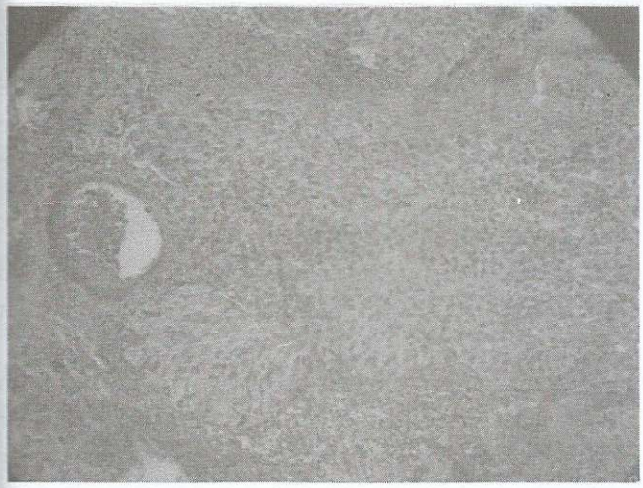

Figure 6. High power view of the cutaneous lesions.

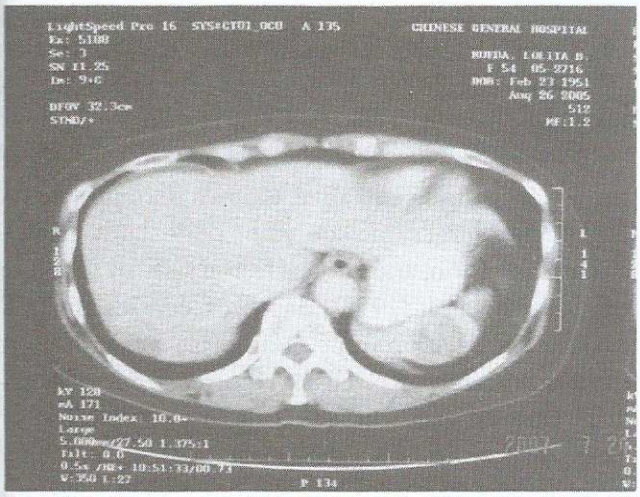

Figure 7. Liver metastasis.

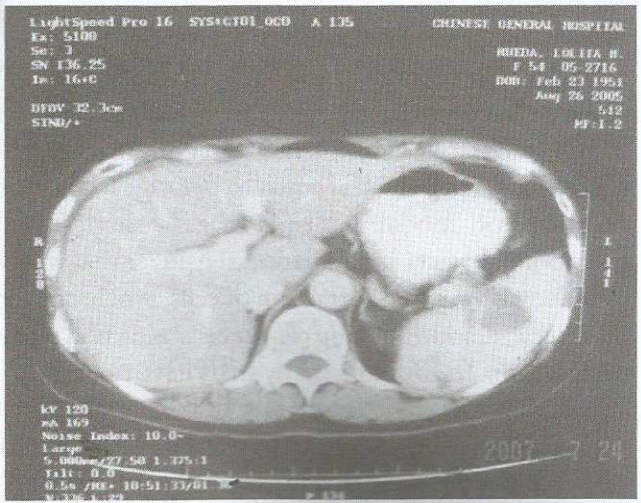

Figure 8. Splenic metastasis.

Chemotherapy with double-agent cisplatin-cyclophosphamide was advised but she got lost to follow again for another 7 months (August 2005 to March 2006) despite thorough counseling. Upon her return, there was no significant change in the size of the masses and hypogastric lesions. While seeking funds in the next four months, the lesions gradually increased in size and became more edematous and erythematous extending to the entire hypogastric area. Three cycles of cisplatin-cyclophosphamide were given every 3 weeks with delays in between from July to October 2006, which failed to afford significant improvement (Figure 9). Due to problems in funding, the fourth course of chemotherapy was not given until five months later. The lesions were observed to be progressive (Figure 10).

A decision to change the chemotherapeutic regimen to cisplatin-topotecan combination was arrived at with palliative intent. She has so far received one course of salvage therapy.

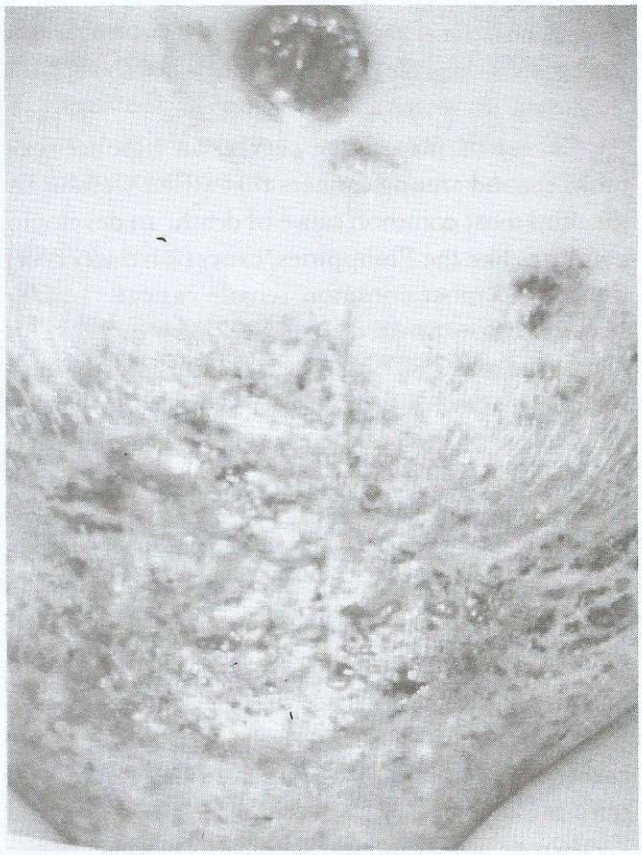

Figure 9. Skin lesions during cisplatin-cyclophosphamide.

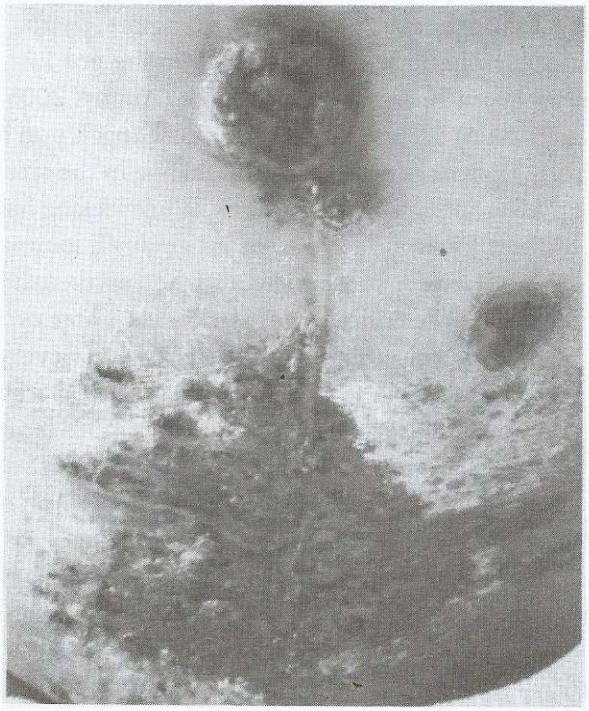

Figure 10. Skin lesions prior to Cisplatin-Topotecan chemotherapy.

Discussion

Cancer of the uterine cervix, on a global scale, ranks second among cancers that afflict women and the third most common cause of death. In developing countries like the Philippines, cancer of the cervix is the second most common female cancer. In 2005 alone, it was estimated that 7,277 new cases will be diagnosed and 3,807 cases will result to death due to this malignancy.[1]

Cancer of the uterine cervix is preventable. The presence of good screening test in an equally effective program leads to the early diagnosis of precursor lesions, hence, the dramatic decrease in the incidence from being the second to the ninth most common cancer in women in the developed countries. In the United States, majority of cases are diagnosed in the premalignant or early-stage disease. In the report of SEER program on 13,456 staged patients with cervical carcinoma, 71% were in FIGO stages I-IIA tumors.[2]

In cancer of the uterine cervix, early-stage diseases include those in stages I-IIA while late-stage diseases are those from stages IIB and above. In a study by Cabanela, et al. (2003) in a local tertiary hospital, it showed that majority of cancer of the cervix are diagnosed in the advanced stage. The stage distributions are as follows: Stage I at 16.13%, Stage II - 35.98%, Stage III - 46.03% and Stage IV -1.25%.[21] The index case, having been diagnosed at an early stage (IB1), underwent radical surgery after thorough counseling on the different treatment options and their efficacies.

