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Review article

The oncologic and safety outcomes of low-dose-rate brachytherapy for the treatment of prostate cancer

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ABSTRACT

Around 40 years have passed since a modern low-dose-rate (LDR) brachytherapy for prostate cancer was introduced. LDR brachytherapy has become one of the definitive treatment options besides radical prostatectomy (RP) and external beam radiation therapy (EBRT). LDR brachytherapy has several advantages over EBRT such as a higher prescribed dose to the prostate gland while avoiding unnecessary irradiation of organs at risk, a precipitous dose gradient, a brief treatment time, and a short hospital stay. Previous reports revealed that the long-term oncologic outcomes of LDR brachytherapy are superior to those of EBRT. The oncologic outcomes of low- to intermediate-risk patients are equivalent to those of RP using the recurrence definition of surgery of prostate specific antigen (PSA) >0.2 ng/mL, while the oncologic outcomes of LDR brachytherapy as tri-modality (combined EBRT and androgen deprivation therapy) for high-risk patients is superior to that of RP using the recurrence definition of surgery. In respect of toxicity, urinary disorders such as urgency and frequency are often observed after the acute phase of treatment, but these events usually resolve, while the quality of life of urinary continence is well preserved for a long time. Erectile function decreases yearly, but is relatively preserved compared to RP. In conclusion, the most noteworthy strength of LDR brachytherapy for low- to intermediate-risk patients is the "brief treatment time" that provides long recurrence-free survival, while that for high-risk patients who received LDR brachytherapy (tri-modality) is "excellent disease control."

1. Introduction

Approximately 40 years have passed since Holm et al from Denmark first reported the modern low-dose-rate (LDR) brachytherapy for prostate cancer using a transrectal ultrasound-guided procedure in 1983.[1] Nowadays, LDR brachytherapy has become one of the definitive treatment options alongside radical prostatectomy (RP) and external beam radiation therapy (EBRT). As a definitive radiation therapy, LDR brachytherapy has several advantages over EBRT, including a higher prescribed dose to the prostate gland, while avoiding unnecessary irradiation of organs at risk (the bladder, rectum and urethra), a precipitous dose gradient, a brief treatment time (around 1–2 hours), a short hospital stay (2–3 nights), and so on. Approximately 20 years have passed since LDR brachytherapy became available in Japan in 2003. In Japan, the Prostate Permanent Seed Implantation Study Group was established in 2005, and a nationwide prospective cohort study, Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 Seed Implantation (J-POPS),[2] was initiated in July 2005. During these two decades, robot-assisted RP has been approved under the health insurance and it has widely spread in Japan, while hypofractionated radiation therapy and particle radiation therapy have also spread in the field of EBRT. Under these contemporary conditions, the author re-evaluated the strength of LDR brachytherapy in respect of oncologic outcomes and quality of life (QOL) in this review article.

2. Oncologic outcomes

2.1. LDR brachytherapy versus EBRT, LDR brachytherapy versus RP

Table 1 shows the oncologic outcomes of LDR brachytherapy in a series of a large number US and Japanese patients (204–2316 patients) with a medium follow-up period (median: 49–95 months).[3–8] The biochemical recurrence (BCR)-free rate using the Phoenix definition (nadir + 2 ng/mL) for low-, intermediate-,

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Table 1
The oncologic outcomes of LDR brachytherapy

	Number of patients	Procedure	Definition	Median follow-up	Outcomes
Stone et al[3] (2010)	584	LDR ± EBRT	Phoenix	7.1 yr	7-yr bFFF Low: 92% Int: 84% High: 70%
Zelefsky et al[4] (2012)	1466	LDR or HDR ± EBRT	Phoenix	49 mo	5-yr PSA-RFS Low: 98% Int: 95% High: 80%
Yorozu et al[5] (2015)	1313	LDR ± EBRT	Phoenix	67 mo	7-yr bFFF Low: 98% Int: 93% High: 81%
Katayama et al[6] (2019)	2316	LDR ± EBRT	Phoenix	60 mo	5-yr bFFF Low: 95% Int: 93% High: 91%
Tanaka et al[7] (2022)	944	LDR ± EBRT	Phoenix	91 mo	7-yr BCR-free rate Low: 95% Int: 95% High: 91%
Tsumura et al[8] (2022)	204	LDR ($n = 102$) vs. LDR + EBRT ($n = 102$)	Phoenix	95 mo	8-yr BCR-free rate LDR vs. LDR + EBRT Int: 93% vs. 88% $P = 0.047$

BCR, biochemical recurrence; bFFF: biochemical freedom from failure; EBRT, external beam radiation therapy; HDR, high-dose rate brachytherapy; High, high-risk; Int., intermediate-risk; Low, Low-risk; LDR, low-dose-rate brachytherapy; PSA-RFS, prostate specific antigen relapse-free survival.

and high-risk groups ranged between 92–98%, 84–95%, and 70–91%, respectively. The BCR-free rate for each risk group shows favorable outcomes.

