


Stereotactic Body Radiotherapy for Prostate Cancer

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Abstract

Prostate cancer remains the most common and second most deadly cancer diagnosed amongst U.S. men. External beam radiotherapy is a standard-of-care definitive treatment option for localized prostate cancer and historically constituted an 8–9-week treatment course comprised of 39–45 doses of 1.8–2.0 Gy each (conventional fractionation, CF). Based on the notion that prostate cancer may respond favorably to a higher dose per day, considerable research efforts have been focused on characterizing the safety and efficacy profile of shorter and shorter radiation courses. Ultrahypofractionation (UHF) involves condensing the radiation course into just 5–7 treatments of 6–8 Gy each. When utilizing modern techniques that allow the precise sculpting of a dose distribution that delivers high doses to the prostate and lower doses to surrounding normal tissues over five or fewer treatments, this treatment is called stereotactic body radiotherapy (SBRT). Two randomized trials (HYPO-RT-PC and PACE-B) have compared UHF to longer radiation courses. The former demonstrated that UHF and CF have similar long-term toxicity and efficacy, while the latter demonstrated that modern SBRT has equivalent short-term toxicity as well. A separate report from a consortium of studies data provides prospective, albeit nonrandomized, data supporting the longer-term safety and efficacy of SBRT specifically. Thus, mounting high-level evidence suggests that SBRT is an acceptable standard care of option for men with localized prostate cancer.

Keywords

prostate cancer, oncology/cancer, PSA testing, general health and wellness

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Prostate cancer currently remains the most common and second most deadly cancer diagnosed amongst U.S. men—with an incidence of 118.2 cases per 100,000 men and 19.5 deaths per 100,000 men—both figures age-standardized to the 2000 U.S. standard population (Cronin et al., 2018). For localized prostate cancer—defined as disease confined to prostate and has not spread to regional lymph nodes or distant organs—treatment options generally center around surgery or radiation therapy to treat the prostate cancer locally.

In accordance with risk stratification as defined by the National Comprehensive Cancer Network (NCCN), the definitive treatment options available for localized prostate cancer generally depend on a patient's risk, as determined by prostate specific antigen (PSA) level, clinical T-stage, Gleason pattern, and number cores positive (National Comprehensive Cancer Network). Treatment options generally consist of surgery, brachytherapy, external beam radiotherapy (EBRT), active surveillance, or a combination of these treatments.

Surgery for prostate cancer generally consists of radical prostatectomy possibly with a pelvic lymph node dissection dependent on risk of lymph node metastasis. Brachytherapy, which involves placing radioactive sources placed inside the body to treat tumor, may be performed via low-dose rate (LDR) techniques involving placement of permanent radioactive seeds, or high-dose rate (HDR) techniques involving placement of temporary catheters which transport high-dose radioactive sources in and subsequently out of the prostate. EBRT, the focus

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of this article, involves beams of ionizing radiation externally directed toward the tumor.

Although historically, EBRT for prostate had involved a treatment course spanning approximately 8 to 9 weeks with five 1.8–2.0 Gy fractions per week (conventional fractionation CF), there has been a recent trend toward hypofractionation (HF) with modern regimens clustered around ~60–72 Gy delivered in fractions of ~2.4–3.4 Gy/fraction each (Morgan et al., 2018), and even more recently, toward ultrahypofractionation (UHF) with total ~36–43 Gy treatment condensed in five to seven treatments with ~6–8 Gy delivered per fraction. When UHF is employed in five or fewer treatments with sophisticated modern radiotherapy delivery platforms, it is called stereotactic body radiotherapy (SBRT).

Radiobiologic Basis for Hypofractionation

The rationale for hypofractionation in prostate cancer arises from favorable radiobiology to high doses of radiation per fraction. This phenomenon is best described by the α/β ratio, which is a loose proxy describing the curvature of a curve plotting cell survival as a function of dose of radiation per fraction (Figure 1). Cells with a low α/β ratio are more likely to survive small doses per fraction than cells with a high α/β ratio; the converse is true as well, with cells with low α/β ratios preferentially being killed at high doses per fraction. Prostate cancer cells are thought to have particularly low α/β ratios compared to other tumors (Brenner & Hall, 1999), thereby providing the basis for treating prostate cancer with large doses per fraction (thus in significantly fewer fractions).

