Title
A critical ACR appropriateness Criteria omission.

Journal
Brachytherapy, 13(5)

ISSN
1538-4721

Authors
Rogers, Leland
Hayes, John
Demanes, D Jeffrey

Publication Date
2014-09-01

DOI
10.1016/j.brachy.2014.05.002

Peer reviewed

ELSEVIER

BRACHYTHERAPY

Brachytherapy 13 (2014) 522–528

Letters to the Editor

A critical ACR Appropriateness Criteria omission

An ACR panel (*Hsu et al.* (1)) recently published Appropriateness Criteria for high-dose-rate (HDR) brachytherapy of prostate cancer. With all due respect to the committee, we believe that there has been a significant oversight that requires comment, especially with regard to HDR brachytherapy as monotherapy. We acknowledge that there are a variety of acceptable ultrahypofractionated (one to three fractions) regimens, but there are yet no randomized comparisons. As a matter of fact, the four to six or more fraction regimens have an excellent safety profile, have much longer follow-up, and should be considered the standard against which the new programs are measured. However, the Appropriateness Criteria document appears to have discounted this approach altogether. The authors state correctly that "further exploration of hypofractionation is needed to determine a way to lower the number of fractions" and comment further that "future studies are likely to continue to push toward fewer highly hypofractionated treatments."

We agree that identifying the optimal dosing regimen should be the objective of comparative studies and cooperative group efforts and that abbreviating hospital stay, the number of implant procedures, and the number of brachytherapy fractions are meritorious, so long as they are accomplished without compromising tumor control or late effects.

The ACR panel omitted altogether the largest single-institution series of HDR monotherapy, published in the *Journal of Urology* in 2012 (2). This study described 284 patients with intermediate-risk prostate cancer treated with HDR monotherapy using six fractions of 6.5 Gy. The 5-year results with this approach have set a high standard. Cause-specific survival and clinical local control (LC) were 100%, and distant metastasis-free survival was 98.8%. Five-year biochemical disease-free survival was 94.4% for the entire cohort and 97.5% excluding the minority of cases with clinical stage T2c tumors or >75% positive biopsy cores. The toxicity was also favorable. International Prostate Symptom Scores remained stable over the entire follow-up range of 2–8 years. There were no urethral strictures, and potency preservation was 83%. Radiation Therapy Oncology Group (RTOG) Grade I rectal toxicity was 4.2%, and there were 0% G2–G4 (2).

Our intent with this editorial is to draw attention to the body of evidence that supports six-fraction monotherapy. The ACR panel referenced the large two-institution series by Demanes *et al.* but seemed to ignore more than half of the patients' data. There 298 patients treated with HDR monotherapy for either low-risk or low-intermediate-risk disease. Two HDR regimens were used: 7 Gy × 6 or 9.5 Gy × 4. For this favorable disease cohort, 8-year biochemical disease-free survival was 97% and 8-year LC, distant metastasis-free survival, and cause-specific survival each 99% (3). The authors did not directly compare outcomes between the two regimens, but their excellent results validate a six-fraction regimen.

The ACR guidelines also omitted several significant additional studies reporting treatment results with six or more fractions (Table 1). Yoshioka *et al.* (4) published a series of 112 patients (68 high risk) treated with nine fractions of HDR monotherapy in 2011. The 5-year prostate-specific antigen (PSA) control by risk group was 85% (low risk), 93% (intermediate risk), and 79% (high risk). LC was 97%, disease-free survival 87%, and overall survival 96%. Toxicity rates were low. Komiya and colleagues (5) evaluated quality of life in 51 patients treated with 45.5 Gy in seven fractions. Quality of life outcome scores for physical and well-being and sexual function recovered to baseline status by 12 weeks and social/family well-being by 1 year. There were few severe complications. Mark *et al.* (6) reported 8-year results in 301 patients treated with HDR monotherapy as 7 Gy × 6 fractions in two implants. PSA progression-free survival was 88%, and toxicity rates were low.

Although the one- to three-fraction regimens are convenient and therefore appealing, long-term (>5 years) outcomes and toxicity are not yet available, and there is basis for concern. Sullivan and coauthors evaluated 474 patients for urethral stricture risk with varying HDR boost fraction schedules as low as 4 Gy × 4 or 6.5 Gy × 3 up to HDR monotherapy regimens of 11 Gy × 3, with many intervening fraction sizes. The strongest predictor of urethral stricture was HDR brachytherapy dose per fraction. In multivariate analysis, the hazard ratio for urethral stricture was 1.33 per Gy of HDR fraction size (7). Urethral strictures are, needless to say, an important toxicity to avoid.

