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Defining the Place of Adjuvant Chemotherapy and Radiation for High-Risk Endometrial Cancer From Recent Randomized Clinical Trials: Some Answers, More Questions

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Endometrial carcinoma is the most common gynecologic malignancy. Most patients present with early stage disease, but in about 10% to 15% of all new cases of endometrial cancer, disease is found outside the uterus at diagnosis. These patients account for more than 50% of all uterine cancer–related deaths. They are treated with adjuvant chemotherapy (CT) and/or radiation therapy (RT), although we do not know the true impact of adjuvant treatment on survival (1). This issue's Oncology Scan covers 3 recently presented or published prospective trials—Gynecology Oncology Group (GOG)-258 (2), GOG-249 (3), and Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC-3) (4)—and a National Cancer Database (NCDB) (5) analysis that tried to define optimal adjuvant treatment for high- or high-intermediate-risk endometrial cancer.

PORTEC-3 and GOG-258 were 2 large clinical trials for high-risk endometrial cancer conducted in 2 different continents with key differences in inclusion criteria. They both have the same combined CTRT schedule in the experimental arm, but the control arms are different. In PORTEC-3, the control arm is RT alone, whereas in GOG-258, it is CT alone. PORTEC-3 included a heterogeneous population of high-risk patients, which complicates our interpretation of the results. The stage III subset saw a significant benefit with chemoradiation therapy (CRT) of about 10% in 5-year failure-free survival (FFS), but stage I-II patients and those with serous histology did not see a benefit in FFS. The initial report of GOG-258 found no significant difference in recurrence-free survival (RFS) between the 2 arms, although locoregional relapses were significantly reduced with radiation (26% vs 13%).

GOG-249—which had some overlap with the early-stage high-risk patient population also included in PORTEC-3—did not demonstrate superiority of vaginal brachytherapy plus CT over pelvic radiation (PXRT). These conflicting results are reflected in practice patterns seen in the NCDB analysis: Among those who received adjuvant treatment for stage III or greater disease, CT alone was used in 65%, whereas the remaining patients received a combination of CT and RT.

These recent results have posed more questions than answers about optimal adjuvant treatment for the high-risk population. These differences could be explained partly by including heterogeneous patient populations in terms of stage and histology in these studies. Moreover, not all stage III disease has the same recurrence pattern (nodal disease vs adnexal disease), and not all histologies have similar chemosensitivity (endometroid vs clear cell vs papillary serous) (6). Future studies should consider these heterogeneities along with molecular predictors to identify patients who would benefit from CT and/or RT. The ongoing PORTEC-4A, a randomized phase III trial using molecular profile–based versus standard recommendations for adjuvant RT for women with early-stage endometrial cancer, is a step in that direction (7).

Conflict of interest: None.

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de Boer et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): Final results of an international, open-label, multicenter, randomized, phase 3 trial. *Lancet Oncology* 2018. (4)

Summary: PORTEC-3 enrolled patients with endometrial cancer who were found to have high-risk disease after standard surgery (endometrioid: 2009 FIGO IA+G3+LVI, IB+G3; II, IIIA, IIIB [parametrial invasion], IIIC; serous/clear cell: IA [with invasion], IB, II, or III). The patients were randomized in the adjuvant setting to receive either RT alone or CRT. RTOG-9708 served as the basis for the regimen used in the CRT arm, in which patients received 2 cycles of cisplatin 50 mg/m^2 during the first and fourth weeks of external beam RT, followed by 4 cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 at 21-day intervals. The external beam was 45 to 50.4 Gy, and a vaginal cuff brachytherapy boost was given for cervical involvement with a recommended dose of 5 Gy × 2 fractions prescribed to 5 mm depth. Most patients were treated using a 4-field technique. The co-primary endpoints of the study were overall survival (OS) and FFS (defined as any relapse or death related to endometrial cancer). The trial was powered to detect a 10% difference in 5-year OS or FFS.

A total of 660 patients were included in the primary analysis (330 CRT and 330 RT). An approximate summary of the patients treated is as follows: median patient age was 62 years; 45% of patients were stage III; 25% of patients were serous/clear cell; 60% had surgery with lymphadenectomy, lymph node sampling, or full surgical staging (median of 15 nodes removed); half received a brachytherapy boost; and 75% completed all 4 cycles of adjuvant CT.

