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Prostate Cancer Appraisal Addendum:
Stereotactic Body Radiation Therapy (SBRT)

The Institute for Clinical and Economic Review (ICER) has published appraisals on multiple management options for clinically-localized, low risk prostate cancer, including active surveillance, open, laparoscopic, and robot-assisted prostatectomy, and several forms of radiation therapy: brachytherapy, 3D conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and proton beam therapy. A distinct form of radiation therapy known as stereotactic body radiation therapy (SBRT) has also been gaining popularity for the treatment of many types of cancers, including prostate. Below we describe SBRT and review the current evidence on SBRT's effectiveness, potential harms, and economic impact among patients with low-risk prostate cancer.

The Procedure

SBRT involves the delivery of precisely focused radiation to solid tumors using advanced computer simulation, imaging via PET or CT scans as well as MRI, and rigid immobilization via body framesets or placement of "fiducials" (gold seeds or coils) to allow for dose tracking and adjustment for movement and breathing effects (UCLA Radiation Oncology, 2011). Treatment is delivered in up to 5 fractions; the most common radiation doses for prostate cancer range between 32 and 38 Gray.

Multiple technologies exist for delivering SBRT; the most common of these is known as CyberKnife® (Accuray, Inc.), a robotic system that uses image guidance software rather than the above-described procedures to account for movement and breathing effects. Proponents of SBRT cite the limited number of treatment sessions and patient comfort during treatment as advantages over more conventional forms of radiation therapy. Others have described concerns with the lower total radiation dose with SBRT as compared to other forms of external beam radiation, and dose escalation regimens are currently undergoing testing (Boike et al., 2011).

Review of the Evidence

ICER examined the published literature on all forms of SBRT for low-risk prostate cancer. English-language studies and reports published between January 2001 (the year of FDA approval for CyberKnife) through August 2011. Consistent with the approach taken for ICER's previous prostate cancer appraisals, studies were retained if all or a preponderance of treated patients were diagnosed with low-risk prostate cancer. As was done in our evaluation of proton beam therapy, studies of SBRT were restricted to those involving delivery of SBRT monotherapy only. Studies of SBRT as a dose escalation "boost" to other forms of radiation therapy were not considered. ICER's previous sample-size restriction of ≥50 patients was removed to allow for as complete an evaluation as possible.

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Evidence Quality

A total of 12 published studies, all of which were prospective or retrospective case series, were identified, comprising 800 patients overall. Only three studies included more than 50 patients (see evidence table on page 5). As with proton beam therapy, published evidence was concentrated at a small number of academic centers. A total of 8 centers worldwide published at least one case series in this sample. However, five of the 12 reports identified were published based on a pooled cohort from two of these centers (Stanford University and Naples, Florida). In addition, it is unclear in some reports from these two centers whether the patients studied represent new cases or longer-term follow-up on existing cases.

In general, patients were followed for relatively short periods of time. Median follow-up ranged from 1-3 years in most studies, and a single study reported a median follow-up duration of 5 years or longer.

Clinical Benefits

Overall & Disease-Specific Survival

None of the available studies reported the impact of SBRT on overall or prostate cancer-specific survival.

Biochemical Freedom from Failure (bFFF)

ICER previously limited analyses of bFFF to those studies with median follow-up of 5 years or longer in order to mitigate the effects of different definitions of bFFF across studies and management options. As mentioned above, a single study reporting outcomes for 41 patients with low-risk prostate cancer was identified that met this criterion (Freeman, 2011). The Kaplan-Meier estimate of bFFF at 5 years in this study was 92.7%.

Harms

Information on Radiation Therapy Oncology Group (RTOG) grade 2 or higher gastrointestinal (GI) and genitourinary (GU) toxicity was reported in 10 of the 12 studies (one study was limited to data on sexual side effects only, and the other did not use RTOG or similar grading for toxicity information). Of the 10 studies, three reported information only for acute toxicity (up to 90 days following treatment), three reported data for late toxicity alone, and four reported both types of toxicity.

