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Management of high-risk endometrial cancer: are we there yet?

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Endometrial cancer is a diverse disease that includes varying stages and histologies. As a result, the design, completion, and interpretation of large randomised trials comparing adjuvant therapies for this disease, even when well conducted and well analysed, is problematic. This situation is especially true in the study of adjuvant therapy for advanced endometrial cancer, since many patients are diagnosed and treated surgically for early disease, with no indication for adjuvant treatment.

The PORTEC Study Group is to be commended for its work in refining the use of adjuvant therapy across various types of non-metastatic endometrial cancer. In the PORTEC-3 study, eligible patients included those with stages II and III and high-risk stage I endometrioid endometrial cancer and stages I–III serous and clear cell histologies.[1] With more than 650 women enrolled, the combination of systemic chemotherapy and radiotherapy was shown to improve outcomes compared with radiotherapy alone. For example, 5-year overall survival was 81·4% (95% CI 77·2–85·8) with chemoradiotherapy versus 76·1% (71·6–80·9) with radiotherapy alone (adjusted hazard ratio [HR] 0·70 [95% CI 0·51–0·97], p=0·034), and 5-year failure-free survival was 76·5% (95% CI 71·5–80·7) versus 69·1% (63·8–73·8; HR 0·70 [0·52–0·94], p=0·016). In the aftermath of these potentially practice-changing results, additional questions are raised.

First, do these findings apply broadly to all subgroups included in the study? In addition to the broad eligibility criteria of PORTEC-3 (ie, different tumour stages and histologies), many clinicopathological variables have prognostic significance, such as tumour grade, depth of myometrial invasion, patient age, lymphovascular space invasion (in the absence of positive lymph nodes), and the patient's general condition. Even within similar or identical subgroups, substantial differences exist among patients, such as extent of nodal dissection, which are potentially confounding variables.

Whether or not the results from PORTEC-3 are generally applicable across patient subgroups remains unknown. However, taking into account the statistical limitations of subgroup analyses, the therapeutic benefit of combined chemotherapy and radiotherapy (*vs* radiotherapy alone) appeared to remain confined to patients with stage III disease and those with serous carcinomas of all stages.

Second, is chemotherapy alone a sufficient form of adjuvant therapy? The Gynecologic Oncology Group (now NRG Oncology) did separate studies that overlap (in terms of patient eligibility) with PORTEC 3. In the NRG/GOG 249 study, investigators randomly assigned high-risk patients with stage I and II disease, including those with high-risk histologies, to chemotherapy plus vaginal cuff brachytherapy or pelvic radiotherapy with no chemotherapy. In the NRG/GOG 249 study, the chemotherapy plus vaginal cuff brachytherapy group did not show improved overall survival or relapse-free survival compared with the group that received pelvic radiotherapy alone. However, the incidence of nodal failure was significantly higher in the absence of pelvic radiation therapy, and acute toxicity was greater in the vaginal cuff brachytherapy group.[2] In the NRG/GOG 258 trial, patients with stage III–IVA uterine cancer were randomly assigned to received adjuvant chemotherapy alone or combined chemotherapy with pelvic radiotherapy (and para-aortic radiotherapy if nodal metastases were present). Although recurrence-free survival and overall survival were not improved with the combined therapy, nodal and vaginal failures were significantly lower when radiotherapy was given.[3]

In these and other previous studies of adjuvant therapy within the PORTEC-3 eligibility groups, locoregional failure has been a notable and often predominant failure pattern in the absence of pelvic radiotherapy.

The apparent complementarity of chemotherapy (in limiting distant failure) and radiotherapy (in limiting local failure), is a consistent finding that is a reasonable basis for subsequent clinical investigation. Several studies support the use of combined modality therapy rather than monotherapy.[4,5]

Finally, is there a preferred way of combining chemotherapy with radiotherapy? In both PORTEC-3 and NRG/GOG 258, the combined chemotherapy plus radiotherapy schedule was based on a phase 2 regimen piloted by the Radiation Therapy Oncology Group, RTOG 9708.[6] When NRG/GOG 258 was designed, there was vigorous debate about the combined modality group, with various investigators favoring a sandwich regimen typically involving three cycles of chemotherapy, followed by involved-field radiotherapy, and then additional chemotherapy. The combined therapy approach taken in RTOG 9708 was ultimately chosen, because the data were prospectively obtained. However, multiple studies (retrospective and prospective) have demonstrated the safety and efficacy of the so-called sandwich approach.[5,7–9] Increasing evidence supports the use of upfront systemic therapy, when combined with radiotherapy, as a strategy to maximise both systemic and local control.[10] Many clinicians often use this regimen as a preferred adjuvant approach in locally advanced endometrial cancer.

Based on outstanding work done by the PORTEC Study Group and others, we have made good progress in improving outcomes for women with high-risk and locally advanced endometrial cancers. However, we are not there yet.

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I have received an honorarium from Isoray Medical within the past 2 years.

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The emerging role of PET-CT scan after radical prostatectomy: still a long way to go

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The management of biochemical recurrence after radical prostatectomy is a common challenge for urologists and radiation oncologists, because about 30% of patients have an increase in prostate-specific antigen (PSA) concentrations after surgical treatment.[1] However, the outcome of these patients is not always poor, varying substantially according to the site and the extent of recurrence.[2] In this context, the role of imaging is of the utmost importance to establish the real burden of recurrent disease. The increasing use of PET-CT has led to a shift towards early detection of low-volume metastatic prostate cancer,[3] whereas several novel and promising PET tracers have been reported.[4] However, no prospective clinical trials had tested the superiority of one tracer over the others in terms of diagnostic accuracy.