In this issue of the Journal, Kong and colleagues (1) have tried to improve our understanding of the role of adjuvant radiation therapy for early-stage endometrial cancer through an updated Cochrane review of existing trials. Their final conclusion, that adjuvant radiation therapy reduces the incidence of local recurrence but increases treatment-related morbidity without improving overall survival, recapitulates that of their earlier analysis (2) and is consistent with the conclusions of each of the individual trials referenced in their systematic review. It is tempting to decide that the authors’ skillful summary of trial evidence allows us finally to conclude that there is no role for adjuvant pelvic radiation therapy in patients with early-stage disease. However, the data, even when combined in this summary analysis, simply do not support this generalization.

The primary purposes of meta-analyses are to increase statistical power, to address conflicting trial data, and, in some cases, to systematically address new clinical questions that may not have been posed in the contributing trials. Meta-analyses have yielded important insights and strengthened our confidence in trial results for cancers of the breast, head and neck, and other sites. However, the value and generalizability of meta-analyses remain highly dependent on the quality of the data analyzed. In his textbook on clinical trial design, Spilker (3) introduced his discussion of potential problems with meta-analysis with the question, “Can tons of garbage yield a single diamond?” Of course, his term would be an inappropriately harsh characterization of the trials of adjuvant radiation therapy for endometrial cancer, but his question does bring into relief the importance of careful assessment of the input before we put too much faith in the interpretations of summary analyses.

The goal of Kong and colleagues’ analysis, as stated in their abstract, was to determine the role of adjuvant radiation therapy in patients with stage I endometrial cancer. Their conclusion is that radiation has no statistically significant impact on overall survival or cancer-related deaths in this group. However, their implication—that the lack of benefit applies to the stage I group as a whole—cannot be justified because the high-intermediate-risk patients who had most to gain from adjuvant treatment were barely represented in the contributing trials. The authors try to address this problem by analyzing outcomes of patients divided into different risk groups. However, the validity of this subset analysis is severely compromised because the estimates of risk were seriously flawed in many of the original trials.

Endometrial cancer is by far the most common gynecologic malignancy affecting women in the United States. However, most endometrial cancers are cured with hysterectomy alone. The annual death rate from uterine cancer is much less than that from ovarian cancer and only modestly higher than that from cervical cancer, suggesting that high-risk endometrial cancer is actually a relatively rare disease (4). In Northern Europe, where most of the randomized trials were conducted, racial and other demographic characteristics differ from those in the United States, and high-risk endometrial cancer may be even less common. For example, in the Netherlands, home of the PORTEC trials, the annual death rate from endometrial cancer is about 3 per 100,000 women, compared with an annual rate of 5 per 100,000 women in the United States (4,5).

We know from these data and from numerous clinical-pathologic analyses that uterine cancer has a heterogeneous presentation and that most of the recurrence (and death) risk, particularly for patients with stage I disease, resides in a relatively small subset of patients whose tumors exhibit multiple risk factors. Ideally, clinical trials would focus on these higher-risk patients for whom the margin for improvement is substantial. However, the desire to assure rapid accrual often leads investigators to broaden inclusion criteria. In fact, this has been one of the primary weaknesses of the endometrial cancer trials. Studies have tended to include large numbers of patients with low-grade or minimally invasive cancers—patients whose baseline risk of recurrence may be less than 5% to 10%. For these patients, even relatively minor side effects from radiation therapy (or lymphadenectomy or chemotherapy) will outweigh the most optimistic level of benefit from that treatment. If the proportion of patients with low-grade or minimally invasive cancers in a trial is large, treatment-related morbidity experienced by patients with low-risk tumors can easily obscure real benefits experienced by the smaller number of patients who have a greater margin for improvement. This phenomenon was well described by Kent and Haywood in their discussion of the potential pitfalls of summary statistics (6). The phenomenon is also clearly illustrated in the results of the GOG-99 trial (7). In that trial, subset analysis of a high-intermediate-risk subgroup suggested a fairly large potential benefit that was completely obscured when the entire group of patients, which on average was a relatively low-risk group, was analyzed.

Adding importantly to this problem is the fact that patients included in several of the trials had even more favorable tumor characteristics than was apparent from the original risk assignments. The rules for histologic grading have evolved considerably since the Norwegian trial was conducted in the 1970s. Lindemann and colleagues (8) recently presented updated results of the Norwegian
Combining Molecular Markers With the TNM Staging System to Improve Prognostication in Stage II and III Colon Cancer: Are We Ready Yet?

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In this issue of the Journal, Roth and colleagues (1) report a study entitled “Integrated Analysis of Molecular and Clinical Prognostic Factors in Stage II/III Colon Cancer.” The study population consisted of participants in a randomized adjuvant therapy trial with contemporary pathology review. In the update, 48% of patients were found to have had grade 1 disease (compared with 11% in the original report), and 58% had minimally invasive tumors. PORTEC-1 (9) and PORTEC-2 (10), which relied on the interpretation of community pathologists for registration and classification, also suffered from errors that inflated the grade assignment. When a subset of PORTEC-1 patients were reviewed by experienced gynecologic pathologists, 48% of patients had their disease downgraded from grade 2 to grade 1, resulting in grade 1 designation in 69% of the patients overall. Some patients were actually ineligible for the trial, and many others were shifted to the very lowest risk group in which patients were still eligible. PORTEC-2 had similar problems: after review, the proportion of patients having grade 1 disease increased from 48% to 79%. This remarkable discordance in grade assignments also calls into question the accuracy of the community pathologists’ interpretations of myometrial invasion—a critical prognostic feature that could not be centrally reviewed with the available material. In fact, the only major trial analysis that used central review by experienced gynecologic pathologists was GOG-99, the trial that came closest to defining a high-intermediate-risk group that could benefit from adjuvant treatment.

These shifts in risk assignment are not reflected in the meta-analysis by Kong and colleagues, which relied on published results and initial risk assignments rather than individual patient data. We now know that more than two-thirds of the patients in the trials included in the meta-analysis probably had low-risk or low-intermediate-risk disease. Yes, the data confirm that the risks of adjuvant pelvic radiation therapy outweigh the benefits for patients with these very favorable tumors. However, we have known for decades that such patients probably had an insufficient margin for improvement to justify the morbidity of potentially toxic adjuvant interventions.

The question that has not yet been answered by individual trials or meta-analysis is whether adjuvant treatment can benefit the less common, higher-risk stage I patients who have multiple risk factors. We should not fool ourselves into thinking that this question has been answered. Only focused trials in patients with well-characterized high-intermediate-risk tumors can provide the answer to the question that we have been trying but have failed to answer for more than 30 years.

References

Notes
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