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SUMMARY WITH CRITICAL APPRAISAL

High Dose Rate Brachytherapy versus Low Dose Rate Brachytherapy for the Treatment of Prostate Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness

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Abbreviations

cGy	centigray
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
EBRT	External Beam Radiation Therapy
EPIC-26	Expanded Prostate Cancer Index Composite-26
Gy	Grays
HDR	High-dose-rate
I	Iodine
IPSS	International prostate system score
LDR	Low-dose-rate
mCi	millicurie
NR	Not reported
Pd	Palladium
PRIX	Prostate Risk Index
PSA	Prostate Specific Antigen
SEER	Surveillance, Epidemiology, and End Results
SHIM	Sexual Health Inventory for Men
T stage	Tumour stage
UAE	Urinary Adverse Event

Context and Policy Issues

Prostate cancer is the most common cancer in Canadian adults with prostates and the fourth most common cancer across all Canadians.[1] In 2017, there were an estimated 21,300 new cases of prostate cancer diagnosed in Canada and there were an estimated 4,100 deaths, representing 10% of all cancer deaths in Canadians with a prostate that year.[1]

Radiation therapy is a standard option for the management and treatment of localized prostate cancer.[2] When radiation is delivered using machines outside of the body it is referred to as external beam radiation therapy (EBRT)[3] and when it is delivered internally by placing the source of radiation directly into the prostate gland near the tumour it is called brachytherapy.[3] There are two types of brachytherapy: low-dose-rate (LDR) and high-dose-rate (HDR). LDR brachytherapy involves permanently or temporarily placing radioactive seeds in the prostate to deliver radiation over an extended period of time, while HDR involves inserting flexible needles into the prostate to deliver a high dose of radiation over a period of a few minutes.[3] The total dose of radiation may be delivered as one treatment or divided over two or more treatments, called fractions.[4]

Choice of treatment is based on factors including patient values and preferences, clinician judgement based on initial evaluation (e.g., identification of tumor stage, baseline serum prostate specific antigen levels [PSA], and Gleason score), and resource availability.[3,5]

There is not currently direct clinical evidence supporting the superiority of HDR or LDR brachytherapy with respect to tumor control or reduced toxicity.

Therefore, the purpose of this report is to summarize the evidence regarding the comparative clinical and cost-effectiveness of HDR versus LDR brachytherapy for the treatment of prostate cancer.

Research Questions

1. What is the comparative clinical effectiveness of high-dose-rate versus low-dose-rate brachytherapy for the treatment of prostate cancer?
2. What is the cost-effectiveness of high-dose-rate versus low-dose-rate brachytherapy for the treatment of prostate cancer?

Key Findings

Evidence of limited to moderate quality from five non-randomized cohort studies suggested that there were no significant differences between LDR prostate brachytherapy and HDR prostate brachytherapy delivered as a monotherapy for relapse or serious adverse events. In contrast, LDR prostate brachytherapy was associated with significantly better relapse and serious adverse event profile than HDR brachytherapy when combined with External Beam Radiation Therapy (EBRT). Evidence of limited quality from one study showed that for HRQoL, LDR brachytherapy was either more favourable, less favourable, or did not differ from HDR brachytherapy monotherapy depending on the specific type of HRQoL being examined. The combined HDR and EBRT treatment option was not examined with respect to self-reported HRQoL. No evidence regarding the cost-effectiveness of high-dose-rate (HDR) brachytherapy was identified.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, PubMed (for non-Medline records), the Cochrane Library, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and January 16, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with prostate cancer
Intervention	High-dose-rate brachytherapy, either as monotherapy or in combination with external beam therapy as a boost
Comparator	Low-dose-rate brachytherapy (i.e., seed brachytherapy, usually done with iodine [iodine-125 seeds] or

	palladium [palladium-103 seeds])
Outcomes	Q1: Clinical effectiveness, safety Q2: Cost effectiveness outcomes (e.g., QALY)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, non-randomized studies

QALY = Quality Adjusted Life Years

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014.

Critical Appraisal of Individual Studies

The included non-randomized studies were critically appraised by one reviewer using the Downs and Black Checklist.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 327 citations were identified in the literature search. Following screening of titles and abstracts, 307 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full text review. Of the potentially relevant articles, 15 publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised one prospective- and four retrospective cohort studies. Appendix 1 presents the PRISMA[7] flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Five non-randomized studies published between 2014 and 2017 were included in this report. Among these cohort studies were one single-centre prospective cohort study,[8] and four retrospective cohort studies, consisting of two single-centre studies,[9,10] one multi-centre study,[11] and one study with an unreported number of centres.[12] The studies were conducted between 1998 and 2013 and patient recruitment into the studies was not described.

Country of Origin

Three studies were conducted in the US,[9-11] one was conducted in Germany,[8] and another was conducted in Japan.[12]

Patient Population

Data from a total of 16,863 patients with prostate cancer are summarized in this report. Participants were adults aged between 38 and 86 years undergoing brachytherapy for prostate cancer. Median ages ranged from 64 to 72 when reported.[8,10,12] Participants treated with HDR brachytherapy as monotherapy or in combination with external beam radiation therapy (EBRT) were low, medium and high risk patients (i.e., median PSA scores ranged from 5.0 to 13 ng/mL;[8,10,12] proportion of patients with a Gleason score greater than 6 ranged from 18% of participants to 70.6% of patients;[8,10,12] T stages were between T1c and T4[10-12] and 21% of participants had a T stage above T2a in one study[8]). Patients treated with LDR brachytherapy as monotherapy were mainly low or medium risk patients (i.e., where reported, median PSA scores ranged from 5.1 to 7.0 ng/mL; proportion of patients with a Gleason score of greater than 6 ranged from 0%[10,12] to 3%[8]; T stages were between T1c and T2[10,12] in two studies) although 0.2%[11] and 5% [8] of patients had a T stage above T2a in two studies, putting them in the high risk category. Details on pre-treatment PSA and Gleason score were not reported for one study[11] and, along with clinical T score, these values were not reported by brachytherapy type in another study.[9]