Historical Perspective Toward Hypofractionation

Although there is literature dating back several decades of patients successfully receiving dosing regimens similar to modern “hypofractionation” schedules (Preston et al., 1986) and even “ultrahypofractionation” schedules (Collins et al., 1991), randomized data regarding hypofractionation compared to conventional fractionation have only been available for the last 15 years. Numerous trials have now demonstrated comparable efficacy of hypofractionated regimens to conventionally fractionated regimens including the large RTOG 0415 (Lee et al., 2016), CHHiP (Dearnaley et al., 2016), and PROFIT trials (Catton et al., 2017), with one trial even reporting superior efficacy (Hoffman et al., 2018). Late toxicity in the aforementioned trials was overall comparable, except in PROFIT (lower late Grade 2 GI toxicity in hypofractionated regimen) and in RTOG 0415 (higher late GI grade 2 and higher late GU grade 2 toxicity in

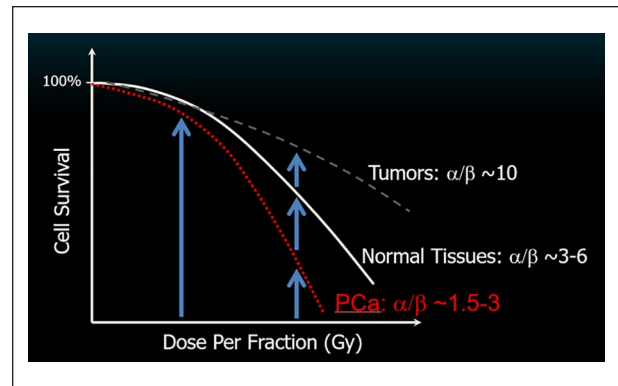


Figure 1. Example of Cell-Survival Curve With Varying Response to Varying α/β Ratio.

hypofractionated regimen, though this trial had biologically unequal doses of radiation in its two arms). As of 2018, the American Society of Radiation Oncology, the American Society of Clinical Oncology, and the American Urological Association have endorsed hypofractionation as a standard of care option for all patients with localized prostate cancer (Morgan et al., 2018).

Background on Prostate SBRT

The ability to further increase dose per fraction into the “ultrahypofractionated” range (i.e., ≥ 5 Gy per fraction) has coincided with important advances in precision related to simulation, treatment planning, and treatment delivery.

First, when treating with radiation, there are uncertainties in targeting related to patient positioning, target visualization, and, importantly, target motion. The prostate in fact exhibits a significant amount of motion both between and during treatments (Dang et al., 2018). This requires that radiation oncologists must place a “margin” around the actual prostate to ensure that, even if there is some uncertainty in position at any given time, the prostate requires adequate dose. This increases the area of tissue receiving radiation, potentially worsening toxicity. Modern advances in image-guided radiotherapy (IGRT), including the use of implanted fiducial markers inside the prostate to help direct radiation treatment both between treatments and potentially during treatment, allow physicians to feel increasingly confident treating patients with smaller margins.

Second, given the proximity of bladder and rectum to the prostate, it is also crucial to note the technological innovations that have allowed for sparing of dose in these surrounding tissues. The utilization of intensity-modulated radiotherapy (IMRT) has allowed for improved dose conformity—that is, the radiation dose can be more adequately sculpted such that the intended target receives

Table 1. Long-Term Efficacy and Toxicity From Prostate SBRT as Seen in Five Pooled Analyses and in One Meta-Analysis.

Reference	# of patients	F/u (years)	Regimen	Risk profile	BCRFS	Physician-reported toxicity
Pooled analyses						
Davis et al. (2015)	437	1.67	36.25 (most common)	Low: 43.2% Int: 49.25% High: 7.6%	Low: 99% Int: 94.5% High: 89.8%	Acute GU 2: 4% GI 2: 1% Late GU 2: 8% GI 2: 2%
Freeman et al. (2014)	1743	2	35–40 Gy in 4–5 fractions	Low: 47% Fav-int: 25% Unfav-int: 11% High: 10% Missing: 7%	Low: 99% Fav-int: 97% Unfav-int: 85% High: 87%	Late GU 3: 0% GI 3: 0.06%
Kishan et al. (2019)	2142	6.9	33.5–40 Gy in 4–5 fractions	Low: 55.3% Fav-int: 32.3% Unfav-int: 12.4%	7-year: Low: 95.5% Fav-int: 91.4% Unfav-int: 85.1%	Acute GU 3+: 0.60% GI 3+: 0.09% Late (7-year) GU 3+: 2.4% GI 3+: 0.4%
Fuller et al. (2018)	259	5	38 Gy in 4 fractions (plans mimicked HDR brachy)	Low: 43% Fav-int: 44% Unfav-int: 13%	5-year: Low: 100% Fav-int: 90.7% Unfav-int: 81.0%	Cumulative 5-year toxicity: GU grade 2/3/4: 12.4%/1.9%/0.4% GI grade 2/3/4: 3.4%/0%/0%
Meier et al. (2018)	309	5.1	40 Gy in 5 fractions	Low: 56% Fav-int: 27% Unfav-int: 17%	5-year DFS: Low: 97.3% Fav-int: 100% Unfav-int: 93.1%	Acute (highest grade): GU 1/2/3-5: 59%/26%/0% GI 1/2/3-5: 55%/8.1%/0% Late (highest grade): GU 1/2/3-5: 28%/12%/1.3% GI 1/2/3-5: 12%/2%/0%
Meta-analysis						
Jackson et al. (2019)	6116 (38 series)	3.25	36.25 Gy in 5 fractions (most common)	Low: 45% Int: 47% High: 8%	5-year bRFS: 95.3% (overall)	Late GU Grade 3+: 2.0% GI Grade 3+: 1.1%

BCRFS = biochemical recurrence-free survival; HDR = high-dose rate.

a high dose of radiation while the dose to nearby critical structures is minimized. Together, the advent of modern IGRT and IMRT have greatly increased physician confidence in delivering SBRT.

