

Editorial



Combined modality therapy in the adjuvant treatment of uterine serous carcinoma

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Uterine serous carcinoma (USC) represents a clinically aggressive and highly malignant endometrial cancer. Initially distinguished from other types of primary endometrial adenocarcinoma in 1982, Hendrickson et al. [1] performed a pathologic review of 256 stage I endometrial cancers treated at Stanford University, with 26 of the cases revealing USC. Of these cases, 40% had deep myometrial invasion compared to 12% of typical adenocarcinomas. With deep invasion, relapse rates for USC were 63% compared to only 30% for adenocarcinomas. As a whole, 50% of the USC patients recurred, with most recurrences occurring on peritoneal surfaces in the upper abdomen. The authors concluded that this type of pattern of spread was similar to ovarian cancer and should be treated as such with either upper abdominal and pelvic radiotherapy or chemotherapy [1].

Several retrospective studies have suggested a benefit to adjuvant chemotherapy specifically in USC, although in the absence of randomized evidence, the impact of chemotherapy remains widely unknown. In a retrospective, multi-institutional study of 142 stage I USC patients treated with platinum and taxane based adjuvant chemotherapy, Fader et al. [2] found five year progression free and cause specific survival benefits compared to adjuvant radiation alone or observation. Similarly, Viswanathan et al. [3] reported improvement in overall survival with taxane based adjuvant chemotherapy compared to those who did not receive chemotherapy in a retrospective review of 135 patients of all stages with USC. In this same review, recurrence free survival was improved with radiation therapy compared to those who did not receive radiation therapy, suggesting that both chemotherapy and radiation play a critical role in the overall management of such patients [3].

To further evaluate the benefits of adjuvant radiation and systemic therapy, the Albert Einstein group conducted a phase 2 trial of pelvic radiation “sandwiched” between taxane and platinum based chemotherapy. Eighty-one patients with USC were enrolled in the study, in which patients were treated with 3 cycles of paclitaxel and carboplatin, followed by pelvic external beam radiation therapy and vaginal brachytherapy, followed by 3 additional cycles of chemotherapy. For stages I–II, overall survival at 3 years was 84%, compared to 50% for stages II–IV. Authors concluded that this method was well tolerated; however, overall survival outcomes were similar to historical controls [4].

In this issue of *Journal of Gynecologic Oncology*, Mahdi et al. [5] report their results of their review of the Surveillance, Epidemiology, and End Results (SEER) program 2000–2009, in which the authors investigated the impact on survival of external beam radiation therapy in stages I–IV USC patients who also received adjuvant chemotherapy. The authors are to be commended for this work, in which a large dataset of 1,838 patients were analyzed with appropriate statistics in order to reach their endpoint. In an era in which it is becoming more difficult to obtain funding to conduct large phase 3 randomized trials, particularly for relatively rare entities such as USC, we often must rely more on high-quality phase 2 studies and large database reviews such as the one presented by Mahdi et al. [5], to guide treatment decisions.

In their study, Mahdi et al. [5] evaluated the benefit of external beam irradiation. Patients who received brachytherapy as their only form of radiation therapy, plus chemotherapy, were excluded. The authors found that patients who received external beam radiation had a significantly better overall survival and disease specific survival than those who did not receive external beam radiation; however, on multivariate analysis controlling for age, stage, race, and extent of pelvic lymph node dissection, the survival benefit persisted only for stage III patients. The authors conclude that combined modality treatment with both chemotherapy and radiation therapy should always be considered for patients with stage III USC.