Gastrointestinal Toxicity

As with other forms of external beam radiation evaluated in the ICER appraisals, reported rates of toxicity varied substantially across studies. Rates of acute GI toxicity ranged from 0-24.4%, while rates of late GI toxicity ranged from 1.8-14.6%. There is not sufficient detail in the available study reports to determine whether differences in methods, such as modifications to the RTOG grading system, contributed to the variability in GI toxicity findings.

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Genitourinary Toxicity

Rates of acute and late GU toxicity also varied widely. Rates of acute GU toxicity ranged between 4.6-60%. It should be noted that the rate at the high end of the range is based on a sample of only 10 patients, all of whom received alpha blocker therapy as part of their treatment plan (6 of the 10 still required such therapy at the end of follow-up) (Fuller, 2008). Rates of late GU toxicity ranged from 2.4-26.8% across studies. As with GI toxicity, there was not sufficient detail available in how toxicity was scored to determine the factors underlying the variability in reported rates.

Sexual Dysfunction

The impact of SBRT on sexual function was reported in five of the 12 available studies, and was measured in multiple ways. In two of these studies, 13-18% of men reporting potency at baseline had erections insufficient for intercourse at 1-2 years of follow-up. In two other studies, sexual function was assessed on the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. In one study, changes in sexual function from baseline were not statistically significant (Oermann, 2011); in the other, the significance of changes from baseline was not reported (Boike, 2011). A fifth study measured the change in erectile dysfunction from baseline to follow-up at 50 months, finding a 53% increase in this rate (from 38% to 71%) (Weigner, 2010).

Summary & Conclusions

The available evidence on SBRT suffers from some of the same shortcomings characteristic of the body of evidence for other low-risk prostate cancer management options: lack of randomized clinical trials or comparative observational studies, small sample sizes, and inconsistent measurement and reporting of key outcomes. However, while the range of SBRT-related harms appears comparable to those reported for other radiation modalities, wide variation in rates seen in studies of relatively small numbers of patients reduces our ability to make reasonable judgments about whether SBRT offers comparable short- and longer-term risks. Most importantly, information on biochemical control of disease is only available from a single small series with sufficient follow-up to allow for comparison to other management alternatives.

Given these serious limitations to the evidence on SBRT outcomes, ICER rates the current level of evidence for SBRT as **"Insufficient"**--in other words, the available evidence on SBRT does not provide high certainty that the net health benefit of SBRT is at least comparable to that provided by other management options for low-risk prostate cancer.

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References

Boike TP, Lotan Y, Cho LC, et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *J Clin Oncol* 2011;29(15):2020-6.

Bolzicco G, Favretto MS, Scremin E, et al. Image-guided stereotactic body radiation therapy for clinically localized prostate cancer: Preliminary clinical results. *Tech Cancer Res Treat* 2010;9(5):473-7.

Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: Five-year outcomes. *Rad Oncol* 2011;6(3). doi:10.1186/1748-717X6-3.

Friedland JL, Freeman DE, Masterson-McGary ME, Spellberg DM. Stereotactic body radiotherapy: An emerging approach for localized prostate cancer. *Tech Cancer Res Treat* 2009;8(5):387-92.

Fuller DB, Naitoh J, Lee C, et al. Virtual HDR CyberKnife treatment for localized prostatic carcinoma: Dosimetry comparison with HDR brachytherapy and preliminary clinical observations. *Int J Radiation Oncology Biol Phys* 2008;70(5):1588-97.

Katz AJ, Santoro M, Ashley R, et al. Stereotactic body radiotherapy for organ-confined prostate cancer. BMC Urology 2010;10:1. doi:10.1186/1471-2490-10-1.