Interventions and Comparators

Four studies examined HDR brachytherapy as monotherapy[9-12] and three studies examined HDR in combination with EBRT.[8,9,11] Two of the studies examining combined therapy included both monotherapy and combined treatment groups.[9,11]

Brachytherapy dose for HDR monotherapy ranged from 28 Gy to 45.5 Gy, delivered in two to seven fractions, with duration between fractions ranging from four hours to three weeks apart.[9,10,12]

When combined with EBRT, HDR brachytherapy dose was 18 Gy[8] or 19 Gy,[9] delivered in two[8] or three[9] fractions, with duration between fractions ranging from four hours[9] to at least seven days.[8]

Dose was not described in the retrospective cohort study by Tward.[11] Data for this study were obtained from 15,878 patients being treated for prostate cancer who were included in a database that captured many US regional areas, and therefore the treatment protocols were likely to have differed widely across patients.[11]

All studies included a LDR brachytherapy monotherapy comparator group.[8-12] LDR brachytherapy was delivered using implants of Iodine-125 seeds[9,10,12] or Palladium-125 seeds.[9] The median brachytherapy dose ranged from 14.5 Gy to 145 Gy and was delivered in one fraction.[9,10,12]

Outcomes

Relapse was assessed in three studies[8,9,12] as biochemical failure free survival rate,[8] biochemical progression free rate,[12] PSA relapse-free survival,[9] metastasis free survival rate,[8] and distant metastasis free survival.[9] Biochemical failure free survival rate was assessed in one study as the percentage of patients who have not experienced biochemical failure (defined as an increased PSA of ≥2 ng/mL above the nadir).[8] This information was collected in regular intervals from patients or their medical practitioners.[8] PSA relapse-free survival was assessed in one study using the same definition of biochemical failure (i.e., increased PSA of ≥2 ng/mL above the nadir) and presented as hazard ratios. [9] This information was collected from patient records.[9] Metastasis-free survival rate was assessed

as the percentage of patients who did not have a diagnosed metastasis.[8] This information was collected in regular intervals from patients or their medical practitioners. Distant metastasis-free survival was assessed as the percentage of the end of radiotherapy to the date of the first report of a distant metastasis and analyzed using hazard ratios.[9] Distant metastasis was defined as "clinical or radiographic evidence of disease outside the pelvis."[9] (p.180) This information was collected from patient records.[9]

Adverse events were assessed in two studies. In one study, cumulative severe urinary adverse event (UAE) incidence was assessed from time of brachytherapy until four and eight years of follow-up.[11] Severe UAE was defined as a diagnosis code and procedure recorded on a single Medicare claim, as this indicated the patient had a UAE that was severe enough to require treatment.[11] Diagnosis categories were defined based on the Common Terminology Criteria for Adverse Events (CTCAE version 4.0).[11] A specific UAE, i.e., bladder outlet obstruction, was also assessed in the same study.[11] This was also reported as cumulative incidence at four and eight year follow-up.[11] In the second study, gentinoury and gastrointestinal adverse events were assessed.[12] This information was collected retrospectively from patient records and defined based on CTCAE version 4.03.[12]

Self-reported Health Related Quality of Life (HRQoL) was measured in one study as Urinary HRQoL, Bowel HRQoL, and Sexual HRQoL. Urinary HRQoL was assessed with the validated 7-item International Prostate System Score (IPSS) scale. Scores ranged from 0 to 5, with higher scores indicating worse HRQoL related to urinary frequency, urgency, and retention. Bowel HRQoL was assessed with the 6-item Expanded Prostate Cancer Index Composite-26 (EPIC-26) short form. Six response options were possible, with higher negative scores indicating worse HRQoL related to stool urgency, frequency, firmness, presence of blood, and pain. Study authors did not describe the measurement properties of the questionnaire. Sexual HRQoL was assessed with the validated 5-item Sexual Health Inventory Measure (SHIM). Five response options were available, with higher negative scores reflecting greater deterioration in HRQoL related to quality of erections and satisfaction with sexual intercourse.

Authors did not describe the minimal clinically important difference of any outcome measure.

Summary of Critical Appraisal

The critical appraisal of the included clinical studies is summarized here. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Non-Randomized Studies

The non-randomized studies[8-12] were assessed using the Downs and Black Checklist[6] and several strengths and limitations were identified. First, it was considered a strength of the identified body of literature that most individual studies were clearly reported.[9-12] The exception to this is the study by Freiberger and colleagues, which provided less detail and was somewhat less clear.[8]

Regarding external validity, the study that contributed 94.2% of participants to this report demonstrated good external validity.[11] All eligible participants in the database were included, and participants were treated in a variety of treatment locations reflecting the care that would normally be received across many cities and states in the US,[11] increasing confidence in the generalizability of the findings. The remaining four studies had various potential threats to external validity due to lack of information about the population from

which patients were drawn, participant recruitment methods, and descriptions about the places (including facilities and staff) treatment occurred.[8-10,12] Without knowing this information, the extent to which the generalizability may be affected is unclear.