Although there have been no randomized trials dedicated to patients with USC, several trials have included patients with this variant. These have suggested that the benefit of chemotherapy alone is modest. Gynecologic Oncology Group (GOG) 249 study was a phase 3 randomized trial comparing adjuvant pelvic radiation therapy versus vaginal cuff brachytherapy followed by taxane/platinum chemotherapy. This study included 601 patients with high risk, early stage endometrial cancer, in which 15% of the cohort consisted of stages I–II USC. At 24 months, preliminary data presented in 2014 reported no difference in recurrence free or overall survival between the two adjuvant treatment strategies [6]. These data suggest, although with short follow-up thus far, that chemotherapy was not superior to adjuvant pelvic radiation. Similarly, the Nordic Society of Gynecologic Oncology/European Organization for the Research and Treatment of Cancer (NSOG-9501/EORTC 55991) trial randomized patients to adjuvant pelvic radiation therapy plus or minus sequential chemotherapy [7]. This study included 141 stages I–III USC and clear cell carcinoma patients, and for this subset of patients with high risk histologies, progression free survival at 5 years was equivalent in both study arms, suggesting a lack of benefit of sequential chemotherapy to adjuvant radiation therapy.

Each of the patients analyzed in this issue's SEER program analysis of 1,838 USC patients received adjuvant chemotherapy. However, patients who also received radiation therapy either with or without a brachytherapy boost, appeared to have a better outcome particularly if they had stage III disease. This is not surprising given the known local control and progression free survival benefit from adjuvant radiation. It is unclear whether radiation therapy alone, with the omission of chemotherapy, would confer the same improvement in survival. In their introduction, Mahdi et al. [5] report that "given the aggressive nature of this disease and its propensity for systemic spread, adjuvant chemotherapy has become the standard adjuvant therapy in patients with USC." We agree that chemotherapy is the most often utilized adjuvant treatment for patients in USC, however, data, particularly randomized data, does not support such a claim that chemotherapy is the standard of care as the most appropriate adjuvant treatment.

In summary, we agree with the conclusion drawn from the authors' well written and well analyzed SEER database review of adjuvant treatment strategies for USC—this review validates the findings of previous studies and suggests that the improved local control achieved with external beam radiation may translate into improved survival for some patients. USC remains an uncommon, but highly malignant and clinically aggressive form of endometrial cancer. The adjuvant treatment of this entity remains controversial, and individual cases should be routinely discussed in a multidisciplinary setting in order to guide patient care. Limited randomized data do not confirm the superiority of chemotherapy over radiation therapy for patients with locoregionally-confined USC. Phase 2 series and retrospective reviews discussed previously, including this large SEER review by Mahdi et al. [5] suggest a continued benefit to external beam radiation therapy in the adjuvant treatment of USC.

REFERENCES

1. Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. *Am J Surg Pathol* 1982;6:93-108.
[PUBMED](#) | [CROSSREF](#)
2. Fader AN, Drake RD, O'Malley DM, Gibbons HE, Huh WK, Havrilesky LJ, et al. Platinum/taxane-based chemotherapy with or without radiation therapy favorably impacts survival outcomes in stage I uterine papillary serous carcinoma. *Cancer* 2009;115:2119-27.
[PUBMED](#) | [CROSSREF](#)
3. Viswanathan AN, Macklin EA, Berkowitz R, Matulonis U. The importance of chemotherapy and radiation in uterine papillary serous carcinoma. *Gynecol Oncol* 2011;123:542-7.
[PUBMED](#) | [CROSSREF](#)
4. Einstein MH, Frimer M, Kuo DY, Reimers LL, Mehta K, Mutyala S, et al. Phase II trial of adjuvant pelvic radiation "sandwiched" between combination paclitaxel and carboplatin in women with uterine papillary serous carcinoma. *Gynecol Oncol* 2012;124:21-5.
[PUBMED](#) | [CROSSREF](#)
5. Mahdi H, Nutter B, Abdul-Karim F, Amarnath S, Rose PG. The impact of combined radiation and chemotherapy on outcome in uterine papillary serous carcinoma compared to chemotherapy alone. *J Gynecol Oncol* 2015;27:e19.
[PUBMED](#) | [CROSSREF](#)
6. McMeekin DS, Filiaci VL, Aghajanian C, Cho J, Kim JW, DiSilvestro PA, et al. A randomized phase III trial of pelvic radiation therapy (PXRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk (HR), early stage endometrial cancer (EC): a Gynecologic Oncology Group trial. *Gynecol Oncol* 2014;134:438.
[CROSSREF](#)
7. Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. *Eur J Cancer* 2010;46:2422-31.
[PUBMED](#) | [CROSSREF](#)