Original Articles

Clinical outcomes of adjuvant chemotherapy and vaginal brachytherapy with or without pelvic radiation for surgical Stage I-II uterine serous carcinoma

J.R. Robbins[1], M.S. Siddiqui[1], Z. Al-Wahab[2], B. Laser[1], M. Lu[3], R. Ali-Fehmi[4], A. Munkarah[5], M.A. Elshaikh[1]

[1]Department of Radiation Oncology, Henry Ford Hospital, Detroit, MI
[2]Department of Obstetrics and Gynecology. Wayne State University School of Medicine Detroit, MI
[3]Public Health Science, Henry Ford Hospital, Detroit, MI
[4]Department of Pathology, Wayne State University School of Medicine Detroit, MI
[5]Division of Gynecologic Oncology, Department of Women' Health Services. Henry Ford Hospital, Detroit, MI (USA)

Summary

Objective(s): To evaluate the benefit of adding pelvic radiation treatment (EBRT) to vaginal cuff brachytherapy (VB) for women with early stage uterine serous carcinoma (USC) treated with adjuvant chemotherapy. *Materials and Methods:* After institutional review board (IRB) approval, the authors retrospectively identified 56 patients with 2009 International Federation of Gynecology and Obstetrics (FIGO) Stage I-II USC treated with hysterectomy, bilateral oophorectomy ± lymphadenectomy, adjuvant chemotherapy, and radiation therapy with either VB alone (n = 33) or VB + EBRT (n = 23) between July 1998 and August 2009. *Results:* Median age and follow-up were 68.5 years and 54 months respectively. Median VB alone surface dose was 37.5 Gy and median pelvic EBRT dose was 45 Gy. The prevalence of lower uterine segment involvement, > 50% myometrial invasion, and Stage II disease were higher for patients receiving VB+EBRT. Overall, only one vaginal recurrence was observed. Pelvic recurrence rate was 26% for VB + EBRT compared to 12% for VB alone (p = 0.179). The five-year recurrence-free survival (RFS) was 80.5% for VB vs 67.3% for VB + EBRT (p = 0.3847), and the five-year overall survival (OS) was 65.9% for VB vs 66.7% for VB + EBRT (p = 0.7159). On univariate and multivariate analysis, radiation treatment modality was not a predictor for local control or survival. *Conclusions:* In this cohort, there was no significant clinical benefit of adding pelvic EBRT to the adjuvant management of early stage uterine serous carcinoma. The higher prevalence of high-risk features in the VB + EBRT group may underestimate the value of this treatment. Further investigation is warranted to identify the optimal radiation treatment regiment for early stage USC treated with surgery and adjuvant chemotherapy.

Key words: Endometrial carcinoma; Serous; Brachytherapy; Adjuvant; Radiation treatment.

Introduction

Endometrial cancer is the fourth most common malignancy in females and the most common gynecological malignancy in the United States with an estimated number of 43,470 cases and 7,950 deaths in 2010 [1]. Although most patients with endometrial cancer will not die from their disease, some subsets of patients are at much higher risk for recurrence and death. USC is a relatively rare subset of endometrial cancer representing less than 10% of all cases, but accounts for a disproportionate 39% of the total uterine cancer deaths [2]. Its aggressive nature is manifested by its propensity for deep myometrial invasion, extensive vascular space invasion, and early metastasis to lymph nodes with approximately 60 to 70 percent of women with USC having disease spread outside of the uterus at the time of presentation [3, 4]. These features of USC lead to high recurrence rates and poor prognosis, and only a relatively small portion of patients with early stage disease (Stage I-II) [3, 4].

Due to the infrequency of early-stage disease, there is a lack of randomized evidence to support optimal adjuvant management in this setting, and most recommendations are based on small retrospective series. In this light, it is generally accepted that all patients with USC should undergo comprehensive surgical staging, which includes a total hysterectomy, bilateral salphingo-oophorectomy, pelvic washings, and pelvic and para-aortic lymphadenectomy ± omentectomy [5-7]. A high risk of distant recurrence led to the use of adjuvant platinum-based chemotherapies, which have been shown to improve recurrence rates, progression-free, and overall survival [6, 8, 9].