Regarding internal validity, the lack of randomization to treatment groups is a key source of potential bias in all of the included studies.[8-12] Given that participants with a lower risk forms of prostate cancer are more likely to be recommended to LDR brachytherapy and patients with higher risk forms are more likely to be recommended to HDR brachytherapy (with or without EBRT), it is likely that the prognosis of patients in the comparator group was fundamentally different from those in the intervention groups. In the largest study, which was a well conducted retrospective cohort study, these differences were accounted for in the analysis, which increases our confidence in the overall findings.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of HDR vs LDR Brachytherapy

Relapse

Two studies examined biochemical failure free survival rate.[8,12] One study showed survival rates were statistically significantly better for LDR brachytherapy than for HDR plus EBRT at 10 year follow-up (this study also provided information based on risk group. See Table 4).[8] In contrast, another study did not show any difference in biochemical free progression rates between LDR and HDR brachytherapy monotherapy at two-year follow-up.[12] Similarly, a third study examined PSA relapse-free survival and showed no significant difference between LDR and HDR brachytherapy monotherapy at follow-up.[9]

Both LDR brachytherapy and HDR plus EBRT had favourable metastasis free survival (94% and 90%, respectively) at 10-year follow-up, with no significant differences between the groups.[8] Similarly, one study examined distant metastasis-free survival and showed no significant difference between LDR and HDR brachytherapy monotherapy.[9]

Adverse Events

Cumulative incidence of severe UAE was statistically significantly lower with LDR brachytherapy compared with HDR brachytherapy plus EBRT at four-year follow up.[11] There were no differences at four-years between LDR or HDR plus EBRT with HDR monotherapy.[11] At eight-year follow-up, LDR and HDR monotherapies were each associated with significantly lower cumulative incidence of severe UAE than HDR plus EBRT, but did not significantly differ from each other.[11] For bladder outlet obstruction specifically, LDR brachytherapy was associated with a significantly lower cumulative incidence than HDR plus EBRT at four- and eight year follow-up.[11] HDR monotherapy did not differ significantly from LDR brachytherapy or HDR plus EBRT over either time frame.[11] There were no significant differences in the frequency of grade 1 or 2 genitourinary or gastrointestinal adverse events experienced by six-month follow-up between patients who received HDR or LDR brachytherapy.[12]

HRQoL

Patients who underwent HDR brachytherapy experienced statistically significantly less decline in urinary HRQoL than LDR brachytherapy patients at one and three month follow-up. Between the six- and 18-month follow-up statistical differences were no longer present.[10] There were no significant differences between HDR and LDR brachytherapy in reported bowel HRQoL at any time point.[10] Patients treated with HDR brachytherapy experienced greater decreases in Sexual HRQoL at one-, six-, nine-, and 18-month follow up compared with LDR brachytherapy.[10] Differences between groups were not significant at three or 12 months.[10]

Cost-Effectiveness of HDR vs LDR Brachytherapy

No relevant evidence regarding the cost-effectiveness of HDR brachytherapy for prostate cancer was identified; therefore, no summary can be provided.

Limitations

Overall, the include studies were of low-to-moderate methodological quality. In addition, there are a few limitations to note beyond study methodological quality. For instance, not all

studies reported systematically collecting data about adverse events. Among those that did, data related to the quantity of adverse events was reported, while potentially meaningful information about the event such as duration of symptoms was not examined. This issue was raised by the authors of the largest included study, who noted that their decision to examine time to the first urinary adverse event experienced may underestimate the severity of urinary toxicities, as it doesn't account for subsequent events or duration of toxicity.[11] As such, our understanding of the toxicity of LDR and HDR brachytherapies is incomplete.

A further limitation is related to patient-reported HRQoL. One study showed that HRQoL differed or did not differ between LDR and HDR brachytherapy depending on the type of HRQoL being examined. No studies examined HDR brachytherapy with EBRT boost, and therefore it is not known how this treatment option may affect these outcomes.

Finally, no studies were identified regarding the cost-effectiveness of HDR prostate brachytherapy versus LDR prostate brachytherapy for the treatment of prostate cancer. With few clinical differences between LDR and HDR prostate brachytherapy monotherapy identified, cost-effectiveness studies are needed to help inform decisions regarding the most appropriate treatment options to recommend and under what conditions.

Conclusions and Implications for Decision or Policy Making

Five non-randomized cohort studies were identified to address the effectiveness of HDR brachytherapy versus LDR brachytherapy for the treatment of prostate cancer. Overall, there were no significant differences between LDR brachytherapy and HDR brachytherapy monotherapies for relapse or serious adverse events when brachytherapy was delivered as a monotherapy. In contrast, LDR brachytherapy was associated with significantly better relapse and serious adverse event profile than HDR brachytherapy when combined with EBRT. The combined HDR and EBRT treatment option was not examined with respect to self-reported HRQoL and findings for the comparison of LDR and HDR monotherapies differed depending on the specific type of HRQoL being examined.

Regarding biochemical relapse, findings suggest LDR brachytherapy was associated with better outcomes than HDR therapy combined with EBRT in one study, and that there was no difference between LDR and HDR brachytherapy monotherapy.[8,9] Regarding metastasis, there were no differences between LDR brachytherapy and HDR brachytherapy monotherapy or HDR combined with EBRT with respect to metastasis-free survival.[8,9]

Regarding adverse events, patients who underwent LDR brachytherapy experienced lower cumulative incidence of severe UAEs and of bladder outlet obstruction compared with HDR brachytherapy combined with EBRT.[11] There were no differences between LDR and HDR monotherapy for incidence of severe UAEs, incidence of bladder outlet obstruction,[11] or frequency of grade 1 or 2 genitourinary or gastrointestinal adverse events.[12]

Findings regarding HRQoL varied by across the specific areas assessed. Specifically, HDR brachytherapy was associated with lower decline than LDR in urinary HRQoL immediately following treatment but these differences disappeared after six months.[10] In contrast, HDR brachytherapy was associated with greater decline than LDR in Sexual HRQoL at up to 18 months following treatment.[10] No differences were identified HDR and LDR for bowel HRQoL at any time point.[10] As no comparison was made between LDR brachytherapy with combined HDR plus EBRT, it is unknown if any differences exist with regard to patient-rated HRQo. Future research examining HRQoL that compares these treatment options would incrase our understanding of this outcome.

Although the findings are based on data from a large number of patients and the study contributing the most to this report was well done, there remains a degree of uncertainty about the conclusions due to the lack of randomized controlled trials and the pre-treatment differences in patient prognostic and demographic characteristics. Randomized controlled trials comparing LDR with HDR monotherapy and HDR combined with EBRT would reduce this uncertainty.