2.2. Comparison of oncologic outcomes between LDR brachytherapy and EBRT

It is a simple and natural question whether the oncologic outcomes of surgery, EBRT, and LDR brachytherapy are similar.

Table 2 shows a comparison of oncologic outcomes between LDR brachytherapy and intensity-modulated radiation therapy (IMRT) in low- and intermediate-risk patients at Memorial Sloan-Kettering Cancer Center[9,10] and between LDR brachytherapy combined with EBRT and dose-escalated EBRT (DE-EBRT) in intermediate- and high-risk patients in the ASENDE-RT trial.[11] In low-risk patients, 7-year biochemical progression-free survival of patients who underwent LDR brachytherapy was significantly higher than that of patients who underwent IMRT (81 Gy) (95% vs. 89%, $P = 0.004$).[9] This trend can be seen in intermediate-risk patients (7-year: LDR: 92% vs. IMRT: 81%, $P = 0.004$).[10] In intermediate- to high-risk patients, the biochemical progression-free survival with LDR brachytherapy was significantly higher than that with DE-EBRT (86% vs. 75%, $P < 0.001$).[11] Taken together, it is beyond question that LDR brachytherapy, both with and without EBRT, has an advantage of biochemical control over EBRT for all risk patients. The discriminative difference between LDR brachytherapy and EBRT must be a significant local high-dose concentration. Stock et al demonstrated a significant difference in BCR-free survival stratified by biological effective dose (BED) in patients who underwent LDR brachytherapy.[12] We also recently reported that a higher local radiation dose (BED >180 Gy2) is an independent prognostic factor predicting BCR after LDR brachytherapy.[7] Gul et al also reported that BED >200 Gy2, which cannot be achieved without the addition of brachytherapy, is associated with better BCR-free survival and cancer-specific survival.[13] Apart from the oncologic superiority of LDR brachytherapy, another advantage of LDR brachytherapy is the short time of the procedure (around 1–2 hours) compared to EBRT (not only conventional fractionated radiation therapy but also hypofractionated and ultra-hypofractionated radiation therapy).

2.3. Comparison of oncologic outcomes between LDR brachytherapy and RP

Then, what are the results when the oncologic outcomes of LDR brachytherapy and RP are compared? First, the recurrence

Table 2
The comparison of oncologic outcomes between LDR brachytherapy and IMRT

	Number of patients	Procedure	Definition	Median follow-up	Outcomes
Zelefsky et al[9] (2011)	729	LDR (144 Gy) ($n = 448$) vs. IMRT (81 Gy) ($n = 281$)	Phoenix	77 mo	Low 7-yr bPFS LDR: 95% IMRT: 89% $P = 0.004$
Spratt et al[10] (2014)	870	LDR + EBRT ($n = 400$) vs. IMRT (86.4 Gy) ($n = 470$)	Phoenix	5.3 yr	Int. 7-yr bPFS LDR: 92% IMRT: 81% $P = 0.004$
Morris et al[11] (ASCENDE-RT) (2017)	398	DE-EBRT (78 Gy) ($n = 195$) vs. LDR + EBRT ($n = 188$)	Phoenix	78 mo	Int. ~ High 7-yr bPFS LDR vs. DE-EBRT 86% vs. 75% $P < 0.001$

bPFS, biochemical progression-free survival; DE, dose escalated; EBRT, external beam radiation therapy; High, high-risk; IMRT, intensity modulated radiation therapy; Int., intermediate-risk; LDR, low-dose-rate brachytherapy; Low, low-risk.