Several studies have shown the benefit of adjuvant radiation treatment (RT) for patients with early stage USC [5, 6, 10-12]. A recent Surveillance Epidemiology End Results (SEER) study showed a survival benefit for adjuvant radiation after surgery for patients with early stage USC, which was most pronounced in patients with more than 50% myometrial involvement [12]. However, the optimal treatment volume and technique of adjuvant RT is less defined. Various RT volumes include vaginal brachytherapy alone [5, 9, 11, 13, 14] EBRT to the pelvis [6, 10, 15] combination of VB + EBRT [6, 7, 10] and whole abdominal RT incorporating pelvic boost, with or without vaginal brachytherapy [6, 7, 15].

Revised manuscript accepted for publication April 16, 2012

The purpose of this study was to compare the outcomes of patients with early stage USC treated with surgery followed by adjuvant chemotherapy and RT, with either vaginal brachytherapy alone or in combination with pelvic external beam RT, and to determine the potential benefits, if any, of adding pelvic external beam RT to the adjuvant management of these patients.

Materials and Methods

Following approval from the IRB, this prospectively-maintained database of 1,280 patients with uterine carcinoma and the database of Karmanos Cancer Center were examined to identify patients with 2009 FIGO Stage I-II uterine serous carcinoma. This group was further refined to include only patients who had hysterectomy, bilateral oophorectomy ± lymphadenectomy, ± omentectomy, adjuvant chemotherapy, and RT. Patient demographics, surgico-pathological information, clinical data, and follow-up details were obtained for the Institutions' computerized medical record system.

Surgical staging included: total abdominal hysterectomy (TAH), bilateral salphingo-oophorectomy (BSO), selective pelvic and para-aortic lymph node sampling with dissection of suspicious nodes, ± omentectomy, and peritoneal cytology. All surgeries were performed by gynecologic oncologists.

On pathological evaluation, the following factors were assessed: tumor grade, depth of myometrial invasion (< 50% vs ≥ 50%), angiolymphatic space invasion (ALI), lower uterine segment involvement (LUSI), and number of lymph nodes dissected. All cases met the microscopic criteria for USC according to World Health Organization (WHO) pathology manual [16] and were reviewed and confirmed by one gynecologic pathologist (RA). No patients with mixed tumors were included in this study.

Adjuvant treatments included both chemotherapy and RT. Chemotherapy was three-six cycles of carboplatin and paclitaxel regimen given adjuvantly after hysterectomy with the number of cycles determined by the discretion of the gynecologic oncologist.

All patients received adjuvant RT in the form of VB alone with or without additional pelvic external beam RT (VB + EBRT). RT was in the form of VB delivered using 192-Ir high dose rate (HDR). A median total surface dose of 37.5 Gy was delivered in five to six fractions, one to two fractions per week. The target volume treated was the upper four cm of the length of the vagina. The treatment was delivered using a single-channel cylinder that was connected to a HDR 192-Ir microSelectron (Nucletron, Veenendaal, Netherlands). The diameter of the cylinders used ranged from three to 3.5 cm (median, 3.5 cm). The median dose per fraction for VB alone was 7.5 Gy (range, 6 - 7.5 Gy). The dose was prescribed to the surface of the cylinder. Dose optimization was used in all the patients to ensure uniform dose distribution at depth and to eliminate the potential dose reduction at the vaginal apex because of source anisotropy. A Foley catheter was not used during these procedures. The bladder and rectal doses were not calculated. Pelvic external beam radiation consisted of standard 4-field box technique with a median dose of 45 Gy (range, 44-50.4), 1.8-2.0 Gy per fraction with daily treatments over five to six weeks.