Clinical Utility of SBRT in Localized Prostate Cancer

Definitive Treatment for Low-and Intermediate-Risk Prostate Cancer: Review of Clinical Series

An earlier review (Kishan & King, 2017) compiled 21 studies representing 1812 patients which included regimens ranging from 27.4 Gy to 50 Gy in 4–5 fractions. While several of the studies only studied low-risk or intermediate-risk patients, 13 studies contained some portion of high-risk patients (ranging from 7.4% to 65.9%). Irrespective of risk groups, biochemical recurrence-free survival (BCRFS) rates at 5 years (where

reported) ranged from 81% to 100%. Overall, considerable variation in toxicity was seen—with acute grade 2+ GU/GI toxicity ranging from 4% to 45% and from 0% to 30.8%, respectively, and late grade 2+ GU/GI toxicity ranging from 2.2% to 26.4% and from 1% to 19.8%, respectively.

Several multi-institutional cohorts have also documented long-term efficacy and toxicity outcomes in SBRT patients. As displayed in Table 1, patients within these cohorts received 33.5–40 Gy in 4–5 fractions. Freedom from biochemical recurrence at 5 years varied by risk profile: 95%–100% (low risk), 90.7%–100% (favorable intermediate risk), and 81.0%–93.1% (unfavorable intermediate risk). Regarding acute toxicity, patients were reported to have acute grade 2+ GU toxicity ranging from 4% to 26%, and acute grade 2+ GI toxicity ranging from 1% to 8.1%, respectively. Regarding late toxicity, patients were reported to have late grade 2+ GU toxicity ranging from 8% to 14.7% and late grade 2+ GI toxicity ranging from 2% to 3.4%,