An important gap in the literature is the lack of studies identified regarding the cost-effectiveness of HDR prostate brachytherapy versus LDR prostate brachytherapy for the treatment of prostate cancer, particularly in a Canadian context. Cost-effectiveness studies may help reduce the uncertainty regarding the appropriate use of HDR and LDR prostate brachytherapy.

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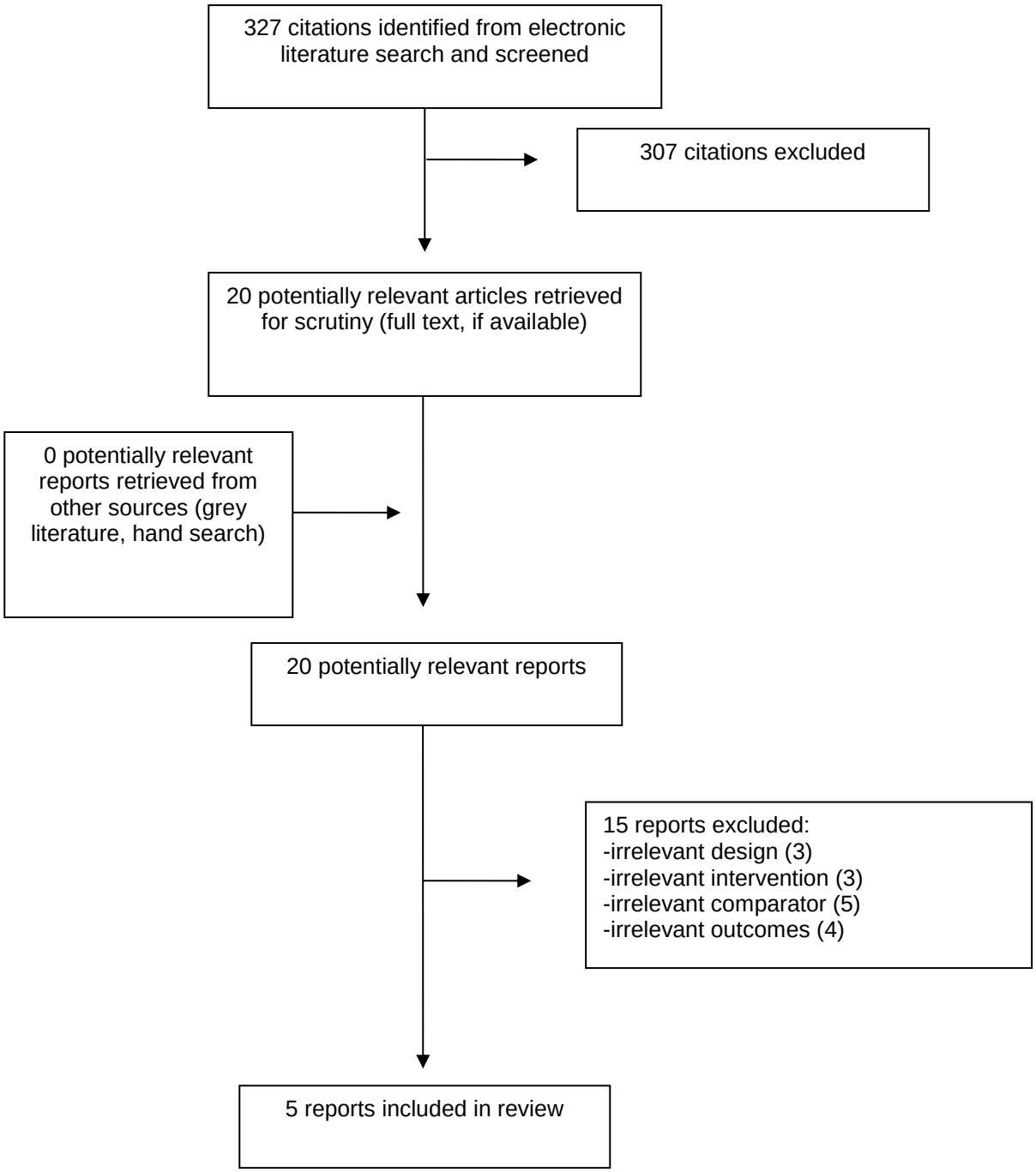
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up

Freiberger, 2017[8]
 	
Germany
	Single-centre prospective cohort study
	
	Centre and method of recruitment not described
	
	Participants were treated between 2000 and 2003
		N = 160 low, medium and high risk patients with cT1-3N0M0 prostate carcinoma
		
		Intervention:
		n = 66;
		Median age (range) = 72 years (63 to 81);
		T stage >2a = 36%;
		Gleason score >6 = 18%;
		Primary PSA [ng/ml] median (range) = 13 (1 to 300)
		
		Comparator:
		n = 94;
		Median age (range) = 69 years (49 to 81);
		T stage >2a = 5%;
		Gleason score >6 = 3%;
		Primary PSA [ng/ml] median (range) = 7 (1 to 15)
			Intervention:
			HDR+EBRT
			• Total minimum dose to prostate = 18 Gy delivered in 2 fractions with ≥7 days between fractions
			• EBRT was initiated 3 weeks after brachytherapy; total median dose to the prostate reference point = 50.4 Gy at 1.8 Gy daily fractions
			
			Comparator:
			Permanent LDR
			• Dose = 145 Gy Median of 54 sources with median activity 0.64 mCi were implanted via modified peripheral loading
				<u>Biochemical failure free survival rate</u>
				Percentage of patients who have not experienced biochemical failure (defined as an increase of ≥2 ng/ml above the nadir)
				
				<u>Metastasis free survival rate</u>
				Percentage of patients who did not have a diagnosed metastasis
				
				10 year follow-up

Tward, 2016[11] US	Retrospective cohort study of a subset of men in the SEER-Medicare database Study was conducted on participants diagnosed between 1998 and 2007	N = 15,878 patients aged between 66 and 80 years with non-metastatic invasive prostate cancer who underwent brachytherapy within 1 year of diagnosis Intervention: HDR, n = 685; T stage, n (%) T1 = 329 (48%) T2a = 117 (17.1%) T2b = unclear	Interventions: HDR; n = 685 HDR+EBRT; n = 2,392 Comparator: LDR; n = 12,801 Intervention conditions not otherwise described	<u>Time to severe UAE</u> Defined by a diagnosis code and procedure recorded on a single Medicare claim indicating that the patient had a UAE significant enough to be managed with a procedure based on the CTCAE; Eligible UAE diagnosis categories were bladder spasm; cystitis; hematuria;