definition is different between the two modalities. A cut-off value of PSA >0.2 ng/mL is adopted for surgery, and of nadir PSA +2 ng/mL or higher for radiation therapy. Is it appropriate to compare surgery and radiation therapy in view of the different definitions? To address this question, several investigators reported the oncologic outcomes using the recurrence definition of surgery (Table 3).[14–17] Critz et al compared the disease-free survival of LDR brachytherapy with that of RP using the recurrence definition of surgery (PSA >0.2 ng/mL). The 10-, 15-, 20-, and 25-year disease-free survival rates of 3546 consecutive hormone-naive men who were treated with a 125I prostate implant (retropubic and later transperineal), followed by external beam irradiation were 75%, 73%, 73%, and 73%, respectively. In men who underwent implantation by the transperineal method since 1995, the 15-year disease-free survival rate was 79%. These results are comparable with those of the RP series.[14] Tanaka et al compared the BCR-free rate of LDR brachytherapy and IMRT using two recurrence definitions (recurrence definition of surgery and the Phoenix definition). The 5-year BCR-free rate using a recurrence definition of surgery with LDR brachytherapy was significantly higher than that of IMRT in all risk groups (low-risk: 77% vs. 38%, $P = 0.001$, intermediate-risk: 79% vs. 37%, $P < 0.001$, and high-risk: 84% vs. 69%, $P < 0.001$, respectively).[15] Morris et al also reported comparison of biochemical progression-free survival between LDR brachytherapy and DE-EBRT in intermediate- and high-risk groups in the ASENDE-RT trial using the recurrence definition of surgery. The 7-year biochemical progression-free survival of LDR brachytherapy was significantly higher than that of DE-EBRT both in intermediate- and high-risk patients (intermediate risk: LDR brachytherapy: 91% vs. DE-EBRT: 40%, $P < 0.001$, and high-risk: LDR brachytherapy: 81% vs. DE-EBRT: 34%, $P < 0.001$, respectively), in the ASENDE-RT trial.[16] On the other hand, Tsumura et al compared the BCR-free rate between RP and LDR brachytherapy using a recurrence definition of surgery and the propensity score matched analysis in intermediate-risk patients in a multi-institutional study (Kitasato University, Nagano City Hospital, and Nara Medical University).[17] The 8-year BCR-free rate of LDR was 76%, while that of RP was 74%. There were no significant differences between LDR brachytherapy and RP ($P = 0.642$). There were also no significant differences in the BCR-free rate in the subgroup propensity score matched analysis of RP patients with resection margin negative (LDR brachytherapy: 76% vs. RP: 83%, $P = 0.136$).

Under a syllogistic approach, the oncologic outcomes of LDR brachytherapy are superior to those of IMRT using the Phoenix definition and the recurrence definition of surgery and are comparable to those of RP using the recurrence definition of surgery for low- to intermediate-risk patients. On the other hand, around half of the high-risk patients who underwent RP showed BCR,[18,19] while the BCR-free rate of so-called tri-modality (LDR brachytherapy + EBRT + androgen deprivation therapy: ADT) showed favorable outcomes (81%–84%) using the recurrence definition of surgery.[15,16] This excellent BCR-free rate of high-risk patients compared to RP is another strength of LDR brachytherapy.

2.4. Is LDR brachytherapy monotherapy sufficient for unfavorable intermediate-risk patients?

Monotherapy with LDR brachytherapy is a good treatment option indicated for low-risk and favorable intermediate-risk patients, while tri-modality (LDR brachytherapy + EBRT + ADT) is a suitable and promising treatment for high-risk patients. On the other hand, it is controversial whether combination therapy with EBRT is necessary or not for unfavorable intermediate-risk patients. The National Comprehensive Cancer Network guideline (2022 ver.3 [cited 2022 Oct 26], available from: https://www.nccn.org/guidelines/category_1) for prostate cancer recommends combination therapy (LDR brachytherapy combined with EBRT) for unfavorable intermediate-risk patients. On the other hand, Prestidge et al compared the oncologic outcomes of LDR brachytherapy alone and LDR brachytherapy combined with EBRT in a phase 3 randomized controlled trial (RTOG 0232) for intermediate-risk patients.[20] Combination therapy was shown to be non-superior to

Table 3
The oncologic outcomes of LDR brachytherapy using a definition of surgery (PSA >0.2 ng/mL)