After completion of adjuvant treatment, patients were regularly followed-up with clinical examination, Pap smear, and appropriate imaging studies. Survival curves were generated according to Kaplan-Meier product-limit method calculated from the date of hysterectomy. These were compared using the log-rank test to determine the rates of local control, Recurrence-Free Survival (RFS), Disease Specific Survival (DSS), and Overall Survival (OS). Cox regression analysis was used to explore relationships between various factors and outcomes using both univariate (UNA) and multivariate (MVA) models. The Fischer exact and χ^2 tests were used to determine significant differences ($p < 0.05$) in demographics, patient factors, and tumor characteristics between the VB and VB + EBRT groups.

Table 1. — *Patient characteristics between treatment groups.*

Variable	VB alone (n = 33)	VB + EBRT (n = 23)	*p* value
Race			
White	10 (30%)	10 (43%)	0.311
African American	23 (70%)	13 (57%)	
Median follow-up (months)	54.0 (range 18 - 151)	56 (range 19 - 134)	0.686
Median age at diagnosis (years)	64.0 (range 59 - 83)	69.0 (range 59 - 81)	0.052
Age group			
≤ 60	13 (39%)	3 (13%)	0.043
61-70	7 (21%)	11 (48%)	
≥ 71	13 (39%)	9 (39%)	
Cancer Stage			
I	31 (94%)	14 (61%)	0.002
II	2 (6%)	9 (39%)	
> 50% myometrial invasion	3 (9%)	7 (30%)	0.040
Lower uterine segment invasion	2 (6%)	8 (35%)	0.006
Angiolymphatic invasion	11 (33%)	6 (26%)	0.562
Median # of lymph nodes removed	8 (range 0 - 21)	8 (range 0 - 30)	0.147
No lymph nodes removed	9 (27%)	5 (22%)	0.641
1 - 9 lymph nodes removed	13 (39%)	7 (30%)	0.496
≥ 10 lymph nodes removed	11 (33%)	11 (48%)	0.067
Median # of paraaortic lymph nodes removed	2 (range 0 - 6)	2 (range 0 - 4)	0.635
Omentectomy	22 (67%)	16 (70%)	0.234
Treatment-related toxicity (diarrhea ≥ Grade II)	0 (0%)	4 (25%)	0.002
Overall recurrence	6 (18%)	7 (30%)	0.285
Vaginal	1 (3%)	0 (0%)	0.400
Pelvic	4 (12%)	6 (26%)	0.179
Distant	6 (18%)	6 (26%)	0.478

VB = vaginal brachytherapy; VB + EBRT = vaginal brachytherapy with pelvic external beam radiaiton treatment.

Table 2. — *Patterns of failure by treatment and stage.*

	Overall recurrence	Vaginal	Pelvic	Distant	Death from disease
Stage I					
VB alone (n = 31)	5 (16%)	1 (3%)	3 (10%)	5 (16%)	5 (16%)
VB + EBRT (n = 14)	1 (7%)	0 (0%)	1 (7%)	1 (7%)	1 (7%)
Overall (n = 45)	6 (13%)	1 (2%)	4 (9%)	6 (13%)	6 (13%)
Stage II					
VB alone (n = 2)	1 (50%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)
VB + EBRT (n = 9)	6 (66%)	0 (0%)	5 (56%)	5 (56%)	4 (44%)
Overall (n = 11)	7 (64%)	0 (0%)	6 (55%)	6 (55%)	5 (45%)

VB = vaginal brachytherapy; VB + EBRT = vaginal brachytherapy with pelvic external beam radiaiton treatment.

Results

The authors identified 56 patients with pathologic Stages I-II uterine serous carcinoma treated at the Institutions that had surgery from July 1998 to August 2009. Table 1 shows the demographic, pathological, and recurrence compar-

Table 3. — *Patterns of failure by treatment and stage*.

