Studies of Adjuvant Treatment for Endometrial Cancer

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This article is a review of The Role of Adjuvant Radiation in Endometrial Cancer.

In this issue of ONCOLOGY, Diavolitis et al have provided an excellent overview of the literature and state of our understanding of the role of adjuvant therapy in the treatment of endometrial cancer. Their analysis brings some order to the confusing array of empirical evidence, traditional beliefs, and prospective trial results that have shaped our understanding of endometrial cancer and options for its treatment. The authors make a strong case for limiting the use of tailored adjuvant treatment to the minority of patients who have multiple risk factors for recurrence. However, the authors’ recommendations regarding specific indications for vaginal irradiation, external-beam irradiation, and chemotherapy remain somewhat vague, reflecting uncertainties that have persisted as a result of the long use of poorly defined risk classifications systems and the related large gaps in the available level 1 evidence.

The Price of Imprecise Language
Imprecise risk classification systems have made it difficult to interpret patient characteristics in reports of prospective and retrospective studies and have, therefore, made it difficult to generalize findings to individual patients. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) tried to improve its classification system by incorporating important prognostic information obtained at the time of hysterectomy. However, this staging system remains problematic for a number of reasons.

First, although the predictive value of the staging system was improved by addition of an assessment of the depth of myometrial invasion—one-half or less of the myometrium vs more than one-half of the myometrium—this dichotomy is controversial because the relationship between myometrial invasion and outcome is probably continuous. Second, two groups of patients—those with cancer cells in peritoneal washings and those with positive regional (pelvic or aortic) lymph nodes—were advanced to the stage III group, and this created an extremely heterogeneous category that places patients whose only risk factor is positive peritoneal cytology (now considered to have little independent predictive value) alongside patients who have bulky regional disease or other very high-risk features. Third, although FIGO’s histologic grading system was improved, special variants that have a vastly more aggressive behavior than endometrioid carcinomas, and that probably require very different treatments, were relegated to a footnote.

Complicating the issues of the surgical staging system itself are inconsistencies in the way this system is applied. In particular, surgeons vary widely in the extent of surgical staging performed at the time of hysterectomy, causing a form of stage migration that compromises the generalizability of outcomes from one experience to another.

Although we know that individual FIGO stage groupings contain patients whose tumors are associated with vastly different prognoses and patterns of failure, and although clinicians often make treatment decisions using much more information than FIGO stage category, we still tend to design broadly inclusive clinical trials in which the same treatment is given to a spectrum of patient subgroups, including some for which the protocol treatment is probably not the best option.

Gap in Level 1 Evidence
These problems with the staging system and its application and with clinical trial design have contributed to major gaps in the level 1 evidence supporting adjuvant treatments for intermediate-risk and high-risk endometrial cancer. For more than 25 years, clinicians had only one major phase III randomized trial to guide management decisions for patients with locoregionally confined disease. [1] In recent years, the Post
Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) Study Group [2] and the Gynecologic Oncology Group (GOG)[3] have published several new trials, but as is evident from the review by Diavolitsis et al, these studies have not resolved important questions about the indications for intracavitary or external-beam irradiation or the value of adjuvant chemotherapy. In each of the large trials that evaluated patients with intermediaterisk endometrial cancer, the majority of risk was concentrated in a small number of patients—generally less than one-third of the study population—who had multiple high-risk features. When studies are designed with such heterogeneous inclusion criteria, the risk-benefit ratio is likely to be underestimated for low-risk patients, while benefits to relatively high-risk patients are obscured [4]. Although the PORTEC and GOG studies tended to confirm the belief of many clinicians that patients with superficially invasive grade 1 or 2 disease required no adjuvant treatment, the inclusion of many relatively low-risk patients in the trials severely compromised their ability to detect possible benefits of adjuvant pelvic radiotherapy in patients with “high intermediaterisk” disease. Where subset analyses suggested a possible gain, the failure to stratify risk groups obscured the significance of the findings for individual risk subgroups, and the question remains whether any real effect could have been achieved with fewer side effects using vaginal cuff irradiation. The PORTEC 2 trial[5] may help to answer this question, but that trial also had fairly broad eligibility criteria, and by excluding patients with deeply invasive grade 3 cancers, it will not be able to answer the question for an important subgroup. Also, variations in regional staging—particularly in surgical evaluation of the high aortic lymph nodes—probably influence the value of pelvic treatment and the generalizability of trial results to other clinical settings.

The only large trial that evaluated adjuvant treatment in patients with high-risk endometrial cancer, GOG- 122,[6] also was compromised by the extreme heterogeneity of the study population. The trial, which compared the use of adjuvant chemotherapy with whole-abdominal irradiation, included some patients who had gross residual disease unlikely to be controlled by the dose of radiation specified in the trial. Additionally, patients with stage IIIC endometrioid endometrial cancers, which rarely disseminate intraperitoneally, underwent irradiation of the entire abdomen when more focused treatment of lymph node-bearing areas may have been more effective. Finally, patients whose only risk factor was positive peritoneal cytology underwent aggressive whole-abdominal irradiation even though in some cases the risk of recurrence was probably minimal.

Conclusions
Radiation therapy is a locoregional treatment that, like surgery, must be carefully tailored to the sites at risk for disease involvement in individual patients. The benefit of radiation therapy can only be demonstrated in trials that carefully focus on risk groups for whom a specific field of treatment makes sense. There continues to be a real need for trials that truly test the potential benefit of local and regional treatment in appropriately selected patients.

References:

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