

Treatment Outcomes of ^{125}I Low-Dose-Rate Brachytherapy vs Radical Prostatectomy for Patients with Intermediate-Risk Prostate Cancer

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Research Article

Keywords: Prostatic neoplasms, Low-dose-rate brachytherapy, Radical prostatectomy, Treatment outcomes, Comparative effectiveness

Posted Date: October 6th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-29556/v2>

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Abstract

Objective: To compare the efficacy of radical prostatectomy vs low-dose-rate brachytherapy for patients with intermediate-risk prostate cancer.

Materials and methods: A retrospective analysis was performed on 361 intermediate-risk prostate cancer patients who underwent treatment from January 2010 and August 2019. 160 underwent radical prostatectomy and 201 underwent low-dose-rate brachytherapy using Iodine-125. Biochemical failure for radical prostatectomy was defined as prostate-specific antigen levels > 0.2 ng/ml, and for low-dose-rate brachytherapy as nadir PSA level $+ 2$ ng/ml. The log-rank test compared biochemical relapse-free survival between the two modalities, and Cox regression identified factors associated with biochemical relapse-free survival.

Results: Median follow-up was 54 months for radical prostatectomy and 69 months for low-dose-rate brachytherapy. The 5- and 8-year biochemical relapse-free survival rates were 70.2% and 63.1% in the radical prostatectomy group, and 83.2% and 68.9% in the low-dose-rate brachytherapy group, respectively, $P=0.003$. There were no significant differences in terms of clinical relapse-free survival, cancer-specific survival or overall survival between the two groups.

Conclusion: Low-dose-rate brachytherapy is a reasonable treatment option for intermediate-risk prostate cancer patients, yielding improved biochemical relapse-free survival and equivalent rates of clinical relapse-free survival, cancer-specific survival and overall survival compared with radical prostatectomy.

1. Introduction

Prostate cancer (Pca) is the second most common cause of cancer-related death in U.S. men in 2018[1]. Although the incidence of Pca in China is lower than in western countries, it keeps growing in recent years due to aging and the improvements in healthcare [2]. Radical prostatectomy (RP), low-dose-rate brachytherapy (LDR), and external beam radiation therapy (EBRT) are the three major definitive treatment options for localized prostate cancer. Established clinical guidelines recommend that treatment decisions should be made based on tumor features, baseline prostate specific antigen (PSA) levels, patient age, comorbidity, life expectancy, and quality of life [3–5]. However, which of these treatments is the best for patients with localized prostate cancer remains a subject of debate.

LDR has shown impressive 10-year results [6, 7]. However, most of these patients were low risk, for which there is no significant benefit to local therapy [8]. The National Comprehensive Cancer Network (NCCN) guidelines recommend local therapy for intermediate-risk prostate cancer (IRPC) [5]. Randomized trials of IRPC patients treated with RP vs LDR have not been done. Thus, there is no clear evidence to inform clinical decisions regarding adequate treatment for IRPC patients. Our aim was to perform a retrospective study of IRPC, comparing the long term of outcomes of RP vs LDR at a single institution in China. We sought to identify variables that may predict differences in biochemical control, including treatment modality as a variable, using the most recent consensus definitions of biochemical failure (BF).

2. Materials And Methods

2.1 Patients

A group of 361 consecutive IRPC patients treated with curative intent between January 2010 and August 2019 at the Peking Union Medical College Hospital were identified. Of these patients, 160 (44.3%) underwent RP and 201 (55.7%) received LDR. All patients had biopsy-proven prostate adenocarcinoma, and all external pathological specimens were reviewed by pathologists in our institution. All patients were categorized according to the US NCCN risk classification criteria[5], which define IRPC by clinical stage T2b-c, Gleason score (GS) 3 + 4 (group 2) or 4 + 3 (group 3), and/or initial PSA (iPSA) of 10.1–20.0 ng/ml. Percentage positive biopsy cores (PPBC) > 50% was calculated from the pathology report. Favorable IRPC was described as patients with no more than 1 intermediate adverse risk factor, such as GS 3 + 4 (group 2), iPSA 10.1–20.0 ng/ml, or clinical stage T2b-c, and PPBC ≤ 50%. Patients with multiple intermediate adverse risk factors, which included PPBC > 50%, or any IRPC with GS 4 + 3 (group 3), were classified as unfavorable IRPC [9].

The following information was evaluated for all patients: medical history, physical examination, digital rectal examination and iPSA (serum PSA prior to treatment). Clinical staging was based on digital rectal examination and, when clinically indicated, chest radiography, bone scintigraphy, CT-scan and/or magnetic resonance imaging (MRI) of the pelvis. Staging was carried out by at least two surgeons at our institution.