Overall, approximately 35 percent of patients with invasive cervical cancer will develop recurrent or persistent disease after therapy.[4] Recurrence after surgery is defined as evidence of a tumor mass after all gross tumor was removed and the margins of the specimen were histologically free of disease.

Early-stage disease adequately treated with surgery has a reported recurrence rate of 10-20%.[4] Sotto, et al. (1994) reported a higher recurrence rate of 20.8% for stage I and 31% for stage IIA disease.[5]

Disease recurrence remains essential to both patients and physicians alike. Known poor prognostic factors after surgery include lymph node status, cervical stromal invasion, and clinical lesion size. In the study of Cuenca, et al. (1998), depth of cervical stromal invasion and lymph node metastases were found to have significantly affected the recurrence rate of early–stage cervical cancer treated primarily with surgery.[22] Postoperative findings in the case of L.R. include such poor prognostic factors as large tumor size (> 2.0 cm), tumor metastasis to the right obturator lymph nodes and more than 50% stromal invasion, which all called for adjuvant chemoradiation in a concurrent setting using cisplatin as a single-agent.

Adjuvant therapy in the form of radiation (RT) alone or in combination with chemotherapy may be administered to reduce the risk of recurrence in high-risk groups where L.R. seemed to belong. In the said combination modality, cisplatin as a single-agent chemotherapy acts as a radiation sensitizer that works by reducing the hypoxic fraction of cells, synchronizing the cell cycle, and inhibiting cancer cells' radiation repair mechanism. In addition, many trials have now shown a reduction in distant failure rate following the use of such combination therapy. In the GOG 109 study that compared the use of adjuvant radiotherapy alone versus radiotherapy plus cisplatin chemotherapy after

radical hysterectomy, the latter showed to be beneficial among high-risk patients with an estimated 5-year survival of 82% versus 77% in the first group of patients with $\leq$ 2 cm, while those with tumors > 2 cm, it was 58% for the RT alone versus 77% with cisplatin. The same study also demonstrated fewer local and distant relapses in the RT plus cisplatin group.[2]

The average time to recurrence is about 24 months following therapy.[4] Krebs and associates reported that recurrence for early invasive cancer of the cervix occurred in 58% within 12 months after surgery and 83% within the first 2 years.[4] In the index case, the disease recurred 20 months after surgery.

The recurrence pattern of cervical cancer is usually local and predominantly involves the vagina and/or the pelvis.[5] For those patients who underwent radical hysterectomy, about 25% of recurrences occur in the upper vagina or in the area previously occupied by the cervix.[4] Once distant organs are involved, the more commonly involved are the lungs, bone and liver.[7] The latter was present in our patient.

Cutaneous metastases from primary carcinoma elsewhere in the body are relatively rare with a reported incidence range of 0.7% to 4.4%.[15] According to Connor, et al. the most common sites of primary disease in decreasing order of frequency are the breast (38%), gastro-intestinal tract (17.4%), lungs (16.3%) and kidney (6.8%).[14]

Cervical cancer developing cutaneous types of recurrence accounts for only 0.1% to 2.0% of cases.[7] In terms of the histological types of the primary disease, undifferentiated carcinoma accounts for 20% of cases, followed by adenocarcinoma (5.8%). Squamous cell carcinoma of the cervix is rarely associated with cutaneous metastasis (0.9%) and is considered the rarest form of cutaneous metastasis from cervical cancer. These aforementioned data make the index case of L.R. even more peculiar, if not extremely rare.

The most common sites of cutaneous involvement from cervical carcinoma are the abdominal wall and vulva as demonstrated by L.R., followed by the anterior chest wall, upper extremity and lower extremity.[6]

The average time to develop cutaneous lesions is about 10 years.[7] L.R. developed cutaneous metastasis only 20 months after surgery, which is a far-cry from the average reported incidence rate. This can be a function of the interplay of the three poor prognostic factors identified in her case after radical surgery.

Skin as the solely involved site of recurrence has been reported in 26.6 percent of cases.[6] Imachi, et al. on the other hand, reported that majority of cases with skin metastasis have concomitant metastases in other organ systems, both local and distant. These organs usually involve the lungs (40%), contiguous structures (33.3%), bones (33.3%), peritoneal carcinomatosis (26.7%) and liver (13.3%).[6] In effect, a metastatic work-up is always in order. L.R., following a whole abdominal CT scan, showed metastatic liver and splenic involvement.

Cutaneous metastases most commonly mimic the primary tumor although they tend to have more anaplastic features. Macroscopically, three cutaneous metastatic patterns have been recognized, namely the nodules, the plaques and the inflammatory telangiectatic lesions. The latter may resemble an acute, infectious process where the involved skin is frequently tender, edematous and erythematous. Fine needle aspiration cytology may be useful to diagnose skin metastasis with nodular lesions while tissue biopsy is recommended for the plaques and inflammatory telangiectatic lesions. L.R. presented a weeping nodular mass at the umbilical area and multiple pruritic plaques at the incision scar over the hypogastrium.

Pathophysiology

It was initially thought that cancer of the uterine cervix metastasizes to the skin via the lymphatic route.[6] However, those not in favor of this postulate emphasized that the skin is not in the efferent route of lymphatic drainage from the cervix. In effect, other reports suggested that the tumor spread happened in a retrograde fashion secondary to lymphatic obstruction. Such obstruction eventually leads to skin metastasis from either vessel permeation or tumor embolization.[6,8]

Another postulate being advanced is the possible cutaneous spillage of tumor cells during the primary surgery. This mechanism was best demonstrated by the use of laparoscopy in cancer surgery. Ramirez, et al. proposed the following mechanisms for cutaneous metastasis: 1) wound contamination from surgical technique and instrumentation, 2) leakage of insufflation

gas through the port, and 3) disturbed immune function within the peritoneal cavity.

Direct wound contamination from instrumentation classically explains the development of port-site metastasis after laparoscopy. This mechanism, however, may not single-handedly bring about cutaneous metastasis. DiSaia explained that few viable cells from residual tumors after radical surgery are likely to grow and proliferate.

Also, leakage of insufflation gas like carbon dioxide (CO_2) during laparoscopy may be a likely cause. This led to the concept of employing a gasless laparoscopy that may hopefully reduce the rate of skin or wound recurrences.[18] But Iwanaka, et al. (1998) showed no difference in the recurrence rate in both gasless and conventional laparoscopy models.[18]

Impaired local immune response in the peritoneal cavity secondary to trauma during surgery is also believed to play a role in the development of port-site metastasis. It is theorized that hypoxia and subsequent acidosis of the fat tissue in the abdominal wound may induce an angiogenic process,[10] through the expression of interleukin-8 (IL-8), an important molecule in the regulation of angiogenesis through the vascular endothelial growth factor (VEGF).

Hematogenous route is also a plausible mechanism that results from large circulating tumor cell burden.[9] This route commonly operates in advanced-stage diseases. The lungs, liver and bone and less commonly the bowels, adrenals, spleen and brain may be involved.[8] Martinez-Palones et al, however, cautioned that only 1.0 percent of cancer cells that reach the circulation may survive and of such, only 0.1 percent can successfully effect viable metastatic growth.[10]

In the case of L.R., the mechanism of cutaneous metastasis is obviously difficult to establish in the absence of good in-vivo models from the different postulates so far proposed. What is definitely known and documented in her case are the poor prognostic factors like large tumor volume, > 50% cervical stromal invasion, and lymph node metastasis plus the concomitant liver and spleen metastases seen on tomography. For such given factors, the possible role of lymphovascular route of spread can be highly considered.