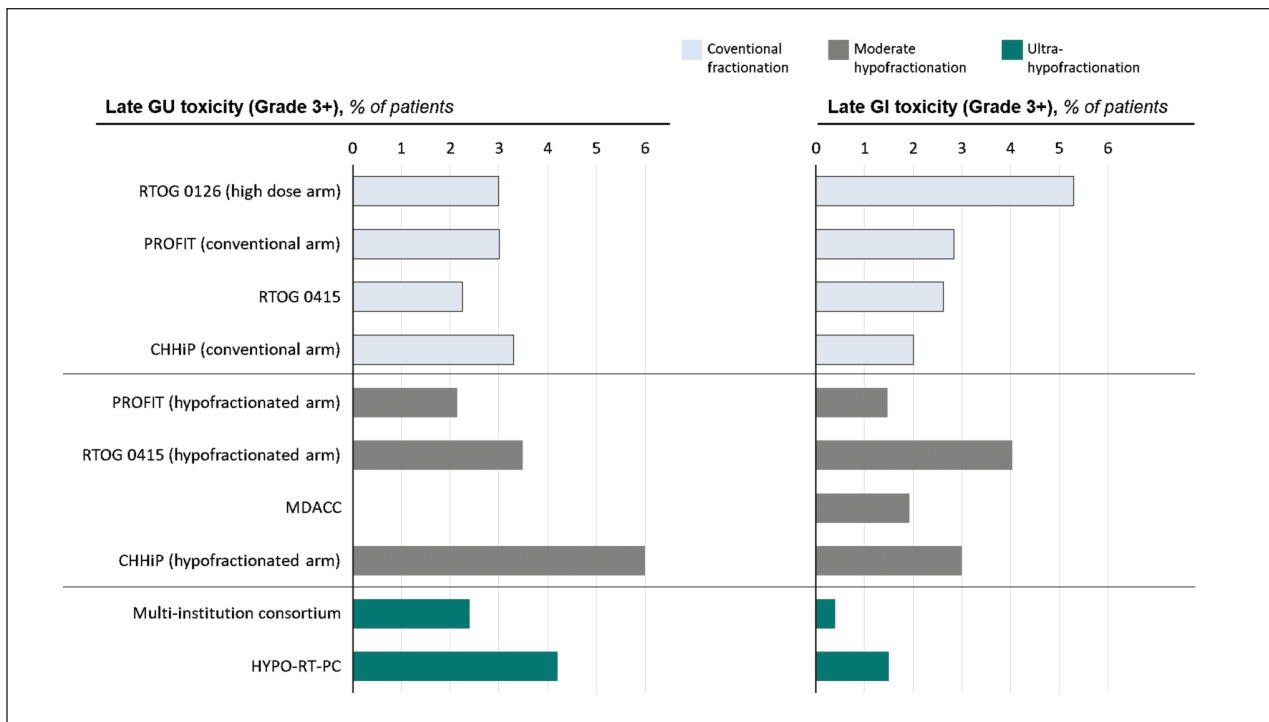


Figure 2. Review of Toxicity Comparing SBRT With Other RT Modalities. Adapted From Kishan et al. (2019); RTOG 0126 (Michalski et al., 2018); PROFIT (Cattton et al., 2017); RTOG 0415 (Lee et al., 2016); CHHIP (Dearnaley et al., 2016); MDACC (Hoffman et al., 2018); Multi-Institution Consortium (Kishan et al., 2019); and HYPO-RT-PC (Widmark et al., 2019).

respectively. As of early 2020, the largest multi-institutional series with long-term follow-up included 2142 patients with a median follow-up of 6.9 years and reported 7-year biochemical recurrence cumulative incidences of 4.5%, 8.6%, and 14.9% for low-, favorable intermediate-, and unfavorable intermediate-risk disease (Kishan et al., 2019). Seven-year cumulative incidences of grade 3+ GU and GI toxicity were 2.4% and 0.4%, respectively. A comparison of long-term toxicity between SBRT and other fractionation schemes is shown in Figure 2.

A recent meta-analysis compiled data from 38 prospective studies totaling 6116 patients who received SBRT for localized prostate cancer (Jackson et al., 2019). This aggregate cohort was made up of patients with low risk (45%), intermediate risk (47%), and high risk (8%). Median follow-up was 39 months. Median dose per fraction and number of fractions were 7.4 Gy (range 5–10 Gy) and 5 (range 4–9), respectively. Fifteen percent of patients received ADT with SBRT. In studies where available, 5-year BCRFS was reported to be 95.3% (95% CI: 91.3%–97.5%)—further broken down by risk group as 96.7% for low risk (95% CI: 95.2%–97.8%) and 92.1% for intermediate risk (95% CI: 89.2%–94.3%). Notably, meta-regression revealed dose, % of cohort receiving ADT, and NCCN risk group all as significant factors in BCRFS. Serious adverse events were uncommon, with

acute grade 3/4 GU toxicity reported in 0.5/0% patients and grade 3/4 GI toxicity reported in 0.06/0.03% of patients. Late grade 3+ GU toxicity was reported in 2.0% of patients with late grade 3+ GI toxicity in 1.1% of patients. Dose was reported to be associated with grade 3+ GU toxicity but not for grade 3+ GI toxicity; this may be biased by the inclusion of studies that delivered >8 Gy per day of radiation, which is considered nonstandard off protocol.

Patient-Reported Outcomes Comparing SBRT With Other Modalities

In a pooled multi-institutional analysis of patients undergoing moderate hypofractionation (<5 Gy/fraction, $n = 378$) or SBRT (5–10 Gy/fraction, $n = 534$) for prostate cancer, patient-reported outcomes were collected at 1 and 2 years of follow-up (Johnson et al., 2016). After adjusting for age and cancer characteristics, patients receiving hypofractionation were more likely to experience worsening urinary symptoms at 2 years.

A population-based cohort of prospectively enrolled, newly diagnosed prostate cancer patients pursuing SBRT ($n = 104$), EBRT ($n = 189$), or active surveillance ($n = 387$) has studied patient-reported outcomes in patients at 3, 12, and 24 months after treatment (Moon et al., 2019). Although SBRT had favorable quality-of-life (QoL)

Table 2. Ongoing Clinical Trials Currently Studying SBRT in Prostate Cancer.

Category	National Clinical Trial (NCT) Registry Numbers
Combination with other modalities	
Combination with IMRT	NCT01508390, NCT03380806
Combination with systemic therapies	NCT03477864, NCT03056638
Combination with surgery	NCT03477864, NCT02830165
Alternate dosing/fractionation schema	
Single-fraction SBRT	NCT04004312, NCT03294889
Dose escalation	NCT03822494
Prostate SBRT in additional clinical settings	
SBRT for recurrent disease after prior RT	NCT03253744, NCT03541850
SBRT as salvage after prior surgery	NCT04067570
SBRT for high-risk prostate cancer	
SBRT alone	NCT02296229
SBRT boost	NCT03380806, NCT01985828
Aims to limit toxicity with help of technology	
MR-guided SBRT	NCT03778112, NCT03664193, NCT03935308, NCT01976962, NCT02163317, NCT03822494
Moderate-dose SBRT with urethral-sparing SIB	NCT02470897
Utilization of intra-urethral radio transponder	NCT03458234
Comparison with other modalities	
Comparison with surgery and/or conventional fractionation	NCT01584258
Comparison with brachytherapy	NCT03830788

IMRT = intensity-modulated radiotherapy; SIB = simultaneous integrated boost; SBRT = stereotactic body radiotherapy.

results when compared to EBRT and comparable results when compared to active surveillance at 2 years of follow-up, the study's small sample size is noted as a potential limiting factor.