	Number of patients	Procedure	Definition	Median follow-up	Outcomes
Critz et al[14] (2013)	3546	LDR + EBRT	3 consecutive increase (Less than 5 years) Thereafter 0.2 ng/mL	11 yr	10-yr DFS Low: 93% Int: 74% High: 44%
Tanaka et al[15] (2017)	445	LDR ± EBRT ($n = 445$) vs. IMRT ($n = 165$)	0.2 ng/mL	75 mo	5-yr BCR-free rate LDR vs. IMRT Low: 77% vs. 38% $P = 0.001$ Int: 79% vs. 37% $P < 0.001$ High: 84% vs. 69% $P < 0.001$
Morris et al[16] (ASCENDE-RT) (2018)	398	DE-EBRT ($n = 195$) vs. LDR + EBRT ($n = 188$)	0.2 ng/mL	78 mo	7-yr bPFS LDR vs. DE-EBRT Int: 91% vs. 40% High: 81% vs. 34% $P < 0.001$
Tsumura et al[17] (2022)	428	RP ($n = 214$) vs. LDR ± EBRT ($n = 214$)	0.2 ng/mL	96 mo	8-yr BCR-free rate LDR vs. RP Int: 76% vs. 74% $P = 0.642$
	302	RP without PSM ($n = 151$) vs. LDR ± EBRT ($n = 151$)	0.2 ng/mL	96 mo	8-yr BCR-free rate LDR vs. RP Int: 76% vs. 83% $P = 0.136$

BCR, biochemical recurrence; bPFS, biochemical progression-free survival; DE, dose escalated; DFS, disease-free survival; EBRT, external beam radiation therapy; High, high-risk; IMRT, intensity modulated radiation therapy; Int., intermediate-risk; LDR, low-dose-rate brachytherapy; Low, low-risk; PSM, positive surgical margin; RP, radical prostatectomy.

LDR brachytherapy alone (5-year progression-free survival, LDR brachytherapy alone: 86% vs. LDR brachytherapy combined with EBRT: 85%) (Table 4).

Recently, Tsumura et al reported an interesting study concerning oncologic outcomes using a propensity score matched analysis between LDR brachytherapy and LDR brachytherapy combined with EBRT for intermediate-risk patients.[21] The 8-year BCR-free rate of LDR brachytherapy alone was significantly higher than that of LDR brachytherapy combined with EBRT (93% vs. 88%, $P = 0.047$). The 8-year BCR-free rate was not significantly different in favorable intermediate-risk patients (LDR brachytherapy alone: 92% vs. LDR brachytherapy combined with EBRT: 90%, $P = 0.886$). On the other hand, the 8-year BCR-free rate of LDR brachytherapy alone was significantly higher than that of LDR brachytherapy combined with EBRT for unfavorable intermediate-risk patients (94% vs. 88%, $P = 0.033$). The cumulative incidence of late grade 2 or greater genitourinary (GU) toxicity of LDR brachytherapy combined with EBRT was significantly higher than that of LDR brachytherapy (8-year: 21.0% vs. 33.2%, $P = 0.015$). The cumulative incidence of late grade 2 or greater gastrointestinal (GI) toxicity of LDR brachytherapy combined with EBRT was significantly higher than that of LDR brachytherapy (8-year: 0% vs. 12.2%, $P < 0.001$).[21] There is no doubt about which of LDR brachytherapy alone or in combination with EBRT is better for intermediate-risk patients both in respect of oncologic outcome and toxicity.

2.5. What is a promising curative PSA cut-off value for radiation therapy?

There is a definition of BCR for RP (PSA >0.2 ng/mL) and radiation therapy (PSA nadir + 2 ng/mL), while there is not a definition of permanent cure. How long should we follow-up patients who had undergone RP and radiation therapy? D'Amico et al[22] assessed whether PSA values can act as an early surrogate for prostate cancer-specific mortality (PCSM) to systematically reviewed two randomized controlled trials (the Dana Farber Cancer Institute trial[23] and the Trans-Tasman Radiation Oncology Group trial[24]—which showed a statistically and clinically significant reduction in PCSM when 6 months of androgen suppression was added to radiotherapy vs. radiotherapy alone). For patients with a nadir PSA value of more than 0.5 ng/mL, 8-year PCSM was 27% (95% confidence interval [CI] 21–33) for those treated with radiotherapy alone compared with 28% (15–42) for those treated with radiotherapy and androgen suppression. For patients with a PSA nadir value of 0.5 ng/mL or less, the 8-year PCSM was 4% (<1–11) for those treated with radiotherapy alone compared with 6% (4–10) for those treated with radiotherapy and androgen suppression. The 8-year PCSM was significantly lower for patients with a PSA nadir value of 0.5 ng/ml or less than those with a nadir PSA value of more than 0.5 ng/mL.