With a median follow-up of 60.2 months, the 5-year OS was similar between the 2 arms (81.8% for CRT and 76.7% for RT), but the 5-year FFS was significantly in favor of CRT (75.5% vs 68.6%; hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.53-0.95; $P = .022$). For the subset of stage III patients, the 5-year OS was not significantly different (78.7% vs 69.8%), but the 5-year FFS was again in favor of CRT (69.3% vs 58.0%; HR 0.66; 95% CI 0.45-0.97; $P = .031$; adjusted $P = .014$). For the stage I to II patients, the 5-year FFS was not significantly different. The 5-year FFS also was not significantly different in the serous (>25% serous component) subgroup (58% CRT vs 48% RT; $P = .11$). The most common site of recurrence was distant (22% CRT vs 28% RT; $P = .108$). The 5-year risk of a pelvic recurrence (isolated and combined pelvic and distant recurrences) was in favor of the CRT group (4.9% CRT vs 9.2% RT; $P = .026$). On multivariable analysis for FFS only, age group was predictive of treatment effect, with women over 70 years of age having the greatest benefit from CRT. At 5 years, the risk of a grade 2 or higher (CTCAE v3) toxicity was lower with RT alone (28% RT vs CRT 40% CRT; $P = .033$). The highest toxicity risk was for grade 2 or higher sensory neuropathy, with rates at 5 years being 0% for RT versus 9% for CRT ($P < .0001$).

Comments: PORTEC-3 included a heterogeneous population of high-risk patients, which complicates our interpretation of the results. The stage III subset saw a significant benefit with CRT of about 10% in 5-year FFS, but stage I to II patients and those with serous histology did not see a benefit in FFS (the lack of benefit in the serous group is thought to be related to the small sample size). It is not clear whether this 10% improvement in FFS will be compelling enough for gynecologic oncologists and medical oncologists to routinely recommend CRT for stage III patients, particularly in light of the data from GOG-258 showing no improvement in relapse-free survival with CRT compared with 6 cycles of CT. From a radiation standpoint, both PORTEC-3 and GOG-258 show that the lowest rates of locoregional recurrence are achieved with a combination of CRT compared with either modality given alone; however, the argument against radiation will continue to be that there was no improvement in OS in PORTEC-3, and OS has not been reported yet for GOG-258. Given that distant metastasis is still the most common site of recurrence, the focus of treatment will reasonably be to continue trying to reduce this. It appears that carboplatin/Taxol is also not a home run regardless of whether 3 (GOG-249), 4 (PORTEC-3), or 6 (GOG-258) cycles are given (granted, different patient populations were included in these trials). It will remain a challenge to explain in tumor board that there is morbidity associated with a pelvic recurrence, that controlling gross disease is more challenging than controlling microscopic disease, and that it is actually possible to administer more CT after prior radiation to the pelvis.

Lester-Coll et al. Who benefits from chemoradiation in stage III–IVA endometrial cancer? An analysis of the National Cancer Data Base. *Gynecol Oncol* 2016. (5)

Summary: Investigators from Yale University reported on an analysis of the NCDB, evaluating 9837 women with stage III or IVA endometrial cancer who were treated after total hysterectomy with either CT alone or a combination of chemotherapy and radiation (CTRT).The investigators specifically excluded those who received either no CT or a single agent, received brachytherapy alone, received a dose either <45 Gy or >50.4 Gy, or had long delays in the initiation of adjuvant treatment (>240 days after surgery). In this study, 65% of the cohort received CT alone, with 35% receiving CTRT. The median follow-up was 59.6 months.

They found a significant increase in OS in those receiving CTRT (HR 0.63; 95% CI 0.57-0.70; $P < .001$) over the entire cohort. They reported additional survival benefits of CTRT in stage IIIA, IIIB, and IIIC and G2 and G3 subgroups, all of which continued to be significant

when adjusting for covariates, both on multivariate Cox regression and propensity score matching. The investigators found only a borderline improvement in stage IVA cancers ($P = .06$) and no significant improvement in grade 1 cancers (HR 0.72; $P = .14$). The absolute survival difference across the entire propensity-matched cohort was 13% at 5 years (70% for CTRT vs 57% with CT alone).

Comments: This study has several interesting aspects that help put recently reported phase 3 trials in context. First, it confirms, on a large scale, several previously reported retrospective experiences that found improved RFS and OS in women treated with combined CTRT compared to CT alone. Second, it suggests that there may be certain cohorts that have more to gain from multimodality therapy, such as high- or intermediate-grade cancers, whereas low-grade cancer may benefit to a lesser extent. It is worth noting, however, that there is no radiation-alone cohort with low-grade cancers to compare with CT alone; it may be that any single modality may be equally beneficial.