Randomized Trials Comparing SBRT With Other Modalities

In 2019, data were published from two randomized trials comparing patients receiving ultrahypofractionation (SBRT) compared to conventional fractionation.

PACE-B was a Phase 3, noninferiority trial which randomized men with low-risk or favorable intermediate-risk prostate adenocarcinoma to conventionally fractionated (78 Gy in 39 fractions over 7–8 weeks) or moderately hypofractionated radiotherapy (62 Gy in 20 fractions over 4 weeks) [$n = 441$], or ultrahypofractionated SBRT (36.25 Gy in five fractions over 1–2 weeks) [$n = 433$]. On report of acute toxicity findings, grade 2+ acute GU toxicity was seen in 27% of patients receiving CF/HF vs. 23% of patients receiving SBRT ($p = .16$) and grade 2+ acute GI toxicity was seen in 12% of patients receiving CF/HF vs. 10% of patients receiving SBRT ($p = .38$) (Brand et al., 2019). Importantly, patient-reported outcomes were not different between the two arms. Results regarding late

toxicity and biochemical control are expected to be reported in the upcoming 3–4 years.

HYPO-RT-PC was a phase 3, noninferiority which randomized men up to 75 years of age with intermediate-to-high-risk prostate cancer to conventional fractionated radiotherapy (78 Gy in 39 fractions, 5 days per week for 8 weeks) [$n = 591$ in per-protocol population] or ultra-hypofractionation (42.7 Gy in seven fractions, 3 days per week for 2.5 weeks) [$n = 598$ in per-protocol population] (Widmark et al., 2019). The estimated failure-free survival at 5 years was 84% (95% CI: 80%–87%) in both treatment groups (HR = 1.002, 95% CI: 0.758–1.325; log-rank $p = .99$). Regarding acute toxicity, Grade 2+ GU toxicity was reported in 28% of patients receiving UHF vs. 23% of patients receiving CF ($p = .057$), while Grade 2+ GI toxicity was reported in 8.5% of patients receiving UHF vs. 6% of patients receiving CF. Regarding late toxicity, Grade 2+ GU toxicity was reported in 18% of patients receiving UHF vs. 17% of patients receiving CF, while Grade 2+ GI toxicity was reported in 10% of patients receiving UHF vs. 10% of patients receiving CF. The ability to achieve an erection for intercourse decreased from approximately 70% at start of radiotherapy to 35% at 5 years, with no significant difference between the two treatment groups—a conclusion also drawn by earlier

studies (Dess et al., 2018; Wiegner & King, 2010). Patient-reported outcomes analysis indicated that urinary and bowel toxicity was slightly more pronounced in the seven-fraction arm at the end of treatment, and that the difference in urinary toxicity might persist for up to 12 months. Importantly, however, this trial used older radiation techniques—only 20% of patients received IMRT plans, and the planning margins used were very large by modern standards. Indeed, the acute rates of acute grade 2+ GU toxicity, for instance, are higher in HYPO-RT-PC than PACE-B (28% vs. 23%), and the late grade 3+ toxicity rates at 5-years are nearly 2–3 times higher in HYPO-RT-PC than in the Kishan et al. consortium study (4.2% vs. 1.8% for GU, and 1.5% vs. 0.4% for GI). Thus, the HYPO-RT-PC trial is in many ways a test of biology more than a test of modern SBRT.

Value of SBRT

Given the rapid rise in expected expenditures on prostate cancer care in the United States (Mariotto et al., 2011)—\$11.85 billion in 2010 to \$16.34 billion by 2020 per base-case estimates from 2011 NCI study—it has become increasingly important for the U.S. healthcare system to identify opportunities to preserve high-level care while improving value in oncology. In this setting, over the last decade, there has been growing interest in turning to SBRT as a source of value compared to conventionally fractionated techniques.

Using a time-driven activity-based costing approach, SBRT in low-risk prostate cancer has been reported to reduce costs to a provider by 50% when compared with a course of IMRT (Laviana et al., 2016). These costs account for personnel, space/equipment, and materials utilized during each phase of care for both treatment modalities. From the perspective of a health system, several Markov-based cost-effectiveness analyses have identified SBRT to be cost-effective to IMRT when treating prostate cancer (Hodges et al., 2012; Parthan et al., 2012; Sher et al., 2014).

Future Directions

Given its efficacy, toxicity profile, value, and convenience, SBRT has unsurprisingly continued to increase in utilization (Halpern et al., 2016). Although NCCN guidelines now list SBRT as a treatment option for very low, low, intermediate, high, and very high-risk disease, clinical trials are currently exploring multiple other indications (Table 2), including recurrent disease after prior RT and salvage after prior surgery. Additional trials are also studying the use of SBRT in combination with other modalities, comparison versus other modalities, alternate

dosing/fractionation schema, and novel technological approaches to further limit toxicity.