Ko et al investigated whether the achievement of nadir PSA <0.5 ng/mL following LDR brachytherapy is associated with decreased PSA failure and/or distant metastasis. Patients achieving nadir PSA <0.5 ng/mL had significantly higher long-term freedom from biochemical failure (FFBF) than non-responders (5-year FFBF: 95.2% vs. 71.5%; $P < 0.0005$). Among the responders, those who achieved nadir PSA <0.5 ng/mL within 5 years had higher FFBF than those requiring >5 years (5-year FFBF: 96.7% vs. 80.8%; $P < 0.0005$). Multivariate analysis indicated that patients who achieved nadir PSA <0.5 ng/mL within 5 years had significantly higher FFBF than other patients. All patients who achieved nadir PSA <0.5 ng/mL were more likely to have freedom from distant metastasis (FFDM) than non-responders (5-year FFDM: 99.7% vs. 91.9%; $P = 0.001$). Patients who achieved nadir PSA <0.2 ng/mL were significantly more likely to experience FFBF and FFDM at 10 years following LDR brachytherapy.[25]

To confirm the biochemical definition of cure after LDR brachytherapy, Crook et al investigated a PSA threshold value at an intermediate follow-up time (median: 8 years) after LDR brachytherapy associated with cure, defined as long-term (10–15 year) freedom from prostate cancer using data of 14,220 patients with localized prostate cancer treated with LDR brachytherapy from 7 institutions. For the 77.1% of patients with 4-year PSA ≤0.2 ng/mL, the freedom-from-recurrence rates were 98.7% (95% CI: 98.3–99.0) at 10 years and 96.1% (95% CI: 94.8–97.2) at 15 years.[26]

Taken together, these results suggest that a PSA cut-off value of at least less than 0.5 ng/mL (if at all possible, less than 0.2 ng/mL) promises significantly better oncologic outcomes (permanent cure).

2.6. Comparison of nadir PSA value after radiation therapy between LDR brachytherapy and EBRT

Jabbari et al studied the biochemical control and PSA nadir achieved with contemporary LDR brachytherapy and evaluated it in comparison with 3 dimensional-conformal radiation therapy and conformal proton beam radiotherapy (CPBRT).[27] A greater proportion of LDR brachytherapy patients achieved a lower PSA nadir than those who achieved it in the CPBRTB trial (a randomized controlled trial of mostly low- to intermediate-risk patients treated with

Table 4
The oncologic outcomes of LDR brachytherapy in intermediate risk (LDR alone vs. LDR + EBRT)

	Number of patients	Procedure risk classification	Definition	Median follow-up	Outcomes
Prestidge et al[20] RTOG 0232 (2016)	588 Phase III	LDR alone ($n = 292$) vs. LDR + EBRT ($n = 287$)	Phoenix	6.7 ys	5-yr PFS LDR alone vs. LDR + EBRT 86% vs. 85% Non-superiority
Tsumura et al[21] (2022)	204	Intermediate all LDR alone ($n = 102$) vs. LDR + EBRT ($n = 102$)	Phoenix	95 mo	8-yr BCR-free rate LDR vs. LDR + EBRT 93% vs. 88% $P = 0.047$
	50	Favorable intermediate LDR alone ($n = 27$) vs. LDR + EBRT ($n = 23$)			8-yr BCR-free rate LDR vs. LDR + EBRT 92% vs. 90% $P = 0.886$
	154	Unfavorable intermediate LDR alone ($n = 75$) vs. LDR + EBRT ($n = 79$)			8-yr BCR-free rate LDR vs. LDR + EBRT 94% vs. 88% $P = 0.033$

BCR, biochemical recurrence; EBRT, external beam radiation therapy;LDR, low-dose-rate brachytherapy; PFS, progression free survival.

50.4 Gy photon EBRT to the prostate and seminal vesicles, followed by either 19.8 Gray equivalent (GyE) or 28.8 GyE CPBRT boost). PSA nadir ≤0.5 ng/mL, LDR brachytherapy: 91% vs. CPBRT boost: 59%, respectively.

