Is There a Standard of Care for Pathologic Stage T3 Prostate Cancer?

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As many as one third of patients undergoing radical prostatectomy will be found to have pathologic stage T3 (pT3) prostate cancer (PCA) with positive margins, extraprostatic extension, or involvement of the seminal vesicles. A debate has raged for decades over the utility of adjuvant radiotherapy in treating these men. Case studies have argued for and against this treatment without the establishment of a clear standard of care.

Three randomized clinical trials have provided initial data from more than 1,800 patients with similar outcomes. The first of these studies, S8794,2 was initiated in 1987 and conducted by the Southwest Oncology Group (SWOG). In this study, 425 men with pT3 PCA were randomly assigned to observation or adjuvant radiotherapy with 60 to 64 Gy within 4 months of surgery. In 2006, with a median follow-up of 10.6 years, the first report of results of this study described a highly significant reduction in biochemical failure rate (median prostate-specific antigen [PSA] relapse-free interval, 10.3 years for radiotherapy v 3.1 years for observation; hazard ratio [HR], 0.43; 95% CI, 0.31 to 0.58; P < .001), but the study fell just short of achieving significance for the primary end point of metastasis-free survival (median metastasis-free estimate, 14.7 years for radiotherapy v 13.2 years for observation; HR, 0.75; 95% CI, 0.55 to 1.02; P = .06). Notable as well was a significant reduction in requirement for hormonal therapy in those receiving radiation. The second study,3 initiated in 1992 by the European Organisation for Research and Treatment of Cancer (EORTC), included 1,005 patients with a design similar to that of the SWOG study. Its first report with 5-year median follow-up indicated significant improvement in biochemical failure (74.0% [95% CI, 68.7% to 79.3%] v 52.6% [95% CI, 46.6% to 58.5%]; P < .0001).

In this issue of *Journal of Clinical Oncology* (JCO), Wiegel et al4 report the results of a third randomized trial of adjuvant radiotherapy for pT3 PCA by the Working Group on Radiation Oncology and Association of Urological Oncology of the German Cancer Society. Beginning in 1996, this study called for random assignment of patients within 2 weeks of surgery before establishment of an undetectable PSA. This unusual study design was developed specifically for local care practices. Three analysis plans were predetermined, including analysis of all eligible patients (ITT1), of patients with an undetectable PSA (ITT2), and by treatment ultimately received (per protocol). The second method of analysis constitutes the report in this issue of JCO. Wiegel et al reach conclusions similar to those of the two previously reported trials,2,3 with a biochemical progression-free survival rate of 72% with adjuvant radiation (95% CI, 65% to 81%) versus 54% in the observation group (95% CI, 45% to 64%; P = .0015). The overall intent-to-treat rates were 55% and 44%, respectively, with a log rank P value (summarized in Fig 2) indicating a one-sided P value of .054. Wiegel et al note few significant complications from radiotherapy.

It is important to place these three trials in a historical perspective. When the SWOG trial2 began, the importance and definition of a detectable PSA after surgery were not yet clear. As a result, an undetectable PSA was not required, and 33% of patients for whom postoperative PSA data were available had a PSA ≥ 0.2 ng/mL after surgery. Similarly, 30.5% of patients in the EORTC trial3 had a PSA > 0.2 ng/mL. The most recent of these studies, the German Cancer Society trial,4 included an analysis plan (ie, ITT2) to exclude the 20% of randomly assigned patients without an undetectable PSA using a range of PSA assays with several lower limits. The results of the SWOG and EORTC studies were reported according to preplanned intent-to-treat analyses, and several subsets of patients were examined. In all three studies, adjuvant radiotherapy was found to delay biochemical progression, including in the subset of patients with an undetectable PSA after surgery.

The question of whether adjuvant radiotherapy should now be the standard of care for these patients remains. The answer is elusive for two reasons. First, the final results of the SWOG trial have just been reported but similar results of the EORTC trial are pending. The updated results of the SWOG trial with median follow-up of 12.6 years found a significant improvement in metastasis-free survival (HR, 0.71; 95% CI, 0.54 to 0.94; P = .016) and overall survival (HR, 0.72; 95% CI, 0.55 to 0.96; P = .023) with radiotherapy.5 We look forward to the results of longer-term follow-up of the EORTC study for these end points; meanwhile, the results of the SWOG trial are compelling.