Direct wound contamination during surgical procedure can be considered, but may be the least likely mechanism because the combined radiotherapy and chemotherapy had post-operatively could have theoretically sterilized the local area from tumor cells, thus making the local cutaneous recurrence unlikely.

Additionally, all the aforementioned mechanisms, no matter how rare they can be, may find their victorious ways to effect cutaneous recurrence in an immuno-compromised setting. Any patient, like L.R., who is afflicted with any form of malignancy, may be theoretically considered to have a compromised immune status.

Treatment

Patients who develop recurrent diseases are the most difficult to treat since recurrence in itself is a poor prognostic factor. Prognosis is expectedly bleak for those who are no longer amenable to surgical resection or additional radiation therapy, as in the case of L.R., who had previously received these two treatment modalities. The median survival rate is dismal so that fewer than 20 percent survive in one year.[11] Moreover, the appearance of the cutaneous form of recurrence is generally thought to be a pre-terminal event and the longest survival reported for this group of patients is 19 months. [6]

Chemotherapy may be the best possible treatment option for such patients with unusual form of recurrence and metastasis. Despite the numerous clinical trials, there exists no widely acclaimed standard chemotherapeutic regimen. Factors seen to deter the success rate of chemotherapy include the following: 1) prior radiation therapy imposes a limited residual bone marrow function; 2) adequate drug distribution may be hampered in previously irradiated tissues; 3) ureteral obstruction resulting from previous therapy may lead to renal dysfunction, thus restricting or precluding the use of drugs such as cisplatin; and 4) the histologic type of squamous cell carcinoma that is seen in 80 percent of cervical cancer patients has a limited and brief response to chemotherapy.[11]

The Gynecologic Oncology Group (GOG) published several trials in an attempt to find the optimal platinum doublet to treat women with metastatic or

recurrent cervical cancer. Four randomized phase III trials were conducted, namely the GOG Protocol 110, 149, 169 and 179. GOG Protocol 110 compared cisplatin plus mitolactol versus cisplatin plus ifosfamide versus cisplatin alone. A significant improvement in the response rate and progression free survival (PFS) was noted among those in the ifosfamide plus cisplatin combination compared to the cisplatin alone group but there was no observed improvement in overall survival.[16] The 1.4-month improvement in median PFS for the ifosfamide plus cisplatin over cisplatin alone was not considered to be worth the added toxicity associated with ifosfamide.

In the GOG Protocol 149, ifosfamide-cisplatin-bleomycin regimen was compared with ifosfamide-cisplatin on 287 patients. The response rates, PFS, and overall survival for both groups were identically high.[17]

Paclitaxel plus cisplatin was compared with cisplatin in GOG 169. This trial added the quality-of-life (QOL) component and again demonstrated an improvement in response rate and PFS without any improvement in overall survival for the combination regimen compared with cisplatin alone.[11]

GOG 179 compared single agent cisplatin with cisplatin-topotecan (CT) and methotrexate-vinblastine-doxorubicin-cisplatin (MVAC). However, the MVAC arm in this study was closed after four treatment-related deaths were reported. This trial showed a response rate of 27% in the combination arm compared to the 13% observed in the single agent cisplatin group.[12] The trial also demonstrated that cisplatin-topotecan regimen did not impair the quality of life, hence, is considered the new standard regimen in advanced stage (Stage IVB) recurrent and persistent cervical cancer.[12]

In an unpublished local study conducted by Cristobal, et al. (2004) using cisplatin-cyclophosphamide, doublet therapy in recurrent cervical carcinoma afforded an overall response rate of 50%.[19] The index patient was initially given this regimen for 3 courses at week interval but due to disease progression, another combination of cisplatin-topotecan was started with palliative intent.

Many other studies have attempted to identify other active chemotherapeutic agents, single or in combination, for this group of patients but majority have established cisplatin to be the most active single agent so far. In effect, it has become and still is the standard systemic chemotherapeutic agent for locally advanced as well as systemically advanced disease recurrence and persistence of squamous cell carcinoma of the uterine cervix.

Other Treatment Modalities

Surgical resection of metastatic skin lesions can be considered if other sites of metastasis are found following a profound metastatic work-up. To control the symptoms, palliative radiation can be resorted to, provided no prior radiotherapy was instituted. Unfortunately, these modalities are no longer appropriate in the case of L.R.

A promising treatment option that is still in the investigative phase is the use of angiogenic inhibitors. These are believed to retard tumor growth and progression and, and in some studies, have shown to help in eliminating small volume residual disease. The ongoing GOG Protocol 227C is a phase II trial, which looks into the role of an immunologic molecule, Bevacizumab, in cervical cancer treatment. Being administered at a dose of 15mg/kg every 21 days, this molecule may find its value in the treatment of cervical cancer in the future.

Summary

A case of early-stage squamous cell carcinoma of the uterine cervix adequately treated with surgery which developed rare cutaneous recurrence has been presented. Factors predictive of recurrence were discussed. The pathophysiology of rare cutaneous recurrence from cervical cancer was extensively discussed. Since there is still no established chemotherapy regimen for this group of patients, the paper also reviewed recent data on this issue.

References

1. Laudico AV, et al. Philippine Cancer Facts and Estimates, 2005.
2. Monk B, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy a clinical-pathologic analysis of Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group Trial. Gynecol Oncol 2005; 96: 721-728.

3. Green J, Kirwan J, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix (Review); The Cochrane Collaboration, 2007.
4. DiSaia PJ, and Creasman WT. Clinical Gynecologic Oncology 6th edition 2002; 53-105.
5. Sotto LSJ, Manalo AM and Limson GM. Gynecologic Oncology for the Clinician, 2nd edition, 1994; 161-170.
6. Imachi M, Tsokanoto N, Kinoshita S and Nakano H. Skin metastasis from carcinoma of the uterine cervix. Gynecol Oncol 1993; 48: 349-354.
7. Behtash N, Ghaemmaghami F, Yarandi F, Ardalan FA, Khanafshar N. Cutaneous metastasis from carcinoma of the cervix at the drain site. Gynecol Oncol 2002; 85: 209-211.
8. Palaia, Innocenza, Angioli, Roberto, et al. Skin relapse from cervical cancer. Gynecol Oncol 2002; 87: 155-156.
9. Pertzborn S, Buekers TE and Sood AK. Hematogenous skin metastases from cervical cancer at primary presentation. Gynecol Oncol 2000; 76: 416-417.
10. Martinez-Palones JM, Gil-Moreno A, Perez-Benavente MA, Garcia-Gimenez A and Xercavins J. Umbilical metastasis after laparoscopic retroperitoneal paraaortic lymphadenectomy for cervical cancer: a true port-site metastasis? Gynecol Oncol 2005; 97: 292-295.
11. Moore DH, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent or persistent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group Study. J Clin Oncol 2004; 22(15): 3113-3119.
12. Long HJ, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A Gynecologic Oncology Group Study. J Clin Oncol 2005; 23(21): 4626-4632.
13. DuPont NC and Monk BJ. Chemotherapy in the management of cervical carcinoma. Clin Adv Hemat Oncol 2006; 4(4): 279-285.
14. Reingold I. Cutaneous metastases from internal carcinoma. Cancer 1986; 19: 162-168.
15. Freeman CR, Rozenfeld M and Schopflocher P. Cutaneous metastases from the carcinoma of the cervix. Arch Dermatol 1992; 118: 40-41.
16. Omura GA, Blessing JA, Vaccarella L, et al. Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol 1997; 15: 165-171.
17. Buxton E, Meanwell C, Hilton C, et al. Combination bleomycin, ifosfamide, and cisplatin chemotherapy in cervical cancer. J Natl Cancer Inst 1989; 81: 359-361.
18. Iwanaka T, Arya G, Ziegler MM. Mechanism and prevention of portsite tumor recurrence after laparoscopy in a murine model. J Pediatr Surg 1998; 33: 457–461.
19. Cristobal R, Gay V. Cisplatin-cyclophosphamide combination therapy for persistent or recurrent carcinoma of the cervix (unpublished).
20. Agarwal U, et al. Scalp metastasis in carcinoma of the uterine cervix – A rare entity. Gynecol Oncol 2002; 87: 310-312.
21. Cabanela J. Clinical profile of cervical cancer at JRRMMC, 2003 (unpublished).
22. Cuenca BD, Limson GM, Manalo AM and Santos RR. Histopathologic factors in predicting recurrence among FIGO stages IB and IIA cervical cancer patients treated with radical hysterectomy, bilateral pelvic lymphadenectomy and adjuvant radiotherapy, 1998.
23. Ngelangel CA, et al. Delineation of an appropriate and replicable cervical cancer screening program for Filipino women. Collaboration by Department of Health, UP Manila and Department of Interior and Local Government, 2001; 7-15.