Tanaka et al compared the PSA value at the last follow-up between LDR brachytherapy and IMRT. The achievement rate of PSA <0.2 ng/mL at the last follow-up was 77.5% in the LDR brachytherapy group and 49.7% in the IMRT group. The LDR brachytherapy group showed significantly lower PSA values at the last follow-up than the IMRT group ($P < 0.001$). They also evaluated the PSA value at the last follow-up in patients who showed a normal testosterone level at the last follow-up to exclude the effect of the testosterone level on PSA fluctuations because most high-risk patients received adjuvant androgen deprivation therapy for two years, and the achievement rate of PSA <0.2 ng/mL at the last follow-up was significantly higher in the LDR brachytherapy group than the IMRT group (LDR brachytherapy group: 79.2% vs. IMRT group: 32.1%, $P < 0.001$).[15]

As mentioned above, one of the advantages of LDR brachytherapy over EBRT is a higher prescribed dose to the prostate gland, avoiding unnecessary irradiation to organs at risk (the bladder, rectum, and urethra). This advantage makes it possible to achieve a lower PSA value (<0.2 ng/mL) after LDR brachytherapy than EBRT. This achieved lower PSA value after LDR brachytherapy also guaranteed higher progression-free survival and metastasis-free survival.

3. Toxicity

The most frequently observed toxicity after LDR brachytherapy is urinary disorder (especially pollakisuria, dysuria, and urgency), while severe urinary adverse events (grade 2+) are not often observed.[28–31] As described above, a nationwide prospective cohort study (JPOPS study) has been conducted in Japan. Three articles have been published concerning toxicities of LDR brachytherapy (Table 5).[29,30,32] First, Ohashi et al reported acute and late GU toxicity (grade 2 or greater) of 7.4% and 5.8%, respectively, while the acute and late GI toxicities (grade 2 or greater) were 1.0% and 1.9%, respectively. Acute GU (grade 2+) toxicity of LDR brachytherapy alone was 8.49%, while that of LDR brachytherapy combined with EBRT was 3.66% ($P = 0.0002$). On the other hand, late GU (grade 2+) toxicity of LDR brachytherapy alone was 6.04%, while that of LDR brachytherapy combined with EBRT was 4.82% ($P = 0.2929$). In contrast, acute GI (grade 2+) toxicity of LDR brachytherapy was 0.84%, while that of LDR brachytherapy combined with EBRT was 1.65% ($P = 0.1003$). On the other hand, late GI (grade 2+) toxicity of LDR brachytherapy was 0.90%, while that of LDR brachytherapy combined with EBRT was 5.01% ($P < 0.0001$).[29] Second, Katayama et al reported GI toxicity of the JPOPS study in detail. The multivariate analysis revealed that the rectal radiation dose ($P < 0.0001$) and EBRT combination ($P = 0.0066$) were prognostic parameters of GI toxicity (grade 2 or greater).[32] Third, Tanaka et al reported GU toxicity of the JPOPS study in detail. Acute and late GU toxicity (grade 3 or greater) of LDR brachytherapy alone were 1.1% and 1.1%, respectively. On the other hand, acute and late GU toxicity (grade 3 or greater) of LDR brachytherapy combined with EBRT were 1.3% and 0.8%, respectively. Acute urinary retention (grade 2 or greater) was 2.3% for all patients. Multivariate analysis showed that older age ($P = 0.0023$), larger prostate volume ($P = 0.0006$), and higher pretreatment International Prostate Symptom Score ($P < 0.0001$) were independent parameters predicting acute GU toxicity (grade 2 or greater), while larger prostate volume ($P < 0.0001$) and higher International Prostate Symptom Score ($P < 0.0001$) were independent parameters predicting GU toxicity (grade 2 or greater).[30]

Unsurprisingly, acute GU and late GI toxicity of LDR brachytherapy combined with EBRT were significantly higher than with LDR brachytherapy alone. These results showed a relative low incidence rate compared with the US patient series (RTOG 9805[33]: acute GU and late toxicity (grade 2 or greater), 24.7% and 5.4%. RTOG 0232[20]: acute GU and late toxicity (grade 3 or greater), 3% and 2%, respectively). The introduction of LDR brachytherapy in Japan lagged approximately 15 years behind the US. Japanese urologists and radiation oncologists obtained knowledge of LDR brachytherapy (oncologic outcomes, toxicity, and QOL) from the US. The J-POPS group provides an educational program, and a useful training course in LDR brachytherapy annually to spread and secure this procedure. These struggles certainly contributed to reduce the toxicity of LDR brachytherapy in Japan.

