High intermediate risk endometrial cancer. What is it?

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Thirty years ago, even minimally invasive stage I, grade 1 endometrial cancers were considered “intermediate risk” and routinely treated with adjuvant radiation therapy. As recently as the mid 1990s, such patients were still being randomized to receive adjuvant pelvic radiation on large multi-institutional trials.^{1,2} As a result, baseline survival rates were high, the margins for improvement were small, and the trials inevitably failed to demonstrate a benefit.

Clearly, even mild treatment-related side effects were unjustifiable for the lower risk patients in these trials. Noting that most recurrences occurred in patients whose tumors exhibited multiple high-risk features, investigators from the GOG (Gynecologic Oncology Group) and PORTEC (Post Operative Radiation Therapy in Endometrial Carcinoma) defined “high intermediate risk” subgroups—about 1/3 of their intermediate risk patients—that had relatively high rates of recurrence and that appeared to benefit from post-operative radiation. However, because the results were derived from unplanned subset analyses, many clinicians remained skeptical about the benefits of adjuvant therapy for these high intermediate risk patients.

Although both the GOG and PORTEC conducted follow-up trials focusing on their high intermediate risk groups,^{3,4} neither study truly tested the benefit of radiation therapy because they included adjuvant treatment in both arms. Baseline survival rates of 80–85% left little room for improvement and neither trial demonstrated a survival advantage of one treatment over another. From these results, one could conclude that the treatments (pelvic radiation, vaginal brachytherapy or brachytherapy plus chemotherapy) were equally effective, equally ineffective, differentially effective for subsets within the trials, or that the trials were simply underpowered. Although some stage I patients undoubtedly benefit from adjuvant therapy, currently defined criteria for high intermediate risk still lead to the potential over-treatment of many patients.

Using the National Cancer Database (NCDB), Li et al⁵ have tried to refine the definition of high intermediate risk by analyzing outcomes of 30 986 patients who met either the PORTEC or GOG high intermediate risk criteria. The authors found no significant benefit from adjuvant radiation therapy for 5920 relatively favorable cancers that were deemed high intermediate risk solely by PORTEC

criteria. Encouragingly, even though patients with deeply invasive grade 3 were excluded, patients who met GOG high intermediate risk criteria did have significantly better outcomes if they received radiation therapy.

NCDB analyses that compare treatments and attempt to correlate risk with outcome should always be viewed with some degree of skepticism because of missing diagnostic information, potentially inaccurate data entry, and because treatment records are often incomplete. These factors were unlikely to have a disproportionate impact on any one of the three groups compared in the study by Li et al. Also, because the NCDB contains limited information about, for example, the depth of myometrial invasion, there could have been biases in the selection of patients for adjuvant treatment; however, it is likely that these biases would result in the selection of patients with more adverse findings for adjuvant treatment, tending to decrease its apparent benefit.

The authors’ findings should help to validate clinicians’ decisions to withhold adjuvant treatment from patients with the most favorable cancers in the PORTEC high intermediate risk group. However, patients fitting the authors’ “revised” definition of high intermediate risk (similar to the GOG definition) still had baseline overall survival rates of >75% and an absolute reduction in the risk of death of 8% or less with adjuvant radiation therapy; this means that many patients in the treated cohort still received unnecessary or ineffective adjuvant therapy.

For decades, clinicians have been juggling the same set of clinical criteria—depth of invasion, grade, lymphovascular invasion and age—to determine the need for treatment. We are probably reaching the limits of what can be learned from these traditional prognostic factors. It is time to focus on what can be learned from newer indicators. Molecular markers promise to yield powerful, independent information about the biology of endometrial cancers, their potential to spread, and their response to various treatments. Sentinel node biopsy may provide more accurate information than lymphadenectomy about the likelihood of regional spread and the need for adjuvant treatment. Armed with these new potential predictors, we need to be open to refining and even re-envisioning our classification systems to optimize the selection of treatments for patients with endometrial cancer.

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REFERENCES

1. 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*. *Lancet* 2000;355:1404–11.
2. 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;92:744–51.
3. Nout RA, Smit VTHBM, 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;375:816–23.
4. Randall ME, Filiaci V, McMeekin DS, *et al.* Phase III trial: adjuvant pelvic radiation therapy versus vaginal brachytherapy plus paclitaxel/carboplatin in high-intermediate and high-risk early stage endometrial cancer. *J Clin Oncol* 2019;37:1810–8.
5. Li. A proposal for a new classification of “unfavorable risk criteria” in patients with stage I endometrial cancer. *Int J Gynecol Oncol* 2019.