Parameter	Local control		Recurrence - free survival		Disease - specific survival		Overall survival	
	Univariate analysis							
	p value	HR (CI)	*p* value	HR (CI)	*p* value	HR (CI)	*p* value	HR (CI)
Stage II	0.012	14.9 (1.8 - 124)	0.009	6.2 (1.6 - 24.1)	0.068	3.8 0.9 - 15.94	0.263	2.5 (0.82 - 7.55)
LUSI	0.003	7.1 (2.0 - 25)	0.002	5.9 (2.0 - 17.7)	0.051	3.3 0.99 - 10.8)	0.149	2.0 (0.77 - 5.25)
≥ 50% MI	0.050	3.5 (0.97 - 12.3)	0.022	2.9 (1.2 - 7.1)	0.014	4.5 (1.4 - 14.7)	0.023	1.0 (1.004 - 1.03)
ALI	0.012	5.2 (1.4 - 18.6)	0.002	5.75 (1.9 - 17.7)	0.001	8.2 (2.3 - 29.2)	0.001	4.6 (1.95 - 10.89)
Parameter	Local control		Recurrence - free survival		Disease - specific survival		Overall survival	
	Multivariate analysis							
	p value	HR (CI)	*p* value	HR (CI)	*p* value	HR (CI)	*p* value	HR (CI)
≥ 50% MI	–		–		0.043	3.6 (1.04 - 12.2)	0.023	2.9 (1.16 - 7.5)
ALI	0.030	4.3 (1.2 - 15.6)	0.002	5.7 (1.9 - 17.8)	0.002	7.4 (2.0 - 27.0)	0.001	4.8 (2.0 - 11.5)

CI = confidence interval; HR = hazard ratio; LUSI = lower uterine segment involvement; MI = myometrial invasion; ALI = angiolymphatic space invasion.

isons between these groups. The median follow-up time for all patients was 54 months (range 18 - 151 months) and the median age was 68.5 years (range 48 - 91 years). African American comprised 63% of patients. The median number of examined lymph nodes was 8 (range 0 - 30).

For the entire cohort of patients, the five-year clinical outcomes were as follows: recurrence-free survival 74.0%; local-regional control 79.6%; disease-specific survival 77.4%; and overall survival 63.4%. Thirty-three (59%) of the patients received VB alone and twenty-three (41%) received VB + EBRT. Patients in the VB + EBRT group were more likely to have Stage II disease (p = 0.002), lower uterine segment involvement (LUS) (p = 0.006), ≥ 50% myometrial invasion (MI) (p = 0.04), and older age (p = 0.043).

Figure 1 shows the Kaplan-Meier plots for survival outcomes for patients who received VB alone compared to those who received VB + EBRT. The five-year local regional control was 87.1% for VB and 71.8% for VB + EBRT. The five-year RFS was 80.5 % for VB versus 67.3 for VB + EBRT. In regards to DSS, the estimated five-year rate was 78.9% for VB alone compared to 78.9% for VB + EBRT, and the five-year OS rates was 65.9% for VB versus 66.7% for VB + EBRT. These are shown in Table 2. Statistically significant differences were not detected between treatment groups for any of the outcome parameters (local control, RFS, DSS, and OS).

As expected, patients with Stage I disease had superior outcomes compared to Stage II patients. Stage II patients had significant worse five-year recurrence-free survival rates (30% vs 85.6%, p = 0.001), five-year local-regional control rates (35.0% vs 90.6%, p = 0.001), and a trend towards worse DSS (54.5% vs 84.8%, p = 0.063) compared to Stage I patients, but differences in OS were not statistically different (45.5% vs 71.9%, p = 0.152). While the extent of lymph node dissection did not appear to impact clinical outcomes (OS, DSS, RFS) for the entire cohort, Stage II patients with limited lymph node dissection (0 - 9) lymph nodes dissection had worse five-year DSS compare to those with 10+ lymph nodes removes (40% vs 83%, p = 0.045).

There were no significant differences between patterns of failure between treatment groups, but there were clear differences between Stage I and II. As Stage increased, so did the propensity for overall recurrence, pelvic recurrence, and distant recurrence. For example the overall recurrence rate for Stage I was 13% compared to 64% for Stage II patients (Table 2).