Since 2018, an absorbable polyethylene glycol hydrogel perirectal spacer (SpaceOAR System) is available in Japan according to the results of a phase III trial.[34,35] It is expected that GI toxicity will consequently decrease in the near future.

4. QOL

The deterioration of urinary function, which is bothersome, after LDR brachytherapy is well-known. Nakai et al[36] conducted a

Table 5
Genitourinary and gastrointestinal toxicity of LDR brachytherapy (JPOPS study)

	Number of patients	Eligible	Scale of adverse event	GU toxicity	GI toxicity
Ohashi et al[29] JPOPS study (2015)	2339	Low-, intermediate-, high-risk	NCI-CTCAE ver. 3.0	Acute (Grade 2+): 7.4% Late (Grade 2+): 5.8%	Acute (Grade 2+): 1.0% Late (Grade 2+): 1.9%
Katayama et al[32] JPOPS study (2016)	2339	Low-, intermediate-, high-risk	NCI-CTCAE ver. 3.0	Not evaluated	LDR alone Acute (Grade 2+): 0.84% Late (Grade 2+): 0.90% LDR + EBRT Acute (Grade 2+): 1.65% Late (Grade 2+): 5.01%
Tanaka et al[30] JPOPS study (2019)	2339	Low-, intermediate-, high-risk	NCI-CTCAE ver. 3.0	Acute urinary retention All patients (G 2+): 2.3% LDR alone Acute (Grade 3+): 1.1% Late (Grade 3+): 1.1% LDR + EBRT Acute (Grade 3+): 1.3% Late (Grade 3+): 0.8%	Not evaluated

EBRT, external beam radiation therapy; GI, gastrointestinal; GU, genitourinary; LDR, low-dose-rate brachytherapy; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

comparison of QOL among LDR brachytherapy, LDR brachytherapy combined with EBRT, and IMRT. Deterioration of the urinary QOL score was less severe with IMRT than with both LDR brachytherapy and LDR brachytherapy combined with EBRT. On the other hand, deterioration of the bowel QOL score was more severe with LDR brachytherapy combined with EBRT than with both IMRT and LDR brachytherapy alone. In contrast, the sexual QOL showed no differences between these three modalities.

In contrast, different deterioration of the QOL score was seen in patients who underwent RP.[37–39] The most severe deterioration of the QOL domain were urinary incontinence and sexual function compared with radiation therapy. Even in the era of robot-assisted RP, some patients suffer from severe continuous urinary incontinence, while most patients recover within 1 year after surgery (Pad: 0–1/day).[40]

Generally, the preservation of sexual function is better with LDR brachytherapy than with RP and is equivalent to that with EBRT.[41,42] In the JPOPS study by Okihara et al,[43] sexual function was preserved in 28.7% of patients at 3 years after LDR brachytherapy, while overall satisfaction significantly improved. Nakai et al evaluated erectile function and sexual QOL.[44] At 24 and 60 months after LDR brachytherapy, erectile dysfunction was noted in 56% of patients and 65% of patients using the Sexual Health Inventory for Men score, respectively. Univariate and multivariate analyses identified baseline SHIM scores as a significant predictor of deterioration in sexual QOL (odds ratio:0.84, 95% CI: 0.72–0.99, $P = 0.03$) at 24 months after LDR brachytherapy, whereas no significant factors were detected 60 months after LDR brachytherapy.

5. Further prospects

Now, 2 randomized controlled studies (the Seed and Hormone for Intermediate-risk Prostate Cancer (SHIP) 0804 study[45] and the trimodality with BT, EBRT, and HT for high-risk PCa (TRIP) study[46]) are underway by JPOPS. The SHIP study compares the length of ADT (3 months vs. 12 months) in intermediate-risk patients undergoing LDR brachytherapy alone. The TRIP study compares the length of ADT (6 months vs. 30 months) in high-risk patients with LDR brachytherapy combined with EBRT. The final results will be published soon, and the optimal length of ADT must be elucidated for intermediate- and high-risk patients.

In conclusion, the most noteworthy strength of LDR brachytherapy for low- to intermediate-risk patients is the “brief treatment time” while achieving high recurrence-free survival, and for high-risk patients who received LDR brachytherapy (tri-modality), it is “excellent disease control.”

Conflict of interest

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