How then does one square the results of this study with the recently reported results of GOG-258, the trial that this study best parallels? The majority of CT in the CTRT cohorts of this study was likely done in a sequential fashion, whereas in GOG-258, CT was done in a partially concurrent manner (2 cycles CDDP [cisplatin] concurrent and 4 cycles of sequential carboplatin plus paclitaxel). Sequential therapy in the NCDB cohort may have been able to even the playing field for distant metastasis, allowing the benefit of improved local control to be fully realized.

NCDB studies are not without their significant limitations. First is the lack of local control data, which are not captured in this dataset; it would be helpful to confirm that a local control benefit was being translated into OS. There is also an inherent bias in the patients who received more aggressive therapies; indeed, in this study, patients who received CTRT were more likely to be white, to be high school graduates, to have higher incomes, and to have private insurance. This bias can be partially overcome by either multivariate Cox regression or propensity matching, but there are undoubtedly other factors not captured by the NCDB that influenced treatment decisions. The bias is partially mitigated in this analysis, in that all patients received at least some adjuvant treatment, therefore excluding those who were too sick or had comorbidities that precluded the use of any adjuvant therapy. A final factor is that, because the dose in this study is limited to what is acceptable in the adjuvant setting (45-50.4 Gy), those who started RT and did not finish it for whatever reason were not included. There is no such exclusion from the CT arm because the NCDB does not report the number of cycles delivered.

Despite these limitations, this series does strongly suggest a continuing role for radiation in advanced-stage uterine cancer, though possibly more in a sequential manner than the concurrent/sequential manner studied in GOG-258.

Matei et al. A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma. *J Clin Oncol* 2017. (2)

Summary: The preliminary results of GOG-258 were presented at the American Society of Clinical Oncology 2017 annual meeting. This trial for women with optimally debulked stage III and IVA endometrial cancer randomized patients to receive volume-directed RT with concurrent cisplatin CT followed by 4 cycles of carboplatin and Taxol or 6 cycles of carboplatin and Taxol CT without radiation. The primary endpoint was RFS with secondary endpoints of OS, acute and late toxicity, and patient-reported assessment of quality of life. The initial report of the study found no significant difference in RFS between the 2 arms (HR 0.9; 95% CI 0.74-1.1). Patients in the CRT arm had significantly lower rates of vaginal (3% vs 7%) and pelvic and para-aortic recurrences (10% vs 19%).

The 2 regimens had comparable rates of significant toxicity. Patients in the CRT arm were more likely to have grade 3 or higher GI toxicity (13% vs 4%), whereas patients receiving 6 cycles of CT were more likely to experience grade 3 hematologic toxicity (52% vs 40%). There were 3 deaths related to treatment in the CT arm and none in the combined-modality treatment arm.

Comment: The comparable disease outcomes and toxicity in the 2 arms suggest that these 2 approaches are both reasonable alternatives for adjuvant therapy for advanced-stage endometrial cancer. RT was once again demonstrated to be a highly effective method to reduce the risk of local recurrence in patients with endometrial cancer. Given that the risk of pelvic recurrence for patients with stage III endometrial cancer treated without external beam RT ranges between 20% and 30%, optimizing local control is an important goal.

The reported results are preliminary, and the mature results have not yet been presented or published. Some critical details that will be important to review in the full publication include the details of radiation treatment, especially for patients with gross residual disease, who were permitted in this trial. The 10% rate of in-field failure in patients receiving radiation is higher than that in other studies of patients with stage III endometrial cancer, suggesting that external beam boosts to gross residual disease may not have been reliably delivered to patients who needed them. In addition, analysis of subsets will be informative to provide guidance on which patients may be more likely to benefit from each treatment approach. Patients with pathologic predictors of local recurrence (eg, multiple positive nodes) versus peritoneal or distant recurrence (eg, adnexal involvement) may be more likely to benefit from radiation treatment. Ultimately, molecular predictors may prove to be the best way to identify patients at high risk of local recurrence who would benefit from CRT.