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		T2 NOS = 184(26.9%) T3 = unclear Unknown = 0 (0%) HDR+EBRT, n = 2,392 T stage, n (%) T1 = 773 (32.3%) T2a = 384 (16.1%) T2b = 310 (13.0%) T2 NOS = 969 (29.1%) T3 = 198 (8.3%) Unknown = 31 (1.3%) Comparator: LDR, n = 12,801; T stage, n (%) T1 = 6708 (52.4%) T2a = 2110 (16.5%) T2b = 742 (5.8%) T2 NOS = 2989 (23.3%) T3 = 29 (0.2%) Unknown = 223 (1.7%) Gleason score and serum PSA not reported		urinary fistula; urinary incontinence; ureteral obstruction; and BOO, which includes urethral stricture and benign prostatic hypertrophy; Measured as time from first treatment until UAE <u>Time to bladder outlet obstruction</u> Defined by a diagnosis code and procedure recorded on a single Medicare claim indicating that the patient had a bladder outlet obstruction Follow-up until the end of 2009
Cuaron, 2015[9] US	Single-center retrospective cohort study Centre and recruitment not described Study conducted on patients treated between 1998 and 2010	N = 427 patients with NCCN intermediate- and high-risk clinically localized prostate cancer Intervention: HDR monotherapy, n = 12 HDR + EBRT, n = 198 Comparator: LDR, n = 217 Clinical stage, Gleason score, and serum PSA not reported by intervention condition or overall	Interventions: HDR monotherapy: Median dose 38 Gy; delivered in 3 fractions, 4 to 6 hours apart; HDR + EBRT: HDR median dose 19.5 Gy; delivered in 3 fractions, 4 to 6 hours apart; EBRT median dose 50.5 Gy HDR, patients were treated with 3 fractions delivered 4 to 6 hours apart. EBRT was delivered 4	<u>PSA relapse-free survival (Hazard ratio)</u> Defined from the date of the end of radiotherapy treatment to the date of PSA relapse (Phoenix nadir + 2) <u>Distant metastasis-free survival (Hazard ratio)</u> Defined from the end of radiotherapy to the date of the first report of a distant metastasis, defined as “clinical or radiographic evidence of disease outside the pelvis.” (p.180)

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			to 8 weeks following brachytherapy using 5 to 7 fields; median dose, 50.4 Gy Comparator: LDR: ^{125}I or ^{103}Pd seeds; Median dose 144 Gy	Follow up 8 years; 6 month intervals for 3 years, then annually
Strom, 2015[10] US	Single-centre retrospective cohort study Study centre and method of recruitment not described Study conducted on patients treated between January 2002 and September 2013	N = 334 patients with low- or favourable intermediate-risk prostate cancer Median age (range) = 72 years (63 to 81) Intervention: Median age (range) = 67 years (44 to 85); Median pre-treatment PSA (ng/ml) = 5.0; Clinical T stage, n (%): T1c = 78 (91.8); T2a = 7 (8.2); T2b = 0 (0); Gleason score, n (%) 6 : 60 (70.6) 3 + 4 = 7 : 25 (29.4) Comparator: Median age (range) = 66 years (38 to 86); Median pre-treatment PSA (ng/ml) = 5.1; Clinical tumor stage, n (%): T1c = 201 (80.7); T2a = 48 (19.3); T2b = 0 (0); Gleason score, n (%) Score 6 : 230 (92.4) Score 3 + 4 = 7 : 19	Intervention: HDR: Median (range) radiation dose: Total = 28 Gy (27 to 28); delivered in two 13.5 to 14 Gy fractions, 2 to 3 weeks apart LDR: Single ^{125}I implant; Median radiation dose: 14.5 Gy delivered in one fraction [reported as 14,500 cGy in abstract and results text; reported as 145,000 cGy in Table 1]	Self-report HRQoL measured as: <u>Urinary HRQoL</u> Assessed with the 7-item IPSS; Responses regarding urinary frequency, urgency, and retention were rated on a scale from 0 (best) to 5 (worst); Authors reported that the scale is validated <u>Bowel HRQoL</u> Assessed with 6-item EPIC-26 short form; Responses regarding stool urgency, frequency, firmness, presence of blood, and abdominal, rectal, or pelvic pain were rated on a scale from 0 (best) to 6 (worst); Measurement properties not reported <u>Sexual HRQoL</u> Assessed with 5-item SHIM; responses regarding quality of erections and

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		(7.6)		satisfaction with sexual intercourse were rated out of 5 response options ranging from best to worst; Authors reported that the scale is validated Higher positive values on IPSS reflected greater decreases in urinary HRQoL Greater negative values of EPIC-26 and SHIM reflected greater deterioration in bowel and sexual HRQoL

Morimoto, 2014[12]
 	
Japan
	Retrospective cohort study (number of centres NR)
	
	Centre(s) and participant recruitment not described
	
	Study conducted with patients treated between February 2008 and July 2010
		N = 64 patients with localized prostate cancer
		
		Intervention:
		n = 27;
		Median age (range) = 69 years (50 to 82);
		T stage
		T1c = 4; T2 = 16; T3 = 6; T4 = 1; unknown = 0
		Gleason Score, n (%):
		score 6 = 4 (14.8%);
		score 7 = 12 (44.4%);
		score 8 = 8 (29.6%);
		score 9 = 3 (11.1%;
		unknown = 0;
		Pretreatment PSA level median (range) (ng/mL) 10 ng/ml (3.9 to 337)
		