Univariate analyses determined that ALI, ≥ 50% MI, Stage II, and LUSI were predictive for local control, RFS, and DSS, while for OS, univariate analysis identified only angiolymphatic invasion and ≥ 50% myometrial invasion as significantly predictive. After multivariable modeling, performed on an exploratory basis, only ALI remained statistically predictive for local control, RFS, DSS and OS (Table 3). In addition, MI ≥ 50% was found to be independent predictive of OS and DSS. RT type (VB compared to VB + EBRT) was not found to be significantly predictive in this patient population for any of the observed outcomes.

Discussion

This is the first study investigating the potential benefits of adding pelvic RT to the adjuvant treatment of patients with 2009 FIGO Stage I-II uterine serous carcinoma in the setting of adjuvant chemotherapy and VB. In this study, excellent vaginal control and good local-regional control was observed for the entire cohort, but the authors were unable to detect a difference in OS, DSS, LR control or RFS between the groups treated with VB or VB + EBRT.

In previously published studies, one of the greatest difficulties determining the role and type of adjuvant RT for early stage USC is the heterogeneity of treatments and patient characteristics existing even in a single study. Often, analysis is performed combining all types of RT modalities into one treatment group "adjuvant radiation", [6, 7, 9, 10, 17] but this approach does not aid in the discussion about which modality and treatment volume is most effective. This controversy is compounded by the relative scarcity of serous histology and the retrospective nature of most studies and creates debate defining specific success rates by treatment modality between groups and studies.

The main objective of the current study was to suggest the appropriate treatment volume for adjuvant RT (VB alone or in combination with pelvic RT) in women with early stage USC who received adjuvant chemotherapy after hysterectomy. The overall results suggest that there is no difference between RT options, but this may mis-