Randall et al. A phase 3 trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early-stage endometrial cancer: A Gynecology Oncology Group Study. *Int J Radiat Oncol Biol Phys* 2017. (3)

Summary: This is the long-term report of a randomized phase III study (GOG-249) that was designed to test whether adjuvant brachytherapy plus CT (VCB/C) improved RFS compared with the standard treatment of pelvic RT (PXRT) for early-stage high-risk endometrial cancer (1). Secondary objectives included comparisons in OS, frequency and severity of adverse events, and recurrence sites between the treatment arms. Eligible patients had stage I endometrioid disease with GOG-99-high intermediate risk (HIR) criteria (based on age, tumor grade, depth of invasion, and presence of lymphovascular space invasion). In addition, there were a few high-risk early-stage patients: stage II endometrioid and stage I to II serous or clear cell tumors. Patients assigned to PXRT (301 patients) were treated with standard 4-field or intensity-modulated RT techniques (median dose 45 Gy/25 fractions). Additional VCB was optional for patients with serous and clear cell tumors or stage II disease. Patients assigned to VCB/C (300 patients) received high dose rate (21 Gy in 3 fractions before chemo) or low dose rate brachytherapy followed by paclitaxel 175 mg/m^2 (3 h) plus carboplatin AUC 6 q 21 days for a total of 3 cycles.

Histology included 71% with endometrioid type, 15% with serous, and 5% with clear cell. With a median follow-up of 53 months, the 36-month RFS was 82% for both PXRT and VCB/C. The 36-month OS was 91% versus 88% for PXRT and VCB/C, respectively. No significant differences were noted between the 2 arms in terms of vaginal or distant failure. However, pelvic or para-aortic nodal recurrences were significantly more common in the VCB/C arm (25 vs 12), an estimated 9% at 5 years versus 4% in the PXRT arm (HR 0.47), largely driven by the difference in pelvic nodal failure (20 vs 6 patients). Acute toxicity was more common and more severe with VCB/C. Grade 3 or higher adverse events were reported in 32 patients (11%) on the PXRT arm versus 187 (64%) patients on the VCB/C arm. Grade 3 or higher late effects were seen in 37 (13%) and 35 (12%) patients on the PXRT and VCB/C arms, respectively. This large, randomized, phase 3 study did not demonstrate superiority of vaginal brachytherapy plus CT over PXRT in a mixed cohort of HIR and high-risk early-stage endometrial carcinoma. This conclusion applies to all subgroups analyzed, including patients with serous and clear cell histology. Analysis of failure patterns showed a significantly lower nodal failure rate in the PXRT arm. Distant failure is the predominant failure pattern in this patient population (18% in both arms).

Comment: For early-stage HIR endometrioid uterine cancer, level I evidence confirmed the benefits of adjuvant RT in reducing local recurrence (PORTEC-1 and GOG-99) (8, 9). The role of adjuvant brachytherapy alone to the vaginal cuff in selected HIR patients was validated by the PORTEC-2 study (10).

However, distant metastases remain a major challenge for women with HIR and especially high-risk (per European Society for Medical Oncology [ESMO] classification) (11) early-stage endometrial carcinoma. The use of adjuvant chemotherapy to improve survival endpoints has been investigated in women with endometrial carcinoma in several clinical trials (1), but these have also included stage III patients. Hence, these trials have been unable to clarify the impact of CT (in addition to RT) in reducing distant risk of distant metastases in early-stage high-risk uterine cancer.

The use of adjuvant PXRT alone for the old ICG3 stage group in an observational PORTEC group study (11) without nodal staging showed a 30% risk of distant metastases at 5 years, raising the question of whether adjuvant chemotherapy could reduce this spread. This group, along with patients with stage II endometrial cancer, was excluded from PORTEC-1 and -2 and generally considered a higher risk group (ESMO high-risk group). In addition, type 2 histology (serous and clear cell) is also considered high risk (for metastatic spread) and has been treated with CRT regimens, specifically a combination of vaginal brachytherapy and CT, in many retrospective series (12-14). The feasibility and safety of this approach were further validated in the Oklahoma University phase 2 study with a design similar to the experimental arm of GOG-249 (15). This study formed the basis for the GOG-249 phase 3 randomized trial comparing standard PXRT with VCB/C, with the aim of showing an RFS benefit with the addition of CT. Sample size calculation was based on an assumption that 3-year RFS would be improved by 7% for combination vaginal brachytherapy and CT compared with PXRT alone (standard arm) (85%-92%). Because this was not an equivalence trial, the negative result for VCB/C and increased acute toxicity meant that PXRT was the preferred modality for the high-risk group as defined by the trial eligibility criteria.