		Comparator:
		n = 37;
		Median age, years (range) = 64 (54 to 78);
		T stage
		T1c = 22;
			Assignment to treatment:
			Patients with PRIX 1 or intermediate risk (T2b-c, PSA levels ≥10/<20 ng/ml, or Gleason score 7) were recommended HRD, but decision was patient choice
			
			Patients with PRIX 0 or low risk (T1c-T2a, pretreatment PSA levels <10ng/ml, Gleason score 2-6) were recommended LDR, but decision was patient choice
			
			<u>Intervention</u>
			HDR:
			Dose = 45.5 Gy delivered in 7 fractions, twice daily (≥6 hours apart) over 4 days
				<u>Gentinoury and gastrointestinal adverse events</u>
				Retrospectively evaluated using hospital records, evaluated based on CTCAE version 4.03
				
				Follow-up at 1, 3 and 6 months after treatment
				
				<u>Biochemical progression free rates</u>
				Described as treatment failure
				
				Follow-up 2 years

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up

		T2 = 15; T3 = 0;
		T4 = 0; unknown = 0
		Gleason Score, n (%):
		Score 6 = 37 (100%);
		score 7 to 9 = 0;
		unknown = 0;
		Pretreatment PSA level median (range) (ng/mL) = 6.896 (3.04 to 11.43)
		
		Also treated with hormone therapy:
		LDR = 16/37 (43%);
		HDR patients = 14/27 (52%)
			<u>Comparator</u>
			LDR:
			I-125 implant (single fraction),
			Dose = 145 Gy;
			activity of sources adjusted to 0.346 mCi per source	

cGy = centigray; CTCAE = Common Terminology Criteria for Adverse Events; EPIC-26 = expanded prostate cancer index composite-26; Gy = grays; HDR = high-dose-rate; I = iodine; IPSS = international prostate system score; LDR = low-dose-rate; mCi = millicurie; NR = not reported; Pd = palladium; PRIX = Prostate Risk Index; PSA = Prostate Specific Antigen; SEER = Surveillance, Epidemiology, and End Results; SHIM = sexual health inventory for men; T stage = tumor stage; UAE = urinary adverse event

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black Checklist[6]

Strengths	Limitations
Freiberger, 2017[8]	
Reporting • The study aim was clearly described • Patient characteristics were clearly described • Interventions of interest were clearly described • Distributions of principal confounders in each group were clearly described • Actual probability values were reported, where significant **External Validity** • The centre where the patients were treated appears to be same location the majority of patients in the region would be treated **Internal Validity – Bias** • Data dredging does not appear to have been an issue • Follow-up was the same for all patients • Appropriate statistical tests were used to assess main study outcomes • Due to the nature of the study, compliance was not an issue. All patients were likely treated with the prescribed therapy • Internal validity – confounding (selection bias) • Patients were treated over the same period of time	**Reporting** • Not all main outcomes were clearly described • Not all main findings were clearly described • Estimates of random variability were not provided for all important outcomes • It is unclear if there was a comprehensive attempt to measure adverse events • It is unclear if any patients were lost to follow-up • Non-significant probability values were not reported **External Validity** • The source population for patients and patient selection were not described • The proportion of those asked who agreed to participate was not reported **Internal Validity – Bias** • Participants were not blinded to the intervention received • There was no report of blinding outcome assessors to the intervention received • Measurement properties of main study outcomes were not reported **Internal validity – Confounding (Selection bias)** • Patients in the different intervention groups were selected from the same hospital, however they differed with respect to risk, e.g. there was a maximum prostate volume accepted for patients assigned to undergo LDR. Also, patients referred for LBR normally travelled long distances for treatment. • Participants were not randomized to intervention groups • There was no adjustment for confounding • Loss to follow up was not reported **Power** • A power calculation was not reported
Tward, 2016[11]	
Reporting • Study aim was clearly described • Main outcomes were clearly described in the Methods section • Patient characteristics were clearly described • Interventions of interest were clearly described • Distributions of principal confounders were clearly described • Main findings of the study were clearly described • The study provided estimates of random variability in the data for the main outcomes	**Reporting** • Actual probability values were not reported **Internal Validity - Bias** • Interventions were allocated prior to the conduct of the study. No attempt to blind study subjects to the intervention they would receive was possible. • Unclear if main outcomes were measured using valid and reliable tools. “Our outcome variable of interest was time to severe UAE, as defined by a diagnosis code and procedure

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black Checklist[6]

Strengths	Limitations
• All adverse events associated with the intervention were not reported, however this study purposefully targeted urinary adverse events specifically. • Due to the nature of the study, it is unlikely that patients were lost to follow up. **External Validity** • Participants in the study were the entire source population (i.e., participants in the SEER database). • Data from all eligible participants were included • Staff, places, and facilities where patients were treated were representative of the treatment the majority of patients receive. **Internal Validity - Bias** • There were no outcome assessors, per se. Outcomes were extracted from Medicare claim records. • Data dredging does not appear to have been an issue. • Analyses accounted for different lengths of follow up (time to first event) • Statistical tests were appropriate • **Internal Validity – Confounding** • Participants receiving different brachytherapy interventions were all Medicare patients in the SEER database who had undergone brachytherapy and fit the eligibility criteria. • Participants in each group were patients over the same period of time • Participants receiving different brachytherapy interventions differed significantly from each other on demographic characteristics, and differences were accounted for in the analyses using an inverse probability of treatment weighting scheme to balance treatment groups	on a single claim indicating that the patient had a urinary event significant enough to be managed with a procedure based on the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0)" (p. 1444) **Internal Validity – Confounding** • Participants receiving different brachytherapy interventions were all Medicare patients in the SEER database who had undergone brachytherapy and fit the eligibility criteria. • Participants in each group were patients over the same period of time • Participants were not randomized to intervention groups • It is unknown if participants in each treatment group differed in certain prognostic factors. Study authors discussed the possibility that differences in prostate size and baseline bladder function may have been worse in patients receiving more intensive therapy (i.e., HDR or HDR + EBRT). • Unable to determine if losses to follow-up existed. No losses to follow-up were reported. It would be assumed that no Medicare claim reflected no event rather than missing data. **Power** • A power calculation was not reported. The sample size was large, however the subsample of those who received HDR monotherapy was much smaller than other treatment groups. Study authors speculated this may have introduced an issue of insufficient power to detect differences between HDR monotherapy and other groups.
Cuoron, 2015[9]	
Reporting • The study purpose and hypothesis were clearly described • Study outcomes were clearly described in the Methods section • Patient age and pre-treatment cancer characteristics were clearly described for patient subgroups other than those of interest to the current report • Interventions of interest are clearly described • Distributions of principal confounders are reported for subgroups other than those of interest to the current report • Main findings are clearly described • Actual probability values were reported **External Validity** • All men with intermediate and high risk prostate cancer who were treated with brachytherapy at a specialist cancer	**Reporting** • Random variability in the data for the main outcomes is not estimated • It was not reported if a comprehensive attempt to measure adverse events was attempted • It is unclear if any patients were lost to follow up **External Validity** • Staff and facilities where the patients were treated were not described **Internal Validity – Bias** • Participants were not blinded to the intervention received • There was no mention of an attempt to blind outcome assessors • Measurement properties of main outcome measures were