The second reason why adjuvant radiation may not yet be the standard of care is that some experts feel that salvage radiotherapy may be equivalent. Salvage radiotherapy refers to radiation administered at the time a measurable PSA is detected. In the past few decades, the threshold of detection for PSA and the time threshold at which radiotherapy is recommended have changed. A decade or so ago, an undetectable PSA might have been < 0.4 ng/mL; today, with an ultrasensitive assay, it may be < 0.01 ng/mL. Likewise, a decade ago, radiotherapy was initiated before PSA level reached 1.5...
It is important to recognize that in the SWOG trial,² of the patients assigned to observation, about one third ultimately underwent salvage radiotherapy principally because of a detectable PSA. Thus, one interpretation of the outcomes of this study is that the significant improvements in outcome were achieved when adjuvant and salvage radiation were compared. An argument against this is that salvage radiotherapy was given too late because ultrasensitive PSA tests were not available at that time. The SWOG Genitourinary Committee has considered such a follow-on study design (ie, immediate v salvage radiotherapy using an ultrasensitive assay). Unfortunately, such a study with a noninferiority end point would require a sample size larger than 8,000 patients, which would likely be unachievable. Returning to the original premise, what is the standard of care for patients with pT3 PCA? For physicians and patients who want survival outcomes of currently used surgery, radiation, and PSA testing, the answer is clear: we don’t know. Patients and physicians with this expectation will always come up empty handed, because treatments change, and in the case of PCA, meaningful outcomes in treatment require decades to achieve. For example, the final end points of the SWOG study² are only now available 20 years after initiation. Such an approach to clinical decision making reminds us of an individual considering the purchase of a new piece of technology whose action is forever paralyzed by the promise of a newer version. Despite these issues, we do feel that there is an emerging standard of care for patients with pT3 PCA. Such patients should be informed that three randomized clinical trials³⁴ have demonstrated that immediate adjuvant radiation therapy (ie, within several months of surgery)—with comparatively low doses that are relatively well tolerated—is associated with a significant reduction in risk of detectable PCA as manifested by a measurable PSA. The reduction in treatment with hormones, an adjuvant therapy that had considerable morbidity with radiation in the SWOG study,² should also be conveyed to patients. The updated results of radiation on metastasis-free survival in the SWOG trial,³ and as they are released from the EORTC trial, must be added to the discussion. Patients should also be informed of the evaluation and treatment cascade that occurs when PSA becomes detectable after surgery and of the outcomes from salvage radiotherapy. We feel that clinicians cannot tell patients that waiting until a PSA becomes detectable using an ultrasensitive assay is just as good as undergoing adjuvant radiation. Such a statement would be based on faith, not data. Patients may ultimately opt for such an approach, and in the lowest-risk patients with smaller areas of positive margins, low preoperative PSA, and low Gleason scores, or with potentially increased risks from radiation (such as irritable bowel, bladder neck contracture, and urinary incontinence), a delayed approach may be preferred.

In this era of evidence-based medicine, it is imperative that patients be informed of the results of trials such as the study reported by Wiegel et al⁴ in this issue of JCO along with the other two randomized trials.²³ Physicians and patients must similarly be educated regarding the hazards of drawing conclusions on the basis of clinical series. Finally, we must continue to search for predictive biomarkers that will identify which patients need, and which will benefit from, adjuvant therapy.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS
Manuscript writing: Ian M. Thompson, Catherine M. Tangen, Eric A. Klein
Final approval of manuscript: Ian M. Thompson, Catherine M. Tangen, Eric A. Klein

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Acknowledgment
Supported by Public Health Service Cooperative Agreement Grants No. CA38926, CA32102, CA14028, CA58416, CA58658, CA2777, CA27057, CA46136, CA35431, CA58882, CA12644, CA58861, CA35090, CA37981, CA76429, CA04919, CA76132, CA35119, CA35178, CA35176, CA46282, CA67575, CA45377, CA46113, CA74647, CA35261, CA049020, CA20319, CA76447, CA58723, CA12213, CA22433, and CA46441 from the National Cancer Institute, Department of Health and Human Services, and National Cancer Institute of Canada Grant No. PR-2.