The Role of Radiotherapy in Endometrial Cancer

Jericho Thaddeus P. Luna[a], MD; Jean Anne B. Toral[b], MD; Christine Joy G. Garcia[a], MD; Ana Victoria V. Dy Echo[c], MD and Efren J. Domingo[d], MD, PhD

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

Endometrial carcinoma is the third most common genital tract malignancy in the Philippines and it ranks 9th among the leading female cancer sites.[1] Since 1988, the International Federation of Gynecology and Obstetrics (FIGO) staging classification for endometrial cancer has been based on surgicopathologic criteria (Table 1). Surgical staging includes peritoneal fluid cytology (PFC), extrafascial hysterectomy (EH), bilateral salpingo-oophorectomy (BSO), pelvic and paraaortic lymph node dissection.[2] For the past two decades, endometrial cancer has been subdivided further to low, intermediate and high risk groups, depending on their surgicopathologic staging, tumor grade and histologic type, to determine those at high risk for recurrence and cancer death (Table 2).[3] Such subdivision into the three risk groups guides the oncologist in determining the type of adjuvant treatment, if needed.

More than half a century ago, endometrial cancer was found to be sensitive to radiation and adjuvant radiation was observed to decrease the incidence of pelvic recurrences and improve survival. Adjuvant treatment has evolved from preoperative radiation for all patients to postoperative radiation for selected patients. Adjuvant radiation can be delivered using external beam radiation to the pelvic region (EBRT) and/or paraaortic area (EFRT), vaginal brachytherapy, or a combination of both. The aim of EBRT and/or EFRT is to treat the regional lymph nodes which are

Table 1. 1988 FIGO surgical staging for endometrial cancer.

Stage	Extent of Tumor Involvement
IA	Tumor confined to endometrium
IB	Invasion to less than one-half of the myometrium
IC	Invasion to more than one-half of the myometrium
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
IIIA	Tumor invades serosa and/or adnexa and/or (+) peritoneal cytology
IIIB	Vaginal metastases
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal nodes

Table 2. Risk grouping for endometrial cancer.

Risk Group	Stage, Grade & Histologic Type
Low Risk	Stage IA Grade 1/2
	Stage IB Grade 1/2
Intermediate Risk	Stage IA Grade 3
	Stage IB Grade 3
	Stage IC Grade 1/2
	Staeg IIA Grade 1/2
	Stage IIA Grade 3 (< 50% myometrial invasion)
High Risk	Stage IC Grade 3
	Stage IIA Grade 3 (< 50% myometrial invasion)
	Stage III Grades 1,2,3
	Stage IV Grades 1,2,3
	Uterine Papillary Serous Carcinoma, any stage
	Clear Cell Carcinoma, any stage

[a]Associate Professor, [b]Clinical Associate Professor, [c]Fellow-in-Training, [d]Professor, Section of Gynecologic Oncology, Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines Manila

at risk of containing microscopic disease or have macroscopic disease as well as the central pelvic region, which includes the upper vagina.

Adjuvant Therapy for Endometrial Cancer Confined to the Uterus

After complete surgicopathologic staging, most endometrial cancer patients are found to have disease confined in the uterine corpus. Like other gynecologic malignancies, the most important prognostic factor in endometrial cancer is stage, and the expected 5-year survival rates for stage I and stage II diseases (i.e. early stages) are 87% and 76%, respectively. Most patients with early stage disease are cured after surgery, while certain subsets of patients are at higher risk for locoregional and distant relapse. Overall, the risk of locoregional failure after surgery with no adjuvant therapy in stage I and II disease may be as high as 20% and the recurrence is influenced by stage, tumor grade, histologic type, degree of myometrial invasion, and the presence of lymphovascular space invasion (LVSI). Patients with stage IA, grade 1 or 2 disease and stage IB, grade 1 or 2 disease are at low risk for failure, and complete surgical staging alone is an adequate treatment. Failure patterns in patients with stage IA, grade 3 disease, a relatively rare subset, are poorly defined. However, surgicopathologic data suggest that these patients are likely to be at low risk for lymph node metastases, and reasonable postsurgical options include vaginal brachytherapy and observation. The remainder of patients with stage I or II disease has historically been grouped into an "intermediate-risk" category and been the subject of prospective trials.

Randomized Trials in Stage I and II Disease

The Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial (which did not use lymph node sampling) randomized 715 patients with grade 2 and 3 disease and $< 50\%$ myometrial invasion (stage IB) as well as patients with $\geq 50\%$ myometrial invasion (stage IC) and grade 1–2 disease to receive either pelvic radiotherapy or no further treatment. (Table 3) The PORTEC investigators felt that patients with $> 50\%$ myometrial invasion and grade 3 disease represented a "high risk" subgroup presumed to benefit from pelvic radiotherapy, and these patients were excluded from the trial. The Gynecologic Oncology Group (GOG) performed a similar trial in patients with lymph node staging (GOG 99). That trial had a slightly different definition of intermediate risk, and included stage IB, stage IC, and occult stage II (involvement of the cervix) disease of all grades. Both of these trials demonstrated the ability of adjuvant radiation therapy to decrease pelvic and vaginal recurrences; local-regional relapse rates were 15% and 4% in treated versus non-treated patients, respectively, at 8 years in the PORTEC trial, and 9% versus 1.5%, respectively, at 4 years in the GOG trial.[4,5] Overall survival, however, was not better for patients treated with radiotherapy in the PORTEC trial (71% with radiotherapy versus 77% with observation at 8 years, $p = 0.18$) or in the GOG study (estimated 4-year survival rate of 92% in the radiotherapy arm versus 86% with observation, $p = 0.557$). A third trial by Aalders, et al.[6] randomized 540 clinical stage I patients after hysterectomy and vaginal brachytherapy to receive either pelvic radiotherapy or no further treatment. The local control rate was 2% with vaginal brachytherapy and pelvic radiotherapy versus 6.9% with vaginal brachytherapy alone.[6] Again, no survival benefit was seen with the addition of pelvic radiotherapy to vaginal brachytherapy.

There are many potential reasons for the lack of a survival advantage, including the predominance of patients with a relatively low risk for recurrence, a high death rate from intercurrent disease, and the possibility of salvage for the most common site of recurrence (vaginal). For example, in the PORTEC study, there were 105 deaths in both arms; only 40 percent of the deaths were due to endometrial cancer. The GOG trial showed similar results, with approximately 50 percent of deaths in both arms attributable to causes other than endometrial cancer or treatment. Another factor impacting survival in stage I and II disease is the locoregional failure pattern. In the control arm of the PORTEC study, more than 70 percent of locoregional failures were in the vagina. As the initial site of failure, more than 70 percent of local failures in the control arm of the GOG study were also in the vagina. The success of salvage therapy for vaginal relapses in the PORTEC study was reported by Creutzberg, et al.[4] in 2003; they reported a 61% durable local control rate

Table 3. Prospective randomized trials of radiotherapy for endometrial cancer confined to the uterus.