The American Brachytherapy Society published a guideline for HDR prostate brachytherapy in 2012 and clearly acknowledged the validity of six fractions of 6.5–7.25 Gy in the monotherapy setting, as well as recognizing the use of more rapid schedules, such as 9.5 Gy × 4 or 10.5 Gy × 3 (8). For the American Brachytherapy Society review, the two reports with the largest number of

1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2014.05.002

Table 1
HDR monotherapy outcome studies using six or more fractions

Study	*N*	Risk	Dose × Fx	PSA–PFS (%)	LC (%)	CSS (%)	FU—years
Demanes *et al.* (3)	157	Low–intermediate	7 Gy × 6	97	99	99	5.2
Komiya *et al.* (5)	51	All	6.5 Gy × 7	96	n/a	n/a	1.5
Mark *et al.* (6)	317	All	7 Gy × 6	88	n/a	n/a	8
Rogers *et al.* (2)	284	Intermediate	6.5 Gy × 6	95	100	100	3
Yoshioka *et al.* (4)	111	Intermediate–high	6 Gy × 9 6.5 Gy × 7	79–93	97	87	5.4

HDR = high-dose rate; LC = local control; CSS = cause-specific survival; PFS = progression-free survival; FU = follow-up.

patients used six-fraction regimens with 6.5–7 Gy per fraction, whereas the next largest experience used four fractions of 9.5 Gy (8).

Although we support the concept of embracing the most convenient and cost-effective treatment, we do not believe that one- to three-fraction regimes have been established as the HDR treatment of choice at the exclusion of an established six-fraction option. By analogy, one might assert that stereotactic body radiation therapy should now be considered the external radiotherapy treatment of choice, at the exclusion of the lower dose per fraction and lengthier course intensity-modulated radiation therapy alternative. The proximity of the prostate to critical organs related to bowel, urinary, and sexual function and the excellent outcomes achieved in each of these respects with a six-fraction HDR regimen (2, 3) must give us pause to consider the potential for worsened long-term effects with more rapid fractionation. Optimally randomized trials should be done to compare programs but, at a minimum, Appropriateness Criteria publications should not ignore the data. We believe that the six-fraction regimens should have been listed in table 2 of the publication.

With a combined experience exceeding 2 decades, having treated more than 6000 men with prostate cancer using HDR brachytherapy and more than 1500 men with six-fraction HDR monotherapy, it is not unreasonable to expect it be included as a viable and standard treatment option in such an important document. We respectfully request that the ACR publish a short note acknowledging the omission and the validity of our request.

Leland Rogers, MD, FACRO
John Hayes, MD, MS
GammaWest Cancer Services
Salt Lake City, UT

D. Jeffrey Demanes, MD, FACRO, FACR, FASTRO
UCLA Health System, Department of Radiation Oncology
Los Angeles, CA

References

[1] Hsu ICJ, Yamada Y, Assimos DG, *et al*. ACR Appropriateness Criteria high-dose-rate brachytherapy for prostate cancer. *Brachytherapy* 2014;13:27–31.

[2] Rogers CL, Alder SC, Rogers RL, *et al*. High dose rate brachytherapy as monotherapy for intermediate risk prostate cancer. *J Urol* 2012; 187:109–116.

[3] Demanes JD, Martinez AA, Ghilezan M, *et al*. High-dose-rate monotherapy: Safe and effective brachytherapy for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;81:1286–1292.

[4] Yoshioka Y, Konishi K, Sumida I, *et al*. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: Five-year results of an extreme hypofractionation regimen with 54 Gy in nine fractions. *Int J Radiat Oncol Biol Phys* 2011;80:469–475.

[5] Komiya A, Fujiuchi Y, Ito T, *et al*. Early quality of life outcomes in patients with prostate cancer managed by high-dose-rate brachytherapy as monotherapy. *Int J Urol* 2013;20:185–192.

[6] Mark RJ, Anderson PJ, Akins RS, *et al*. Interstitial high-dose-rate brachytherapy as monotherapy for early stage prostate cancer: Median 8-year results in 301 patients. *Brachytherapy* 2010;9(suppl 1): S76.

[7] Sullivan L, Williams SG, Tai KH, *et al*. Urethral stricture following high dose rate brachytherapy for prostate cancer. *Radiother Oncol* 2009;91:232–236.

[8] Yomada Y, Rogers L, Demanes DJ, *et al*. American Brachytherapy Society consensus guidelines for HDR prostate brachytherapy. *Brachytherapy* 2012;11:20–32.

Response to Drs Rogers, Hayes, and Demanes

The American College of Radiology Appropriateness Criteria Panel would like to thank Drs Rogers, Hayes, and Demanes for their thoughtful and comprehensive comments and their interest in our work on high-dose-rate (HDR) brachytherapy.

The American College of Radiology guidelines are based on a comprehensive review of the published data available to the panel. They included all the published data on HDR monotherapy that used more than four fractions, including Yoshioka *et al.* (6 Gy × 9) (1, 2). At the time of review, the largest published HDR monotherapy series was by Demanes *et al.*(3), published in 2011. This was a combined report from two institutions; one used 9.5 Gy × 4 and the other used 7 Gy × 6. This study was included in the review. However, the more recent articles by Rogers *et al.* (4) in 2012 and Komiya *et al.* (5) in 2013 were not available at the time of the review and therefore were not included.

We designed the HDR monotherapy variant based on the level of evidence presented. Published full-length articles