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black Checklist[6]

Strengths	Limitations
centre were included • Participants represented the entire source population from which they were recruited **Internal Validity - Bias** • Results do not appear to be based on data dredging • Survival analysis accounted for different lengths of follow up • Appropriate statistical tests were used to assess the main outcomes • Compliance with interventions was unlikely to be an issue due to the nature of the interventions **Internal Validity – Confounding (selection bias)** • Participants receiving each treatment were drawn from the same source population • Participants in different groups were recruited over the same period of time	not described **Internal Validity – Confounding (selection bias)** • Participants were not randomized to intervention groups and it is possible severity of cancer diagnosis influenced treatment decision • Analyses did not adjust for confounding • It is unclear if there were losses to follow-up or how they were treated **Power** • Power was not calculated
Strom, 2015[10]	
Reporting • Study aim was clearly described • Main outcomes were clearly described • Patient characteristics were clearly described • Interventions of interest were clearly described • Distributions of principal confounders in each group were clearly described • Main findings of the study were clearly described • Study provided estimates of random variability in the data for the main outcomes • Actual probability values were reported unless the value was less than 0.001 **Internal Validity - Bias** • No retrospective unplanned subgroup analyses were reported • The time period between intervention and outcome assessment was apparently the same for all patients • All patients included in the study had undergone the treatment • Statistical tests were appropriate • All outcome measures were clearly described. Authors reported the SHIM and IPSS scales were validated **Internal Validity – Confounding** • Patients were selected from the same database • Patients were treated over the same period of time • Patients lost to follow up were analyzed as long as they had completed baseline assessment	**Reporting** • Adverse events were not reported • Characteristics of patients lost to follow-up were not described **External Validity** • It is unclear how patients records were selected or what population they were selected from • It is unclear if selected patients were representative of the entire population from which they were recruited • The staff, places, and facilities were not described **Internal Validity - Bias** • Blinding was not described and was probably not done in this retrospective study of patient records • Measurement properties of the EPIC-26 short form were not reported **Internal Validity – Confounding** • Participants were not randomized to intervention groups • Analyses did not adjust for confounding **Power** • Power was not calculated

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black Checklist[6]

Strengths	Limitations
Morimoto, 2014[12]	
Reporting • Study aim was clearly described • Main outcomes were clearly described • Patient characteristics were clearly described • Interventions of interest were clearly described • Distributions of principal confounders were clearly described • Main findings of the study were clearly described • All adverse events associated with the intervention were not reported as authors purposefully excluded perioperative adverse events. • No patients were reported lost to follow up **External Validity – Bias** • Participants included in the study encompassed the entire eligible population from the particular from which the data were drawn **Internal Validity – Bias** • Length of follow-up did not differ between patients • Statistical tests were appropriate • Compliance does not appear to have been an issue **Internal Validity – Confounding** • Study participants were all drawn from the same centre • Participants in different intervention groups were recruited over the same period of time • No patients were lost to follow up	**Reporting** • The study provided estimates of random variability in the data for the main outcomes • Actual probability values were not reported **External Validity – Bias** • The entire population from which participants were drawn was not described. • The staff, places, and facilities were not described. **Internal Validity – Bias** • Participants were not blinded to the intervention they had received • Outcome assessors were not blinded • Data dredging may have occurred. Indicators of prostate cancer progression were not described until they appeared in the results section. • Validity and reliability of main outcome measures was not described **Internal Validity - Confounding** • Confounding was not adjusted for in the analysis. Further analysis indicated a significant difference between groups in the proportion of participants who were offered hormone therapy as a co-treatment. This was not accounted for in the analysis **Power** • Study power was not calculated

CTCAE = Common Terminology Criteria for Adverse Events; EBRT = external beam radiation therapy; EPIC-26 = Expanded Prostate Cancer Index Composite-26; HDR = high-dose-rate; IPSS = international prostate system score; LDR = low-dose-rate; SEER = surveillance, Epidemiology, and End Results; SHIM = sexual health inventory for men; UAE = urinary adverse event