Trial	# of Patients	Stage	Surgery	Radiotherapy	Results
Aalders, et al.[6]	540	I	TAHBSO	Brachytherapy ± EBRT	Local Relapse: 7% vs 2% Overall Survival: no difference
PORTEC-1[4]	715	IB G2/3 or IC G1/2	TAHBSO	EBRT vs Observe	Local Relapse: 15% vs 4% Overall Survival: no difference
GOG 99[5]	488	IB, IC or occult stage II, all grades	TAHBSO + node dissection	EBRT vs Observe	Local Relapse: 9% vs 1.5% Overall Survival: no difference
PORTEC-2	400	IC G1/2 & IB G3 with age > 60 or IIA G1/2 or IIA G3 with < 50% MI)	TAHBSO	EBRT vs Brachytherapy	Pending
NCICEN 5	400	IA-IB G3 or IC-IIA, all grades	TAHBSO	EBRT vs Observe	Pending
ASTEC	900	IA-IB G3 or IC-IIA, all grades or UPSC/Clear Cell	TAHBSO ± node dissection	EBRT vs Observe	Pending

and an overall 49% salvage rate. Some patients developed distant recurrences despite good local control. Another report of salvage therapy for vaginal recurrences came from the MD Anderson Cancer Center in 2003. In 91 patients with isolated vaginal relapses, the 5-year local control rate was approximately 70% but, due to subsequent distant failure, the survival rate was only 50%.[7] The ultimate outcome of patients with vaginal failures in the GOG study has not been provided. However, in the final report, it was noted that approximately 60 percent of patients with vaginal relapse had not succumbed to their disease; details of disease-free status or salvage treatments were not provided. Analysis of the combined data suggests that approximately 50 percent of the patients who develop vaginal recurrences can be salvaged.

Adjuvant pelvic radiotherapy is associated with toxicity, which must be balanced against the benefit derived from its use. In general, patients experience acute gastrointestinal (frequency, diarrhea), genitourinary (frequency, dysuria), and hematologic toxicities with pelvic radiotherapy. The majority of the acute toxicity is self-limited[8], and treatment interruptions are relatively rare.[9] The PORTEC investigators found that pelvic radiotherapy, as expected, was associated with a higher risk for grade 1–2 late gastrointestinal (17% versus 1%) and genitourinary (8% versus 4%) toxicities.[10] Grade 3–4 toxicity was rare in both arms, but all grade 3–4 toxicities occurred in the radiotherapy arm (3% of patients). Obesity is a risk factor for endometrial cancer, and a two-field technique that generally delivers higher radiation dose to the bowel was associated with greater toxicity in the PORTEC study ($p = 0.06$). The reported toxicity from the PORTEC study is not applicable to patients undergoing lymph node staging, patients treated with doses > 46 Gy, or patients receiving a vaginal brachytherapy boost; the use of a

higher pelvic dose or additional therapies would likely increase the risk of adverse effects from treatment. The GOG study reported results similar to those from the PORTEC study, with statistically significant differences in gastrointestinal, genitourinary, hematologic, and cutaneous toxicities between the treatment arms. As in the PORTEC study, most recorded toxicities were grade 1–2 in the radiotherapy group. Surgical staging did change the toxicity profile in the GOG study; patients in both the surgery and radiotherapy arms were noted to have lymphatic complications (primarily chronic lymphedema, occurring in 2.5 percent of the control patients and in 5 percent of the radiotherapy patients). This complication was not noted in patients from the PORTEC study, in which lymph node dissection was not used.

Stage IA/IB, Grade 1/2 Disease

Both the PORTEC and GOG trials predominantly accrued patients at low risk for locoregional failure. In the absence of LVSI, the overall risk for lymph node disease and locoregional failure in patients with grade 1 or 2 disease and < 50% myometrial invasion is relatively low. In their analysis of the GOG surgicopathologic study, Morrow, et al.[11] reported a 4.4% locoregional recurrence rate in 113 patients with inner- or middle-third invasion, grade 1 or 2 disease, and no LVSI. Approximately 30 percent of patients in the PORTEC study had stage IB, grade 2 disease. Nearly 60 percent of patients in the GOG 99 trial were stage IB, and approximately 80 percent had grade 1 or 2 disease. The inclusion of patients unlikely to benefit from adjuvant pelvic radiotherapy likely blunted the impact of treatment in both these trials. Indeed, many series have reported an excellent outcome in stage IB patients with grade 1 or 2 disease without adjuvant radiation or with limited, targeted radiotherapy. In surgically-staged patients, Straughn, et al.[12] reported a 3.7% overall failure rate in 296 patients, with 64% of failures occurring in the vagina. Other series have reported similar outcomes in patients without surgical staging. For example, the Mayo clinic reported their experience in 261 patients with grade 1 or 2 and stage IB or lower disease treated with surgery alone. Overall, there was only a 2% isolated local recurrence rate without adjuvant radiation. Of the 126 patients not receiving lymphadenectomy, 2 percent failed locally. Other investigators have reported similar outcomes in surgically staged patients treated without adjuvant therapy.[13,14] Given the low risk for pelvic failure, some have advocated vaginal brachytherapy alone in these patients. One of the largest series was reported by Alektiar, et al.[15] from Memorial Sloan-Kettering Cancer Center; in 233 patients without surgical staging, there was an overall 4% relapse rate. Only 2 percent of patients failed in the pelvis; the remainder failed either distantly or in the vagina. Other authors have reported similar results.[16,17] Combination of these data does not support the use of pelvic radiotherapy after surgery for these low-risk patients, defined as grade 1 or 2 disease with < 50% myometrial invasion. Indeed, observation alone is appropriate for stage IB, grade 1 disease, and observation or vaginal brachytherapy is a reasonable treatment option after surgery in stage IB, grade 2 disease. In addition to using grade and surgical stage to define low-risk patients, some groups have investigated the utility of incorporating DNA ploidy as a predictive factor. Based on a previous work showing that ploidy is prognostic in patients with poorly differentiated tumors, Hogberg, et al.[18], in a prospective study, assigned 355 stage I or II patients after surgery (with optional nodal staging) to either low- or high-risk categories based on DNA ploidy. High-risk stage I and II patients were defined as either stage IC or grade 3 with nondiploid tumors, and received adjuvant vaginal brachytherapy. The remaining patients were low risk, and were observed after surgery. In the low risk group, there was an overall 6% locoregional failure rate and 1.4% distant failure rate. However, "low-risk" stage II patients had a significantly higher risk for failure with greater than one third failing, primarily in the vagina or pelvis. The model used in that study may predict for a group of stage I patients that can be safely observed; stage II patients and those identified as high risk likely benefit from adjuvant therapy.

Stage I and II Disease – Who Benefits from Adjuvant Pelvic Treatment?

All of the prospective studies made post hoc attempts to identify subgroups of patients at higher risk for recurrence. In the GOG study, a "high

intermediate" group was defined by a combination of risk factors that included advanced age, LVSI, outer–third invasion, and moderate to high tumor grade. As the first site of failure, the control arm of the low intermediate risk group (which comprised approximately two thirds of the patients) had an observed failure rate of 5%, while the higher risk group had a 13% risk for locoregional failure. The high intermediate risk patients were also at risk for failing distantly, with a 48-month observed distant failure rate of 19% in the control arm. The PORTEC trial identified low-risk patients as those with superficially invasive, grade 1 or 2 tumors and < 60 years of age; these patients had a 5% risk of locoregional relapse. High-risk patients included patients older than 60, patients with stage IC, grade 1 or 2 tumors, and patients with stage IB, grade 3 tumors. This group of patients had a 5-year locoregional relapse rate of 19%, with the majority of relapses occurring in the vagina. In the Aalders, et al.[6] study, a subgroup analysis in patients with deep myometrial invasion revealed that the rate of pelvic relapse was lower in the radiotherapy-treated patients, at 6.6% versus 14.7%. In patients with both grade 3 disease and deep invasion, a 10% improvement in the cancer death rate was seen with the addition of pelvic radiotherapy, and the pelvic relapse rate was lower, at 4.5% versus 20%.