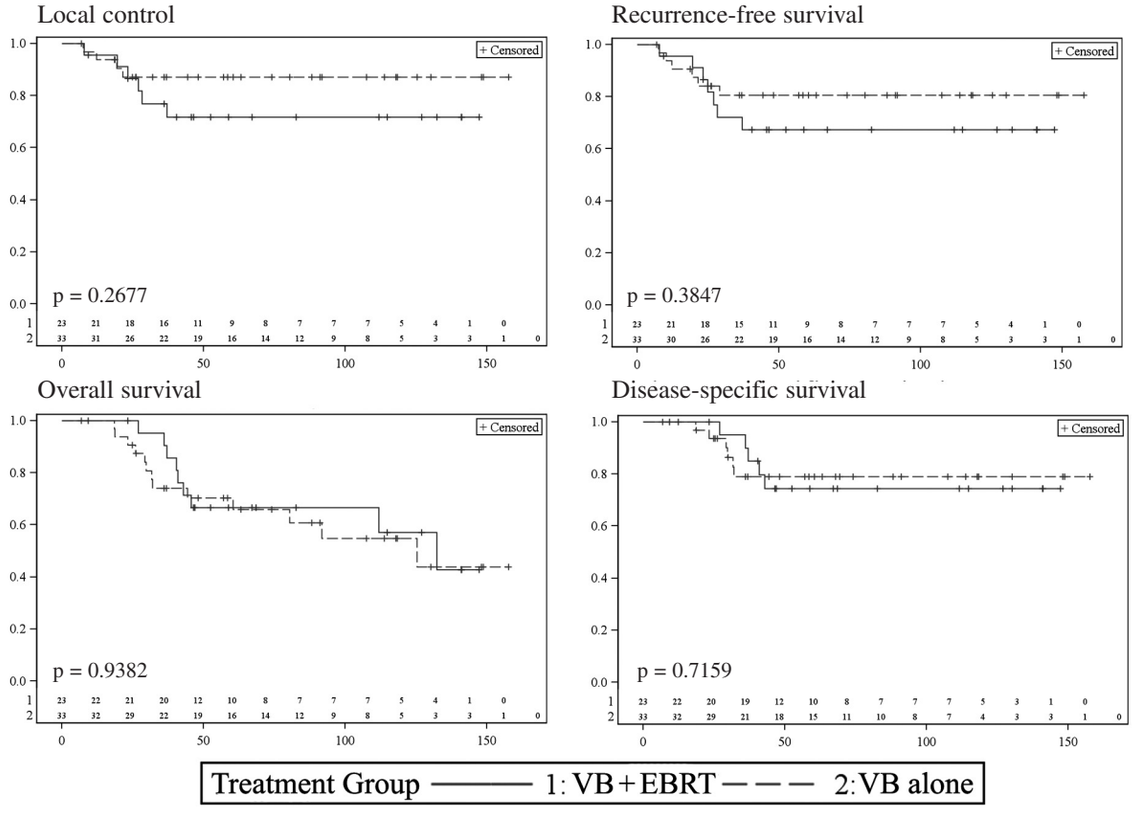

Figure 1. — Kaplan-Meier analysis of clinical outcomes comparing VB to VB + EBRT.
VB = vaginal brachytherapy; VB + EBRT = vaginal brachytherapy with pelvic external beam radiation treatment.

represent the data due to the retrospective nature of this study and the fact that the two treatment groups were not equally weighted. Significantly, more patients receiving VB + EBRT had Stage II disease, LUSI, higher incidence of deep MI, and a trend towards older age. These features likely contributed to the final outcomes and may mitigate any benefit of EBRT. With this in mind, and in light of previously published reports, for patients with surgical Stage I USC treated with adjuvant chemotherapy, VB alone may suffice, but adding pelvic RT may be potentially beneficial to patients with Stage II disease or Stage I patients with adverse prognostic factors (e.g. angiolymphatic invasion, and deep MI).

In this study, only one patient had isolated vaginal cuff recurrence alone. All others with recurrences, had local recurrence as a component of distant failure. The rate of local-regional control at five years was 80% for the entire group, but rates were significantly worse in Stage II patients compared to Stage I, 35% vs 90.6% at five years respectively. Stage II patients also had increased distant metastasis with crude distant failure rates of 55% vs 13% compared to Stage I patients. This study also showed differences between Stage I and Stage II patients for RFS and local control with a trend towards worse DSS for Stage II patients.

In their series of patients treated with chemotherapy and vaginal brachytherapy, Alketiar *et al*. also reported worse outcomes with Stage II patients compared to Stage I patients with two out of five (40%) Stage II patients recurring opposed to only two out of 20 (10%) Stage I patients [11]. This may suggest that VB alone may not be adequate to treat Stage II patients even with chemotherapy and surgical staging.

The authors report a five-year OS rate of 63.4% for the mixed population of Stage I and II patients. The rate in this study was lower than the 88% rate that was reported by Alektiar *et al*. in a small group (n = 25) of Stage I-II patients treated with surgical staging, carboplatin/paclitaxel chemotherapy and intravaginal brachytherapy, but the median follow-up in this study was almost double (54 months vs 30 months) [11]. Turner *et al*. reported a 95% five-year overall survival and disease-free survival in 18 patients with Stage I uterine serous carcinoma who underwent surgical staging, and adjuvant vaginal HDR brachytherapy (five received chemotherapy) and a 100% five-year overall survival for those who underwent comprehensive surgical staging [5]. Two possible explanations for the slightly worse outcomes in this study compared to Turner *et al*. is the lack of comprehensive surgical staging for fewer patients in this study

and the inclusion of Stage II patients. While all patients received hysterectomy, bilaterally oophorectomy, peritoneal washings and evaluations of omentum and lymph nodes, few patients did not undergo routine omental biopsies and pelvic and paraaortic lymph node dissection. One can argue that occult disease may have contributed to poorer outcomes in patients without comprehensive surgical staging in this series. Stage II patients with limited lymph node dissection had worse disease-specific survival in this series. Others have also shown the benefit of comprehensive surgical staging [3, 4, 18]. Surgical staging should help determine both the need for and type of adjuvant treatment. Combining these data show the aggressive nature of USC even in early stage disease and emphasizes the value of appropriate staging for accurate risk assessment and prognostication.