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Freiberger, 2017[8]	
<u>Biochemical failure free survival</u> LDR vs HDR+EBRT 71% vs 58%, *P* = 0.04 Sub-analysis by risk group: **Low-risk patients** LDR vs HDR + EBRT 68% vs 94% free from biochemical failure vs. LDR-BT 68%; *P* < 0.01 Intermediate-risk patients 78% vs 67%; *P* < 0.01 <u>Metastasis free survival</u> LDR vs HDR+EBRT 94% vs 90%, *P* > 0.05	"*Biochemical recurrence free survival rates are dependent on the treatment dose and technique*." (P.6)
Tward, 2016[11]	
<u>UAE, cumulative incidence (%); 95% CI</u> **4 y** LDR = 10.53%; 95% CI = 9.94 to 11.15 HDR = 11.6%; 95% CI = 8.7 to 15.37 HDR + EBRT = 15.39%; 95% CI = 13.68 to 17.29 *LDR significantly lower than HDR + EBRT (P < 0.05)* *HDR monotherapy not significantly different from LDR or HDR + EBRT* **8 y** LDR = 15.67%; 95% CI = 14.77 to 16.63 HDR = 17.37%; 95% CI =13.12 to 22.82 HDR + EBRT = 26.61%; 95% CI = 23.76 to 29.73 *LDR and HDR not significantly different from each other; both significantly different from HDR +EBRT (P < 0.05)* <u>Bladder outlet obstruction</u> <u>Cumulative incidence; 95% CI</u> **4 y** LDR = 8.48%; 95% CI = 7.95 to 9.05 HDR = 9.34%; 95% CI = 6.79 to 12.78	"*In conclusion, this study is the most highly powered urologic toxicity comparative-effectiveness study of brachytherapy performed to date, showing that HDR brachytherapy and LDR brachytherapy have a similar incidence of clinically significant grade 3 toxicity. The excess risk of toxicity occurs primarily in the first 2 to 4 years after therapy and then falls to a rate similar to the baseline hazard of untreated men over the next decade*." (p.1452)

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
HDR + EBRT = 13.11%; 95% CI = 11.54 to 14.88 *LDR significantly lower than HDR + EBRT (P < 0.05), but not HDR monotherapy; HDR monotherapy not different from HDR + EBRT* **8 y** LDR = 12.33; 95% CI = 11.53 to 13.18 HDR = 14.08; 95% CI = 10.21 to 19.25 HDR + EBRT = 21.19; 95% CI = 18.68 to 23.98 *LDR significantly lower than HDR + EBRT (P < 0.05), but not HDR monotherapy; HDR did not differ from HDR + EBRT*	
Cuaron, 2015[9]	
Follow-up for 8 years, median follow-up = 48 months, range = 1 to 156 months PSA relapse-free survival, Hazard ratio LDR vs HDR Hazard ratio = 1.551, *P* = 0.12 Distant metastasis-free survival LDR vs HDR Hazard ratio = 1.299, P = 0.52	Author's conclusion not relevant to this report as the main purpose of the study was to compare statin use vs no statin use
Strom, 2015[10]	
Mean (SD) / OR, 95% CI reported where available Change in Urinary HRQoL (IPSS scores) (Higher positive values indicate greater decrease in HRQoL) HDR vs LDR 1 mo: 5.9 (7.6) vs 8 (7.4); ***P* = 0.04** OR = 0.43, 95% CI, 0.24 to 0.78, ***P* = 0.005** 3 mo: 1.1 (5.8) vs 8.1 (7.9); ***P* < 0.01** OR = 0.18, 95% CI, 0.09–0.35; ***P* < 0.001** 6 mo: 2.8 (6.4) vs 4.6 (7.3); *P* = 0.17 9 mo: 1.3 (5.7) vs 2.6 (6.3); *P* = 0.29 12 mo: –0.6 (5.5) vs 0.8 (5.7); *P* = 0.31 18 mo: 0.5 (5.2) vs 0.1 (5.8) *P* = 0.71 Change in Bowel HRQoL (EPIC-26 scores) (Greater negative values indicate greater decrease in HRQoL) HDR vs LDR 1 mo: –5 (10) vs –4 (10); *P* = 0.54	Author's conclusion not relevant to this report as the main purpose of this study was to compare brachytherapy against intensity-modulated radiation therapy

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
3 mo: –2 (8) vs –5 (10); *P* = 0.19 6 mo: –4 (9) vs –3 (10); *P* = 0.74 9 mo: 0.0 (7) vs –2 (8); *P* = 0.17 12 mo: 0 (10) vs –1 (7); *P* = 0.76 18 mo: 0 (15) vs –2 (7); *P* = 0.31 <u>Change in Sexual HRQoL (SHIM scores)</u> (Greater negative values indicate greater decrease in HRQoL) HDR vs LDR 1 mo: –5.6 (7) vs –3.3 (7.8); ***P* = 0.02** 3 mo: –4.5 (5.4) vs –3.1 (8); *P* = 0.15 6 mo: –8.3 (7.7) vs –3.4 (7.2); ***P* = 0.003** 9 mo: –6.3 (6.4) vs –2.4 (7.3); ***P* = 0.006** 12 mo: –5.7 (8.4) vs –2.9 (7.1); *P* = 0.16 18 mo: –6.8 (8) vs –2.6 (7.4); ***P* = 0.03**	
Morimoto, 2014[12]	
<u>Frequency of genitourinary adverse events at ≤6 months</u> *n (percentage)* HDR (n = 27) vs LDR (n = 37) Grade 1: 14 (52%) vs 20 (54%), *P* > 0.05 Grade 2: 4 (15%) vs 11 (30%), *P* > 0.05 Grade 1 or 2: 18 (67%) vs 31 (84%), *P* > 0.05 <u>Frequency of gastrointestinal adverse events at ≤6 months</u> *n (percentage)* HDR (n = 27) vs LDR (n = 37) Grade 1: 0 vs 4 (11%), *P* > 0.05 Grade 2: 0 vs 0, *P* > 0.05 Grade 1 or 2 0 vs 4 (11%), *P* > 0.05 <u>Biochemical progression free rates at 2-years</u> *n (%)* HRD = 100% vs LDR = 97% (2 cases), *P* > 0.05	Author's conclusion not relevant to this report as the main purpose of this study was to contrast intensity-modulated radiation therapy, three-dimensional conformal radiation therapy, and brachytherapy

CI = confidence interval; EBRT = external beam radiation therapy; EPIC-26 = expanded prostate cancer index composite-26; HDR = high dose rate; HRQoL = health related quality of life; IPSS = international prostate symptom score; LDR = low dose rate; mo = months; OR = odds ratio; UAE = urinary adverse event