Stage IA/IB, Grade 3 and Stage IC Disease

These subgroup analyses provide useful information regarding groups of patients at a relatively higher risk for locoregional failure. The analyses do not, however, address the pattern of local failure, which can be used to tailor adjuvant therapeutic recommendations. For stage IB, grade 3 patients, there are limited observation data. These patients appear to be at a relatively low risk for pelvic nodal metastases, with Creasman, et al.[19] showing an approximately 4%–9% rate of pelvic node metastases with grade 2 or 3 disease and greater than two thirds invasion. In the PORTEC study, there were 37 patients in the control arm with stage IB, grade 3 disease; the authors reported a 14% 5-year locoregional failure rate in those patients. All of the local failures occurred in the vagina.[20] In addition, these patients were as likely to develop distant metastasis, with approximately 20 percent suffering a distant relapse in both the observation and radiotherapy arms. Straughn, et al.[12] reported outcome in 29 patients with stage IB, grade 3 disease treated with surgery alone (including lymphadenectomy). They noted a crude 14% recurrence rate, with nearly all failures distant. Given the patterns of failure without radiotherapy and the low expected rate of pelvic node metastases, it may be reasonable to limit adjuvant radiotherapy to the vagina in these patients, especially in the setting of complete nodal staging. In the GOG surgicopathologic study, outer one-third invasion was associated with an 18% risk for pelvic lymph node disease, suggesting a need for pelvic treatment. Indeed, without surgical staging, Aalders, et al.[6] showed that the pelvic failure rate was approximately 15% with deep myometrial invasion and 20% with deep invasion, grade 3 disease. In contrast, Creutzberg, et al.[20] reported a relatively low pelvic failure rate in the control arm of the PORTEC study in stage IC, grade 1 and 2 patients. In the 67 patients not receiving radiotherapy, there was a 2% actuarial risk for pelvic relapse and a 10% risk for vaginal relapse for stage IC, grade 1 tumors. For the 133 patients with stage IC, grade 2 tumors, there was a 6% risk for pelvic failure and a 13% risk for vaginal failure. There are limited data regarding outcome of surgically-staged stage IC patients treated with observation alone. Straughn, et al.[21] reported the largest series (121 patients) treated with complete surgical staging and no adjuvant radiotherapy; there was a 12% overall failure rate with 6 percent of patients failing locally; again, the vast majority of these locoregional failures were in the vagina. In this subset of patients with stage IC disease, pelvic radiotherapy may provide limited additional local control in the pelvis after surgical staging, and authors have reported results with brachytherapy alone.[22] In at least one study, the use of vaginal brachytherapy over observation was found to be cost-effective in these intermediate-risk patients, with a calculated cost per year of life saved of approximately $38,000.[23] In the absence of surgical staging, however, the expected rate of nodal metastases and failure data from Aalders, et al.[6] suggest that pelvic radiotherapy is needed. It should also be recognized that grade 3 patients are at a much higher risk for failing distantly, with approximately 20 percent of stage IB, grade 3 patients and 30 percent of stage IC, grade 3 patients failing distantly in the PORTEC study.

Stage II Disease

Stage II disease accounts for approximately 5 percent–15 percent of endometrial cancer cases and has a poorer prognosis than stage I disease, with an approximately 75% 5-year overall survival rate. Historically, this stage of disease was often treated with preoperative radiotherapy followed by surgery. There is a relative paucity of data regarding locoregional failure patterns in surgically staged patients with cervical involvement not receiving radiotherapy. In general, treatment recommendations follow those of patients with stage IC disease, and adjuvant pelvic radiotherapy is recommended. In patients with complete surgical staging, there is limited experience using brachytherapy alone without pelvic radiotherapy. Several small series have reported few or no locoregional failures with this approach in stage II disease.[24,25] The need for routine pelvic radiotherapy in stage II disease is being investigated in the current PORTEC-2 study. The original GOG surgicopathologic study found that LVSI placed patients at high risk for lymph node metastases. Other investigators have confirmed this[26], and the risk for lymph node disease with LVSI ranges from 20%–50%.[27] Even in the absence of other risk factors for lymph node metastases, the presence of LVSI places patients at a relatively high risk for nodal disease. Due to this, patients managed surgically without lymphadenectomy should be treated with pelvic radiotherapy in the presence of LVSI, regardless of other risk factors. The pelvic failure rate after lymphadenectomy in patients with LVSI is not well characterized, and the need for routine adjuvant pelvic radiotherapy in these patients is unknown.

Ongoing Trials in Stage I and II Disease

Current trials are attempting to tailor radiotherapy to the area of highest risk, address the need for pelvic radiotherapy in higher risk patients, and address the distant failure rate seen with high-risk histologic types (Table 3). The newest PORTEC trial (PORTEC-2) randomizes intermediate-risk patients to receive either vaginal brachytherapy or pelvic radiotherapy. Patients eligible for this trial are those with stage IC, grade 1–2 disease and age > 60 years; stage IIA, grade 1–2 disease and any age; stage IB, grade 3 and age > 60 years; stage IIA, grade 3 with < 50% myometrial invasion; and stage IIA grade 1–2 disease and age > 60 years. As in the original PORTEC study, lymphadenectomy is not required. A current National 628 Adjuvant Radiotherapy in Endometrial Carcinoma Cancer Institute of Canada (NCIC) study is randomizing patients with grade 3 disease of any invasion and grade 2 tumors with > 50% myometrial invasion to receive either pelvic radiotherapy or observation. Vaginal brachytherapy is allowed in that trial. The Medical Research Council Trial A Study in the Treatment of Endometrial Cancer is evaluating both surgical and radiotherapy questions. Patients with disease confined to the corpus are randomized to receive either lymphadenectomy or conventional surgery without lymph node treatment. Patients found to have high-risk features at the time of surgery are then randomized to receive either pelvic radiotherapy (with or without brachytherapy) or observation. That study defines high-risk disease as stage IC or IIA, any grade 3 tumor, or papillary serous/clear cell histology. The target accrual is 900 patients, and results will be combined with the above-mentioned NCIC study for evaluation. For higher risk disease, the Radiation Therapy Oncology Group (RTOG) opened a trial to evaluate the role of chemotherapy. Patients with stage IC, grade 2 or 3 disease and stage II disease were to be randomized to receive either pelvic radiotherapy or pelvic radiotherapy with chemotherapy. Unfortunately, the study was closed due to poor accrual. A current Nordic Society for Gynecologic Oncology Trial is evaluating the role of chemotherapy in a phase III trial for surgical stage I disease. All patients receive pelvic radiotherapy, and the trial is open to all patients with stage I disease with grade 3, clear cell, or papillary serous histologic types.

Stage III and IV Disease

Approximately 20 percent of patients with endometrial cancer present with or are found to have extrauterine disease at the time of surgery. Most of these patients present with stage III disease, which consists of disease confined to the pelvis or lymph nodes. Stage IV patients are those with either invasion of the bowel or bladder (stage IVA) or distant metastases (stage IVB) and comprise generally 5

percent of patients with endometrial cancer. Adjuvant radiotherapy options in stage IVB disease are usually directed at symptom management. Stage III patients are heterogeneous in terms of prognosis, with 5-year survival rates of 30%–70%. Patients with this subset of disease can present with adnexal or serosal involvement or positive PFC (stage IIIA), vaginal involvement (stage IIIB), or pelvic and/or para-aortic nodal disease (stage IIIC). Patients with vaginal involvement are usually managed with preoperative complete radiotherapy (i.e EBRT plus brachytherapy). A variety of therapies has been used in other stage III patients, including involved-field radiotherapy, whole abdomen radiotherapy (WART), chemotherapy alone, and combined chemoradiation. Developing therapeutic recommendations for patients with advanced disease has been confounded by the presence of numerous small series using various regimens, the relative lack of prospective randomized trials, and the heterogeneous outcomes of patients with stage III disease.