A major limitation of the current study is the retrospective nature of its design with its inherent biases. Although the sample size for this study is small by statistical standards, it is one of the largest series to date for patients with early stage serous carcinoma treated with adjuvant chemotherapy and RT. The authors attempted to eliminate the confounding effect of FIGO stage by only including surgical Stage I - II USC in contrast to other studies, which comprise all Stages including III - IV [9, 17]. In this cohort, all patients received similar treatments with adjuvant chemotherapy, and RT, but not all patients underwent comprehensive surgical staging as noted above. Furthermore, this study only included patients with serous carcinoma and all the pathologic slides were recently reviewed and confirmed by one gynecologic pathologist (RA).

This study had a relatively long follow-up compared to other studies, so adequate time was allowed to detect late recurrences [6, 7, 9-11, 13, 19, 20]. The population studied was predominately African American (AA) (66% of the total) and represents the largest reported AA cohort of early stage USC patients all treated with hysterectomy, bilateral oophorectomy ± lymph nodal evaluation and adjuvant chemotherapy and RT. Several recent population-based studies have suggested that AA patients with USC fair worse than their Caucasian counterparts, but this difference may diminish when accounting for differences in treatment [21, 22].

Due to the aforementioned limitations and questions regarding the most appropriate volume of adjuvant RT for USC, further work defining the most effective adjuvant therapies should include prospective multicenter randomized trials. In fact, a current protocol for high-risk early stage uterine cancer, Gynecologic Oncology Group (GOG) 0249, is comparing EBRT with additional VB for Stage II or Stage I with serous or clear cell histology to VB alone with three cycles of carboplatin and paclitaxel cheomotherapy. Although the GOG study cohort will include different histologies and only half of the patients will receive chemotherapy, it may give additional insight into the most appropriate adjuvant treatment modality.

Conclusion

In this series of Stage I-II patients with USC who received adjuvant chemotherapy, clinical outcomes were similar between patients receiving adjuvant RT in the form of HDR VB alone or in combination with pelvic external beam RT, but some bias may have mitigated the benefit of additional pelvic RT. Even with adequate local treatment, distant failure remains a problem. Further work defining the most appropriate adjuvant therapies should include prospective multicenter randomized trials to better determine the type of adjuvant radiation therapies for these patients.

References

[1] Jemal A., Siegel R., Xu J., Ward E.: "Cancer statistics 2010". *CA Cancer J. Clin*., 2010, *60*, 277.

[2] Ueda S.M., Kapp D.S., Cheung M.K., Shin J.Y., Osann K., Husain A. *et al*.: "Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths". *Am. J. Obstet. Gynecol*., 2008, *198*, 218.

[3] Slomovitz B.M., Burke T.W., Eifel P.J., Ramondetta L.M., Silva E.G., Jhingran A. *et al*.: "Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases". *Gynecol. Oncol*., 2003, *91*, 463.

[4] Goff B.A., Kato D., Schmidt R.A., Ek M., Ferry J.A., Muntz H.G. *et al*.: "Uterine papillary serous carcinoma: patterns of metastatic spread". *Gynecol. Oncol*., 1994, *54,* 264.

[5] Turner B.C., Knisely J.P., Kacinski B.M., Haffty B.G., Gumbs A.A., Roberts K.B. *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.

[6] Havrilesky L.J., Secord A.A., Bae-Jump V., Ayeni T., Calingaert B., Clarke-Pearson D.L. *et al*.: "Outcomes in surgical Stage I uterine papillary serous carcinoma". *Gynecol. Oncol*., 2007, *105,* 677.

[7] Huh W.K., Powell M., Leath C.A. 3rd, Straughn J.M. Jr., Cohn D.E., Gold M.A. *et al*.: "Uterine papillary serous carcinoma: comparisons of outcomes in surgical Stage I patients with and without adjuvant therapy". *Gynecol. Oncol*., 2003, *91,* 470.

[8] Fader A.N., Starks D., Gehrig P.A., Secord A.A., Frasure H.E., O'Malley D.M. *et al*.: "An updated clinicopathologic study of early-stage uterine papillary serous carcinoma (UPSC)". *Gynecol. Oncol*., 2009, *115,* 244.