Declaration of Conflicting Interests

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Authors' Contributions

N.R.P. and A.U.K. contributed equally to this work.

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References

- Brand, D. H., Tree, A. C., Ostler, P., van der Voet, H., Loblaw, A., Chu, W., Ford, D., Tolan, S., Jain, S., Martin, A., Staffurth, J., Camilleri, P., Kancherla, K., Frew, J., Chan, A., Dayes, I. S., Henderson, D., Brown, S., Cruickshank, C., . . . Investigators, P. T. (2019). Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): Acute toxicity findings from an international, randomised, open-label, Phase 3, non-inferiority trial. *The Lancet Oncology*, *20*(11), 1531–1543. [https://doi.org/10.1016/S1470-2045\(19\)30569-8](https://doi.org/10.1016/S1470-2045(19)30569-8)
- Brenner, D. J., & Hall, E. J. (1999). Fractionation and protraction for radiotherapy of prostate carcinoma. *International Journal of Radiation Oncology Biology Physics*, *43*(5), 1095–1101. [https://doi.org/10.1016/s0360-3016\(98\)00438-6](https://doi.org/10.1016/s0360-3016(98)00438-6)
- Catton, C. N., Lukka, H., Gu, C. S., Martin, J. M., Supiot, S., Chung, P. W. M., Bauman, G. S., Bahary, J.-P., Ahmed, S., Cheung, P., Tai, K. H., Wu, J. S., Parliament, M. B., Tsakiridis, T., Corbett, T. B., Tang, C., Dayes, I. S., Warde, P., Craig, T. K., . . . Levine, M. N. (2017). Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *Journal of Clinical Oncology*, *35*(17), 1884–1890. <https://doi.org/10.1200/JCO.2016.71.7397>
- Collins, C. D., Lloyd-Davies, R. W., & Swan, A. V. (1991). Radical external beam radiotherapy for localised carcinoma of the prostate using a hypofractionation technique. *Clinical Oncology*, *3*(3), 127–132. [https://doi.org/10.1016/s0936-6555\(05\)80831-3](https://doi.org/10.1016/s0936-6555(05)80831-3)
- Cronin, K. A., Lake, A. J., Scott, S., Sherman, R. L., Noone, A. M., Howlader, N., Henley, S. J., Anderson, R. N., Firth,