Evaluating risks and patterns of failure allows for some generalizations to be made regarding this group of patients. In the GOG surgicopathologic study, the risk for relapse increased with an increasing number of extrauterine sites of disease. This has been found in other studies as well. For example, Greven, et al.[28] reported on 126 patients with stage III disease; the risk for recurrence after pelvic radiotherapy correlated with increasing grade of disease and sites of extrauterine disease. That series also found a greater risk for abdominal failure in patients with multiple sites of extrauterine disease. Patients with more than two sites had a 31% abdominal failure rate versus 10% for those with one site and grade 1 disease. Mariani, et al.[29] reported on patients with nodal disease alone versus those with nodal and other extrauterine disease. Patients with nodal disease alone had a 3-year cause-specific survival rate of 72%, versus 33% in patients with other extrauterine disease. In addition to evaluating prognosis by number of extrauterine sites, it is important to consider each substage of disease. In stage IIIA disease, patients are found to have extrauterine disease limited to positive cytology, adnexal involvement, and/or uterine serosal involvement. In general, each of these pathologic findings has been associated with the presence of other extrauterine disease; isolated positive PFC, adnexal involvement, or serosal involvement is relatively rare. However, the existing series of patients with these isolated pathologic findings do reveal some differences in outcome among these subgroups. In the GOG surgicopathologic study, positive PFC was found in 12 percent of patients. Of the patients with positive PFC, approximately 50 –60 percent had evidence of extrauterine spread, and the prognosis for these patients is determined by the presence of other extrauterine disease. Isolated positive PFC is rare, occurring in 5–6 percent of patients, and its importance as a prognostic factor is probably minimal. Many series have reported a relatively favorable outcome in this subset of patients, especially in the absence of LVSI or high-grade disease.[30] For example, one recent series reported a > 90% 3-year disease-free survival rate in 46 surgically-staged patients with isolated positive PFC; only three of those patients received adjuvant postoperative radiotherapy.[31] Adnexal involvement was found in 6 percent of patients in the GOG surgicopathologic study and was associated with a higher risk for pelvic and para-aortic metastases. Isolated adnexal involvement has been reported in several small series; most patients in those series received adjuvant pelvic radiotherapy. In general, patients with isolated adnexal involvement have a relatively favorable outcome, with a 5-year disease-free survival rate of approximately 60%–85% with the use of adjuvant radiotherapy.[32,33] In contrast to adnexal involvement, patients with uterine serosal involvement usually have a poor prognosis. As with other subsets of stage IIIA disease, serosal involvement is commonly associated with disease spread to other pelvic and extrapelvic sites. Reports of patients with isolated serosal involvement are limited but show a poor outcome; one series noted a 42% 5-year disease-free survival rate in patients receiving pelvic radiotherapy.[34] Stage IIIC disease includes those patients with involvement of the pelvic or para-aortic lymph nodes. The GOG surgicopathologic study found pelvic lymph node involvement in approximately 11 percent of stage I and occult stage II patients; para-aortic disease was found in approximately 5 percent of those patients. In that study, Morrow, et al.[11] found that the risk for recurrence for patients with stage IIIC disease was influenced by additional risk factors, such as positive

PFC, adnexal disease, and positive LVSI. With several risk factors present, 43 percent – 63 percent of patients failed. Other investigators have confirmed the negative impact of other risk factors on prognosis in patients with stage IIIC disease.[35] In general, patients with pelvic-only lymph node disease have a better outcome, with reported 5-year survival rates of approximately 70%.[36] Patients with disease in the para-aortic nodal chain have a worse outcome, with reported 5-year survival rates of approximately 30%–40% with the use of EFRT.[37] In addition, patients with stage IIIC disease limited to the pelvis and pathologically negative para-aortic nodes may also benefit from EFRT. Nelson, et al.[36] reported on a small series of patients with this subset of disease; approximately 12 percent of patients failed in the para-aortic chain after receiving pelvic radiotherapy alone for pelvic-only stage IIIC disease.

Patients with isolated peritoneal cytology involvement may have a favorable outcome without adjuvant treatment; treatment recommendations in these patients should be guided by other pathologic findings. In addition, patients with limited pelvic nodal disease or isolated adnexal disease have relatively favorable prognoses and have been historically managed with adjuvant EBRT or EFRT. However, recommendations for patients with all subsets of extrauterine disease will likely be strongly influenced by the recent reporting of the GOG 122 trial, the only modern randomized radiotherapy trial in this patient population. This trial randomized stage III and IV patients (without evidence of hematogenous metastases) after surgical staging and optimal debulking to receive either WART or adjuvant chemotherapy using Adriamycin and Cisplatin (AP).[38] At a median follow-up of 52 months, there was improvement in both progression-free and overall survival with the use of AP compared with WART. This improvement resulted in a 13% predicted improvement in disease-free status and an 11% predicted improvement in percent alive at 24 months. Overall, approximately 55 percent of patients recurred, with the majority of initial failures occurring outside the pelvis in both treatment arms. After 2 years, the rates of initial failures in the pelvis were 21% for the WART arm and 26% for the AP arm. The benefit of chemotherapy is in reducing distant recurrences at the site of first failure, from 18% with radiotherapy alone to 10% with systemic treatment. In this trial, chemotherapy was associated with significantly higher adverse effects. Grade 3–4 toxicities were primarily hematologic, gastrointestinal, and cardiac with the use of chemotherapy. With the reporting of the GOG 122 trial, there appears to be little role for the use of WART in stage III and IV endometrial cancer. However, the high local failure rates suggest a continued role for tailored radiotherapy fields in these patients. The recently completed GOG 184 study for patients with stage III and IV disease takes this approach. In that trial, patients were randomized to one of two chemotherapy arms after surgical staging and limited volume radiotherapy. The GOG 122 trial showed significant toxicity with the use of adjuvant chemotherapy, and only approximately two thirds of patients were able to complete all cycles of adjuvant chemotherapy. Given this toxicity, it should be recognized that some subsets of stage III patients (limited pelvic lymphadenopathy, isolated adnexal disease) who do not tolerate chemotherapy may have a relatively favorable outcome with EBRT or EFRT alone or, in the case of isolated positive PFC, no adjuvant therapy, versus vaginal brachytherapy alone.

Papillary Serous and Clear Cell Carcinoma

Papillary serous and clear cell carcinomas are aggressive histologic types with a propensity for upper abdominal spread. Complete surgical staging similar to ovarian cancer (i.e. includes omentectomy and peritoneal biopsies) is important in this disease, as up to 75 percent of patients with clinical stage I or II disease are upstaged with complete surgical staging.[39] Published therapeutic approaches in stage I and II disease include observation[40], chemotherapy and vaginal cuff brachytherapy[41], EBRT[42], WART[43], systemic chemotherapy, and vaginal cuff brachytherapy and intraperitoneal phosphorus-32.[44] The relative paucity of data and heterogeneity of published approaches limit the ability of radiation and gynecologic oncologists to make informed adjuvant treatment recommendations in patients with disease confined to the corpus. In the absence of clear data, limited-volume adjuvant radiotherapy (pelvic or vaginal cuff brachytherapy) may be a reasonable option in these patients. In patients with stage III or IV papillary

serous and clear cell disease, adjuvant radiotherapy has traditionally consisted of WART.[45] The GOG performed a prospective single-arm study of WART in 165 patients with stage III or IV disease, including papillary serous and clear cell patients. For the papillary serous and clear cell variants, that trial showed a 33% survival rate at 3 years.[46] The recently reported GOG 122 study included papillary serous and clear cell variants (approximately 30% of entrants), and the overall trial results revealed an inferior outcome in patients receiving WART when compared with those receiving adjuvant AP. Other investigators have noted a superior outcome using systemic therapy in stage III disease with poor histologic types.[47] Given the results of these studies and the known patterns of failure, patients with advanced-stage papillary serous and clear cell carcinomas should be considered for systemic therapy, with or without tumor volume-directed radiation therapy.