King CR, Brooks JD, Gill H, et al. Stereotactic body radiotherapy for localized prostate cancer: Interim results of a prospective Phase II clinical trial. *Int J Radiation Oncology Biol Phys* 2009;73(4):1043-8.

King CR, Brooks JD, Gill H, Presti JC Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiation Oncology Biol Phys* 2011 (Epub ahead of print);1-6.

Madsen BL, Hsi RA, Pham HT, et al. Stereotactic hypofractionated accurate radiotherapy of the prostate (sharp), 33.5 Gy in five fractions for localized disease: First clinical trial results. *Int J Radiation Oncology Biol Phys* 2007;67(4):1099-1105.

Oermann EK, Suy S, Hanscom HN, et al. Low incidence of new biochemical and clinical hypogonadism following hypofractionated stereotactic body radiation therapy (SBRT) monotherapy for low to intermediate-risk prostate cancer. *J Hemat Oncol* 2011;4:12. doi:10.1186/1756-8722-4-12.

Townsend NC, Huth BJ, Ding W, et al. Acute toxicity after CyberKnife-delivered hypofractionated radiotherapy for treatment of prostate cancer. *Am J Clin Oncol* 2011;34(1):6-10.

Wiegner EA, King CR. Sexual function after stereotactic body radiotherapy for prostate cancer: Results of a prospective clinical trial. *Int J Radiation Oncology Biol Phys* 2010;78(2):442-8.

University of California, Los Angeles (UCLA) Radiation Oncology. Stereotactic Body Radiotherapy. Accessed at: http://radonc.ucla.edu/body.cfm?id=61. September 15, 2011.

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Table. Reported effectiveness and harms of stereotactic body radiation therapy.

						Biochemical freedom from failure (bFFF)		Toxicity				
								Gastrointestinal		Genitourinary		
Author	Year	Sample Size	% Low Risk	Dose (Gy or GyE)	Median Follow-Up	Estimate (%)	Timepoint (yrs)	Acute	Late	Acute	Late	Sexual
Madsen	2007	40	100.0%	33.5	41 mo	70.0%	4 yr	12.5%	7.5%	22.5%	20.0%	NR
Fuller	2008	10	80.0%	38	4 mo	NR	NR	10.0%	NR	60.0%	NR	NR
King	2009	41	100.0%	36.25	33 mo	100.0%	33 mo	NR	14.6%	NR	26.8%	NR
Friedland	2009	112	unk	35-36	24 mo	97.2%	2 yr	unk†	unk†	unk†	unk†	18.0%
Katz	2010	304	unk	35-36.25	17-30 mo	98.7%	1 yr	3.6%	2.0%	4.6%	4.6%	13.0%
Bolzicco	2010	45	48.9%	35	20 mo	NR	NR	24.4%	2.2%	11.1%	2.4%	NR
Wiegner	2010	32	75.0%	36.25	50 mo	NR	NR	NR	NR	NR	NR	53%‡
Oermann	2011	26	53.8%	36.25	15 mo	NR	NR	0.0%	NR	23.1%	NR	NS*
Townsend	2011	37	unk	35-37.5	unk	NR	NR	0.0%	NR	13.5%	NR	NR
King	2011	67	100.0%	36.25	2.7 yr	94.0%	4 yr	NR	1.8%	NR	8.8%	NR
Freeman	2011	41	100.0%	35-36.25	5 yr	92.7%	5 yr	NR	2.4%	NR	9.8%	NR
Boike	2011	45	40.0%	45-50	30 mo	100.0%	30 mo	11.1%	6.7%	22.2%	13.3%	unk¥

GY: Gray; GyE: Gray Equivalent; NR: Not reported; unk: unknown; NS: Not significant
†Toxicity not assessed via Radiation Therapy Oncology Group (RTOG) grading system
‡Reported as percentage change in reported impotence from baseline to follow-up
*No significant changes on patient-reported questionnaire
¥Unable to determine significance of changes on patient-reported questionnaire