[9] Kelly M.G., O'Malley D.M., Hui P., McAlpine J., Yu H., Rutherford T.J. *et al*.: "Improved survival in surgical Stage I patients with uterine papillary serous carcinoma (UPSC) treated with adjuvant platinum-based chemotherapy". *Gynecol. Oncol*., 2005, *98,* 353.

[10] Mehta N., Yamada S.D., Rotmensch J., Mundt A.J.: "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.

[11] Alektiar K.M., Makker V., Abu-Rustum N.R., Soslow R.A., Chi D.S., Barakat R.R. *et al*.: "Concurrent carboplatin/paclitaxel and intravaginal radiation in surgical Stage I-II serous endometrial cancer". *Gynecol. Oncol*., 2009, *112,* 142.

[12] Kim A., Schreiber D., Rineer J., Choi K., Rotman M.: "Impact of adjuvant external-beam radiation therapy in early-stage uterine papillary serous and clear cell carcinoma". *Int. J. Radiat. Oncol. Biol. Phys*., 2011, *81,* e639.

[13] DuBeshter B., Estler K., Altobelli K., McDonald S., Glantz C., Angel C.: "High-dose rate brachytherapy for Stage I/II papillary serous or clear cell endometrial cancer". *Gynecol. Oncol*., 2004, *94,* 383.

[14] Low J.S., Wong E.H., Tan H.S., Yap S.P., Chua E.J., Sethi V.K. *et al*.: "Adjuvant sequential chemotherapy and radiotherapy in uterine papillary serous carcinoma". *Gynecol. Oncol*., 2005, *97,* 171.

[15] Grice J., Ek M., Greer B., Koh W.J., Muntz H.G., Cain J. *et al*.: "Uterine papillary serous carcinoma: evaluation of long-term survival in surgically staged patients". *Gynecol. Oncol*., 1998, *69*, 69.
[16] Devilee P., International Agency for Research on Cancer., World Health Organization: "Pathology and genetics of tumours of the breast and female genital organs". Lyon, IARC Press, 2003.
[17] Goldberg H., Miller R.C., Abdah-Bortnyak R., Steiner M., Yildiz F., Meirovitz A. *et al*.: "Outcome after combined modality treatment for uterine papillary serous carcinoma: a study by the Rare Cancer Network (RCN)". *Gynecol. Oncol*., 2008, *108*, 298.
[18] Gehrig P.A., Groben P.A., Fowler W.C. Jr., Walton L.A., Van Le L.: "Noninvasive papillary serous carcinoma of the endometrium". *Obstet. Gynecol*., 2001, *97*, 153.
[19] Fader A.N., Drake R.D., O'Malley D.M., Gibbons H.E., Huh W.K., Havrilesky L.J. *et al*.: "Platinum/taxane-based chemotherapy with or without radiation therapy favorably impacts survival outcomes in Stage I uterine papillary serous carcinoma". *Cancer,* 2009, *115,* 2119.
[20] Elit L., Kwon J., Bentley J., Trim K., Ackerman I., Carey M.: "Optimal management for surgically Stage I serous cancer of the uterus". *Gynecol. Oncol*., 2004, *92*, 240.
[21] Al-Wahab Z., Ali-Fehmi R., Cote M.L., Elshaikh M.A., Ibrahim D.R., Semaan A. *et al*.: "The impact of race on survival in uterine serous carcinoma: a hospital-based study". *Gynecol. Oncol*., 2011, *121*, 577.
[22] Sherman M.E., Devesa S.S.: "Analysis of racial differences in incidence, survival, and mortality for malignant tumors of the uterine corpus". *Cancer,* 2003, *98,* 176.

Address reprint requests to:
M.A. ELSHAIKH, M.D.
Department of Radiation Oncology
Henry Ford Hospital
2799 West Grand Blvd
Detroit, MI 48202 (USA)
e-mail melshai1@hfhs.org