References

1. Laudico AV, Esteban DB, Redaniel MTM, Mapua CA and Reyes LM. 2005 Philippine Cancer Facts and Estimates. Manila: Philippine Cancer Society, Inc. 2004.
2. International Federation of Gynecology and Obstetrics (FIGO) Stages – 1988 Revision. Gynecol Oncol 1989; 35: 125-127.
3. Kwon JS, Carey MS, Cook EF, Qui F and Pasza L. Patterns of practice and outcomes in intermediate and high-risk stage I and II endometrial cancer: A population-based study. Int J Gynecol Cancer 2007; 17: 433-440.
4. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol 2003; 89: 201–209.
5. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004; 92: 744–751.
6. Aalders J, Abeler V, Kolstad P, et al. Postoperative external radiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980; 56: 419–427.
7. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. Int J Radiat Oncol Biol Phys 2003; 56: 1366–1372.
8. Randall ME, Wilder J, Greven K, et al. Role of intracavitary cuff boost after adjuvant external irradiation in early endometrial carcinoma. Int J Radiat Oncol Biol Phys 1990; 19: 49–54.
9. Potish RA, Dusenbery KE. Enteric morbidity of postoperative pelvic external beam and brachytherapy for uterine cancer. Int J Radiat Oncol Biol Phys 1990; 18: 1005–1010.
10. Creutzberg CL, van Putten WL, Koper PC, et al. The morbidity of treatment for patients with stage I endometrial cancer: results from a randomized trial. Int J Radiat Oncol Biol Phys 2001; 51: 1246–1255.
11. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 1991; 40: 55–65.
12. Straughn JM Jr, Huh WK, Kelly FJ, et al. Conservative management of stage I endometrial carcinoma after surgical staging. Gynecol Oncol 2002; 84: 194–200.
13. Poulsen H, Jacobsen M, Bertelsen K, et al. Adjuvant radiation therapy is not necessary in the management of endometrial carcinoma stage I, low risk cases. Int J Gynecol Cancer 1996; 6: 38–43.
14. Carey MS, O'Connell GJ, Johanson CR, et al. Good outcome associated with a standardized treatment protocol using selective postoperative radiation in patients with clinical stage I adenocarcinoma of the endometrium. Gynecol Oncol 1995; 57: 138–144.
15. Alektiar KM, McKee A, Venkatraman E, et al. Intravaginal high-doserate brachytherapy for Stage IB (FIGO Grade 1, 2) endometrial cancer. Int J Radiat Oncol Biol Phys 2003; 53: 707–713.
16. Anderson JM, Stea B, Hallum AV, et al. High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. Int J Radiat Oncol Biol Phys 2000; 46: 417–425.
17. MacLeod C, Fowler A, Duval P, et al. High-dose-rate brachytherapy alone for post-hysterectomy endometrial cancer. Int J Radiat Oncol Biol Phys 1998; 42: 1033–1039.
18. Hogberg T, Fredstorp-Lidebring M, Alm P, et al. A prospective population-based management program including primary surgery and postoperative risk assessment by means of DNA ploidy and histopathology. Adjuvant radiotherapy is not necessary for the majority of patients with FIGO stage I-II endometrial cancer. Int J Gynecol Cancer 2004; 14: 437–450.
19. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. Cancer 1987;60(suppl):2035–2041.
20. Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, et al. Outcome of high-risk IC, grade 3, compared with stage I endometrial carcinoma patients: the postoperative radiation therapy in endometrial carcinoma trial. J Clin Oncol 2004; 22: 1234–1241.
21. Straughn JM Jr., Huh WK, Orr JM, et al. Stage IC adenocarcinoma of the endometrium: survival comparisons of surgically staged patients with and without adjuvant radiation therapy. Gynecol Oncol 2003; 89: 295–300.
22. Chadha M, Nanavati PJ, Liu P, et al. Patterns of failure in endometrial carcinoma stage IB grade 3 and IC patients treated with postoperative vaginal vault brachytherapy. Gynecol Oncol 1999; 75: 103–107.

23. Fanning J, Hoffman ML, Andrews SJ, et al. Cost-effectiveness analysis of the treatment for intermediate risk endometrial cancer: postoperative brachytherapy versus observation. Gynecol Oncol 2004; 93: 632–636.
24. McCormick TC, Cardenes H, Randall ME. Early-stage endometrial cancer: is intravaginal radiation therapy alone sufficient therapy? Brachytherapy 2002; 1: 61–65.
25. Ng TY, Nicklin JL, Perrin LC, et al. Postoperative vaginal vault brachytherapy for node-negative stage II (occult) endometrial carcinoma. Gynecol Oncol 2001; 81: 193–195.
26. Inoue Y, Obata K, Abe K, et al. The prognostic significance of vascular invasion by endometrial carcinoma. Cancer 1996;78: 1447–1451.
27. Cohn DE, Horowitz NS, Mutch DG, et al. Should the presence of lymphovascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol 2002; 87: 243–246.
28. Greven KM, Corn B, Lanciano RM. Pathologic stage III endometrial carcinoma: significance of extrauterine sites. Radiat Oncol Investig 1996; 4: 122–128.
29. Mariani A, Webb MJ, Keeney GL, et al. Stage IIIC endometroid corpus cancer includes distinct subgroups. Gynecol Oncol 2002; 87: 112–117.
30. Mariani A, Webb MJ, Keeney GL, et al. Assessment of prognostic factors in IIIA endometrial cancer. Gynecol Oncol 2002;86:38–44.
31. Kasamatsu T, Onda T, Katsumata N, et al. Prognostic significance of positive peritoneal cytology in endometrial cancer confined to the uterus. Br J Cancer 2003; 88: 245–250.
32. Connell PP, Rotmensch J, Waggoner S, et al. The significance of adnexal involvement in endometrial carcinoma. Gynecol Oncol 1999; 74: 74–79.
33. Greven KM, Curran WJ Jr, Whittington R, et al. Analysis of failure patterns in stage III endometrial carcinoma and therapeutic implications. Int J Radiat Oncol Biol Phys 1989; 17: 35–39.
34. Ashman JB, Connell PP, Yamada D, et al. Outcome of endometrial carcinoma patients with involvement of the uterine serosa. Gynecol Oncol 2001; 82: 338–343.
35. McMeekin DS, Lashbrook D, Gold M, et al. Analysis of FIGO stage IIIC endometrial cancer patients. Gynecol Oncol 2001; 81: 273–278.
36. Nelson G, Randall M, Sutton G, et al. FIGO stage IIIC endometrial carcinoma with metastases confined to the pelvic lymph nodes: analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy. Gynecol Oncol 1999; 75: 211–214.
37. Potish RA, Twiggs LB, Adcock LL, et al. Paraaortic lymph node radiotherapy in cancer of the uterine corpus. Obstet Gynecol 1985; 65: 251–256.
38. Randall ME, Brunetto VL, Muss H, et al. Whole abdominal radiotherapy versus combination doxorubicin-cisplatin chemotherapy in advanced endometrial carcinoma: a randomized phase III trial of the Gynecologic Oncology Group. Proc Am Soc Clin Oncol 2003; 22: 2.
39. Goff BA, Kato D, Schmidt RA, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. Gynecol Oncol 1994; 54: 264–268.
40. Huh WK, Powell M, Leath CA 3rd, et al. Uterine papillary serous carcinoma: comparisons of outcomes in surgical stage I patients with and without adjuvant therapy. Gynecol Oncol 2003; 91: 470–475.
41. Turner BC, Knisely JP, Kacinski BM, et al. Effective treatment of stage I uterine papillary serous carcinoma with high dose-rate vaginal apex radiation (192Ir) and chemotherapy. Int J Radiat Oncol Biol Phys 1998; 40: 77–84.
42. Mehta N, Yamada SD, Rotmensch J, et al. Outcome and pattern of failure in pathologic stage I-II papillary serous carcinoma of the endometrium: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 2003; 57: 1004–1009.
43. Martinez AA, Weiner S, Podratz K, et al. Improved outcome at 10 years for serous-papillary/clear cell or high-risk endometrial cancer patients treated by adjuvant high-dose whole abdomino-pelvic irradiation. Gynecol Oncol 2003; 90: 537–546.
44. Fakiris AJ, Cardenes MR, Moore DH, et al. Intraperitoneal radioactive phosphorus (32P) and vaginal brachytherapy as adjuvant treatment for uterine papillary serous carcinoma and clear cell carcinoma: a phase II Hoosier Oncology Group (97-1) study. Gynecol Oncol 2005; 96: 818-823.
45. Stewart KD, Martinez AA, Weiner S, et al. Ten-year outcome including patterns of failure and toxicity for adjuvant whole abdominopelvic irradiation in high-risk and poor histologic feature patients with endometrial carcinoma. Int J Radiat Oncol Biol Phys 2002; 54: 527–535.
46. Axelrod J, Bundy J, Roy T, et al. Advanced endometrial carcinoma treated with whole abdomen radiation: a Gynecologic Oncology Group (GOG) study. Gynecol Oncol 1995; 56: 135–136.
47. Slomovitz BM, Burke TW, Eifel PJ, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. Gynecol Oncol 2003; 91: 463–469.