- A. U., Ma, J., Kohler, B. A., & Jemal, A. (2018). Annual report to the nation on the status of cancer, part I: National cancer statistics. *Cancer*, *124*(13), 2785–2800. <https://doi.org/10.1002/cncr.31551>
- Dang, A., Kupelian, P. A., Cao, M., Agazaryan, N., & Kishan, A. U. (2018). Image-guided radiotherapy for prostate cancer. *Translational Andrology and Urology*, *7*(3), 308–320. <https://doi.org/10.21037/tau.2017.12.37>
- Davis, J., Sharma, S., Shumway, R., Perry, D., Bydder, S., Simpson, C. K., & D'Ambrosio, D. (2015). Stereotactic body radiotherapy for clinically localized prostate cancer: Toxicity and biochemical disease-free outcomes from a multi-institutional patient registry. *Cureus*, *7*(12), e395. <https://doi.org/10.7759/cureus.395>
- Dearnaley, D., Syndikus, I., Mossop, H., Khoo, V., Birtle, A., Bloomfield, D., Graham, J., Kirkbride, P., Logue, J., Malik, Z., Money-Kyrle, J., O'Sullivan, J. M., Panades, M., Parker, C., Patterson, H., Scrase, C., Staffurth, J., Stockdale, A., Tremllett, J., . . . CHHiP Investigators (2016). Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *The Lancet Oncology*, *17*(8), 1047–1060. [https://doi.org/10.1016/S1470-2045\(16\)30102-4](https://doi.org/10.1016/S1470-2045(16)30102-4)
- Dess, R. T., Hartman, H. E., Aghdam, N., Jackson, W. C., Soni, P. D., Abugharib, A. E., Suy, S., Desai, N. B., Zumsteg, Z. S., Mehra, R., Morgan, T. M., Feng, F. Y., Hamstra, D. A., Schipper, M. J., Collins, S. P., & Spratt, D. E. (2018). Erectile function after stereotactic body radiotherapy for localized prostate cancer. *BJU International*, *121*(1), 61–68. <https://doi.org/10.1111/bju.13962>
- Freeman, D., Dickerson, G., & Perman, M. (2014). Multi-institutional registry for prostate cancer radiosurgery: A prospective observational clinical trial. *Frontiers in Oncology*, *4*, 369, 1–8. <https://doi.org/10.3389/fonc.2014.00369>
- Fuller, D. B., Falchook, A. D., Crabtree, T., Kane, B. L., Medbery, C. A., Underhill, K., Gray, J. R., Peddada, A., & Chen, R. C. (2018). Phase 2 multicenter trial of heterogeneous-dosing stereotactic body radiotherapy for low- and intermediate-risk prostate cancer: 5-year outcomes. *European Urology Oncology*, *1*(6), 540–547. <https://doi.org/10.1016/j.euo.2018.06.013>
- Halpern, J. A., Sedrakyan, A., Hsu, W. C., Mao, J., Daskivich, T. J., Nguyen, P. L., Golden, E. B., Kang, J., Kang, J., & Hu, J. C. (2016). Use, complications, and costs of stereotactic body radiotherapy for localized prostate cancer. *Cancer*, *122*(16), 2496–2504. <https://doi.org/10.1002/cncr.30101>
- Hodges, J. C., Lotan, Y., Boike, T. P., Benton, R., Barrier, A., & Timmerman, R. D. (2012). Cost-effectiveness analysis of stereotactic body radiation therapy versus intensity-modulated radiation therapy: An emerging initial radiation treatment option for organ-confined prostate cancer. *Journal of Oncology Practice*, *8*(3 Suppl), e31s–37s. <https://doi.org/10.1200/JOP.2012.000548>
- Hoffman, K. E., Voong, K. R., Levy, L. B., Allen, P. K., Choi, S., Schlembach, P. J., Lee, A. K., McGuire, E., Nguyen, Q., Pugh, T. J., Frank, S. J., Kudchadker, R. J., Du, W., & Kuban, D. A. (2018). Randomized trial of hypofractionated, dose-escalated, intensity-modulated radiation therapy (IMRT) versus conventionally fractionated IMRT for localized prostate cancer. *Journal of Clinical Oncology*, *36*(29), 2943–2949. <https://doi.org/10.1200/JCO.2018.77.9868>
- Jackson, W. C., Silva, J., Hartman, H. E., Dess, R. T., Kishan, A. U., Beeler, W. H., Gharzai, L. A., Jaworski, E. M., Mehra, R., Hearn, J. W. D., Morgan, T. M., Salami, S. S., Cooperberg, M. R., Mahal, B. A., Soni, P. D., Kaffenberger, S., Nguyen, P. L., Desai, N., Feng, F. Y., Zumsteg, Z. S., . . . Spratt, D. E. (2019). Stereotactic body radiation therapy for localized prostate cancer: A systematic review and meta-analysis of over 6,000 patients treated on prospective studies. *International Journal of Radiation Oncology Biology Physics*, *104*(4), 778–789. <https://doi.org/10.1016/j.ijrobp.2019.03.051>
- Johnson, S. B., Soulos, P. R., Shafman, T. D., Mantz, C. A., Dosoretz, A. P., Ross, R., Finkelstein, S. E., Collins, S. P., Suy, S., Brower, J. V., Ritter, M. A., King, C. R., Kupelian, P. A., Horwitz, E. M., Pollack, A., Abramowitz, M. C., Hallman, M. A., Faria, S., Gross, C. P., & Yu, J. B. (2016). Patient-reported quality of life after stereotactic body radiation therapy versus moderate hypofractionation for clinically localized prostate cancer. *Radiotherapy & Oncology*, *121*(2), 294–298. <https://doi.org/10.1016/j.radonc.2016.10.013>
- Kishan, A. U., Dang, A., Katz, A. J., Mantz, C. A., Collins, S. P., Aghdam, N., Chu, F.-I., Kaplan, I. D., Appelbaum, L., Fuller, D. B., Meier, R. M., Loblaw, D. A., Cheung, P., Pham, H. T., Shaverdian, N., Jiang, N., Yuan, Y., Bagshaw, H., Prionas, N., . . . King, C. R. (2019). Long-term outcomes of stereotactic body radiotherapy for low-risk and intermediate-risk prostate cancer. *JAMA Network Open*, *2*(2), e188006. <https://doi.org/10.1001/jamanetworkopen.2018.8006>
- Kishan, A. U., & King, C. R. (2017). Stereotactic body radiotherapy for low- and intermediate-risk prostate cancer. *Seminars in Radiation Oncology*, *27*(3), 268–278. <https://doi.org/10.1016/j.semradonc.2017.02.006>
- Laviana, A. A., Ilg, A. M., Veruttipong, D., Tan, H. J., Burke, M. A., Niedzwiecki, D. R., Kupelian, P. A., King, C. R., Steinberg, M. L., Kundavaram, C. R., Kamrava, M., Kaplan, A. L., Moriarity, A. K., Hsu, W., Margolis, D. J. A., Hu, J. C., & Saigal, C. S. (2016). Utilizing time-driven activity-based costing to understand the short- and long-term costs of treating localized, low-risk prostate cancer. *Cancer*, *122*(3), 447–455. <https://doi.org/10.1002/cncr.29743>
- Lee, W. R., Dignam, J. J., Amin, M. B., Bruner, D. W., Low, D., Swanson, G. P., Shah, A. B., D'Souza, D. P., Michalski, J. M., Dayes, I. S., Seaward, S. A., Hall, W. A., Nguyen, P. L., Pisansky, T. M., Faria, S. L., Chen, Y., Koontz, B. F., Paulus, R., & Sandler, H. M. (2016). Randomized phase III non-inferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *Journal of Clinical Oncology*, *34*(20), 2325–2332. <https://doi.org/10.1200/JCO.2016.67.0448>
- Mariotto, A. B., Yabroff, K. R., Shao, Y., Feuer, E. J., & Brown, M. L. (2011). Projections of the cost of cancer care in the United States: 2010–2020. *Journal of the National Cancer Institute*, *103*(2), 117–128. <https://doi.org/10.1093/jnci/djq495>