However, there are several unanswered questions with this still unpublished study (only available in abstract form). Could the results be universally applied to early-stage high-risk histology, especially because they formed only 20% of the patient sample, or was the recurrence risk diluted by inclusion of lower risk patients? Several series have shown significant recurrence rates for serous and clear cell endometrial cancers without CT (even when RT was administered) (12-14). Therefore, in practice, the addition of chemotherapy may be warranted and is reflected in the ESMO and National Comprehensive Cancer Network guidelines (16).

Would the patients have had a greater benefit with an increased number of CT cycles? In practice, there is a tendency to use more than 3 cycles of CT (median 6) based

on a GOG noninferiority phase 3 study establishing the benefit of 6 cycles of combination carboplatin and paclitaxel for advanced endometrial cancer (6).

The sequencing of VBC/C for the GOG-249 study allowed up to 12 weeks to start therapy, and CT was commenced only after vaginal brachytherapy began. There was thus a delay in starting both RT and CT in the study, which could have compromised the efficacy of the adjuvant effect. In practice, it is best to administer these therapies as soon as possible and definitely within 8 weeks. Studies (17, 18) have shown the importance of starting RT on time, with risk of increased recurrence with delay. In practice, it is possible to interdigitate vaginal brachytherapy with CT cycles to reduce delay in commencing adjuvant therapy.

In summary, although RT alone remains the main adjuvant treatment of choice in women with early-stage HIR endometrial carcinoma, further research is warranted for more effective systemic therapy to reduce systemic failure for higher risk early-stage uterine cancer. For early-stage nonendometrioid subtypes, prospective studies to establish type and efficacy of adjuvant CT are needed.

References

1. Yi L, Zhang H, Zou J, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer: A systematic review and meta-analysis. *Gynecol Oncol* 2018;149:612-619.
2. Matei D, Filiaci VL, Randall M, et al. A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma. *J Clin Oncol* 2017; 35(suppl 15):5505.
3. Randall M, Filiaci V, McMeekin D, et al. A phase 3 trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early-stage endometrial cancer: A Gynecology Oncology Group Study. *Int J Radiat Oncol Biol Phys* 2017;99:1313.
4. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): Final results of an international, open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* 2018;19:295-309.
5. Lester-Coll NH, Park HS, Rutter CE, et al. Who benefits from chemoradiation in stage III-IVA endometrial cancer? An analysis of the National Cancer Data Base. *Gynecol Oncol* 2016;142:54-61.
6. Miller D, Filiaci V, Fleming G, et al. Late-breaking abstract 1: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol* 2012;125:771.
7. US National Library of Medicine. Randomised phase III trial of molecular profile-based versus standard recommendations adjuvant radiotherapy for women with early stage endometrial cancer: PORTEC-4a Trial. Available at: https://clinicaltrials.gov/ct2/show/NCT03469674. Accessed May 1, 2018.
8. Creutzberg CL, Van putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 2000;355:1404-1411.
9. 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.
10. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): An open-label, non-inferiority, randomised trial. *Lancet* 2010;375:816-823.
11. Creutzberg CL, Van putten WL, Wárlám-rodenhuis CC, et al. Outcome of high-risk stage 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.
12. Kiess AP, Damast S, Makker V, et al. Five-year outcomes of adjuvant carboplatin/paclitaxel chemotherapy and intravaginal radiation for stage I-II papillary serous endometrial cancer. *Gynecol Oncol* 2012; 127:321-325.
13. Mahdavi A, Tajalli TR, Dalmar A, et al. Role of adjuvant chemotherapy in patients with early stage uterine papillary serous cancer. *Int J Gynecol Cancer* 2011;21:1436-1440.
14. Qu XM, Velker VM, Leung E, et al. The role of adjuvant therapy in stage IA serous and clear cell uterine cancer: A multi-institutional pooled analysis. *Gynecol Oncol* 2018;149:283-290.
15. Landrum LM, Nugent EK, Zuna RE, et al. Phase II trial of vaginal cuff brachytherapy followed by chemotherapy in early stage endometrial cancer patients with high-intermediate risk factors. *Gynecol Oncol* 2014;132:50-54.
16. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, treatment and follow-up. *Ann Oncol* 2016;27:16-41.
17. Ghanem AI, Modh A, Burmeister C, et al. Does interval between hysterectomy and start of radiation treatment influence survival in early stage endometrial carcinoma? A National Cancer Database Analysis. *Int J Radiat Oncol Biol Phys* 2017;99:E292.
18. Luo L, Shi W, Zhang Z, et al. Association of delayed adjuvant therapy and overall survival in early stage endometrial cancer. *J Clin Oncol* 2017;35(suppl 15):E301.