- Meier, R. M., Bloch, D. A., Cotrutz, C., Beckman, A. C., Henning, G. T., Woodhouse, S. A., Williamson, S. K., Mohideen, N., Dombrowski, J. J., Hong, R. L., Brachman, D. G., Linson, P. W., & Kaplan, I. D. (2018). Multicenter trial of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer: Survival and toxicity endpoints. *International Journal of Radiation Oncology Biology Physics*, *102*(2), 296–303. <https://doi.org/10.1016/j.ijrobp.2018.05.040>
- Michalski, J. M., Moughan, J., Purdy, J., Bosch, W., Bruner, D. W., Bahary, J. P., Lau, H., Duclos, M., Parliament, M., Morton, G., Hamstra, D., Seider, M., Lock, M. I., Patel, M., Gay, H., Vigneault, E., Winter, K., & Sandler, H. (2018). Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: The NRG oncology RTOG 0126 randomized clinical trial. *JAMA Oncology*, *4*(6), e180039. <https://doi.org/10.1001/jamaoncol.2018.0039>
- Moon, D. H., Basak, R. S., Usinger, D. S., Dickerson, G. A., Morris, D. E., Perman, M., Lim, M., Wibbelsman, T., Chang, J., Crawford, Z., Broughman, J. R., Godley, P. A., Chen, R. C., & Chen, R. C. (2019). Patient-reported quality of life following stereotactic body radiotherapy and conventionally fractionated external beam radiotherapy compared with active surveillance among men with localized prostate cancer. *European Urology*, *76*(3), 391–397. <https://doi.org/10.1016/j.eururo.2019.02.026>
- Morgan, S. C., Hoffman, K., Loblaw, D. A., Buyyounouski, M. K., Patton, C., Barocas, D., Bentzen, S., Chang, M., Efstathiou, J., Greany, P., Halvorsen, P., Koontz, B. F., Lawton, C., Leyrer, C. M., Lin, D., Ray, M., & Sandler, H. (2018). Hypofractionated radiation therapy for localized prostate cancer: An ASTRO, ASCO, and AUA evidence-based guideline. *Journal of Clinical Oncology*, *36*(34), 3411–3430. JCO1801097. <https://doi.org/10.1200/JCO.18.01097>
- National Comprehensive Cancer Network. Prostate Cancer (Version 1.2020). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
- Parthan, A., Pruttivarasin, N., Davies, D., Taylor, D. C., Pawar, V., Bijlani, A., Hassmiller, K., & Chen, R. C. (2012). Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer. *Frontiers in Oncology*, *2*, 81. <https://doi.org/10.3389/fonc.2012.00081>
- Preston, C. I., Duncan, W., & Kerr, G. R. (1986). Radical treatment of prostatic carcinoma by megavoltage X-ray therapy. *Clinical Radiology*, *37*(5), 473–477. [https://doi.org/10.1016/s0009-9260\(86\)80058-7](https://doi.org/10.1016/s0009-9260(86)80058-7)
- Sher, D. J., Parikh, R. B., Mays-Jackson, S., & Punglia, R. S. (2014). Cost-effectiveness analysis of SBRT versus IMRT for low-risk prostate cancer. *American Journal of Clinical Oncology*, *37*(3), 215–221. <https://doi.org/10.1097/COC.0b013e31827a7d2a>
- Widmark, A., Gunnlaugsson, A., Beckman, L., Thellenberg-Karlsson, C., Hoyer, M., Lagerlund, M., Kindbloom, J., & Nilsson, P. (2019). Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *The Lancet*, *394*(10196), 385–395. [https://doi.org/10.1016/S0140-6736\(19\)31131-6](https://doi.org/10.1016/S0140-6736(19)31131-6)
- Wiegner, E. A., & King, C. R. (2010). Sexual function after stereotactic body radiotherapy for prostate cancer: Results of a prospective clinical trial. *International Journal of Radiation Oncology Biology Physics*, *78*(2), 442–448. <https://doi.org/10.1016/j.ijrobp.2009.07.1748>