2.2 Treatments

The choice of treatment, LDR versus RP, was determined by the patient and/or the doctor. Written informed consent was obtained from all individual participants included in the present study. Patients were informed of the benefits and consequences of each therapeutic option.

RP was performed by a pure laparoscopic prostatectomy. The procedure was performed according to the technique described by Guillonau [10]. Considering the low amount of lymph node metastasis found in the low intermediate-risk group, it is recommended that PLND could be omitted for prognostic reason according to the standard of NCCN, so the extent of pelvic lympho node dissection was not conducted for the included patients. The vesico-urethral anastomosis was made with a running suture with Y604 (Ethieon, USA).

Treatment with LDR was planned, so that the prostate and proximal seminal vesicles received 145 Gy with a 5-mm margin laterally, anteriorly, and inferiorly [11]. No margin was planned superiorly (bladder) and posteriorly (rectum). ¹²⁵I seeds were accurately introduced into preplanned positions by a brachytherapy stepping unit MICK200 (Computerized Medical Systems, Inc, St. Louis, MO, USA) using a standard 0.5 cm brachytherapy template placed over the perineum. One week after implantation, dosimetric analysis was performed by CT scan, and the D90 (defined as the minimum dose covering 90% of the prostate) was obtained for each patient.

2.3 Follow-up and study endpoints

Time zero was the day of RP or LDR. Patients were followed up monthly during the first 3 months and at 3-month intervals thereafter. If PSA level was stable, routine follow-up was scheduled every 6 months after 2 years of treatment. Imaging result for each patient was generally reviewed once a year, and would be rechecked at anytime if any signs of disease progression or biochemical recurrence were observed. The treatment outcomes were assessed in terms of biochemical relapse-free survival (bRFS), clinical relapse-free survival (cRFS), and cancer-specific survival (CSS), and overall survival (OS). BF was defined as a PSA value ≥ 0.2 ng/mL for patients who underwent RP [12] and an increase of 2 ng/mL or $>$ nadir PSA value (Phoenix definition) [13] for patients receiving LDR. If a patient received salvage radiotherapy or endocrine therapy, the patient was counted as having experienced a BF. Clinical relapse was defined as metastases identified by medical imaging, with or without localizing symptoms, or as biopsy-proven local recurrence. Cancer-specific mortality was defined as mortality due to Pca, as noted on the death certificate alongside the biochemical and clinical information, or the presence of uncontrolled metastatic disease at the time the patient succumbed.

2.4 Statistical analysis

Factors considered to influence the endpoint were recorded for baseline analysis. Student's t-test was used to evaluate differences in the mean of continuous variables. A χ^2 test was performed to compare ratios and Mann-Whitney U test to compare medians. Differences between two survival curves were evaluated by log-rank tests. Cox proportional-hazard models were constructed to identify factors associated with bRFS. Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered to be statistically significant in this study.

3. Results

3.1 Patient Characteristics

A total of 361 patients were included in the present study, comprising 201 LDR patients (55.7%) and 160 RP patients (44.3%). The mean (SD) age of the study population was 69.5 ± 6.9 years. Patients in Group RP were slightly younger (66.1 ± 5.9 years) than those in Group LDR (72.3 ± 6.4 years), $P < 0.001$. The median follow-up for RP and LDR was 54 and 69 months, respectively. Median duration of ADT in arms LDR and RP was 60 days (interquartile range [IQR], 58–62) and 183 days (IQR: 176–190), respectively, $P < 0.001$. Median PSA level at baseline was 12.29 ng/mL (range 0.835–20 ng/mL). The median follow-up duration for surviving patients was 63 months (interquartile range [IQR] 44–86). Table 1 presents a full comparison of pretreatment characteristics between the LDR and PR groups. The mean D90 for the LDR group was 144 Gy (1 standard deviation = 20.58Gy). For RP, positive margins were found in 55 (34.4%) patients. Extracapsular extension was found in 31 (19.3%), seminal vesicle invasion in 18 (11.3%), resulting in 42 (26.3%) RP patients upstaged to pathologic T3. Adjuvant androgen deprivation therapy (ADT) was given 31.2% for RP vs 94.5% for LDR, $P < 0.001$. Adjuvant EBRT were used in 15 patients

(9.4%) in the RP group and 5 patients (2.5%) in the LDR group, respectively. Adjuvant EBRT was performed for patients with positive margin and unfavorable PSA level after RP; meanwhile, whether adjuvant EBRT was conducted for LDR patients depends on the result of dosimetric analysis and postoperative PSA results.

3.2 Main Outcomes

The 5- and 8-year bRFS rates were 70.2% and 63.1% in the RP group, and 83.2% and 68.9% in the LDR group, respectively (Figure-1A). The log-rank test indicated that bRFS rates for the RP group were lower compared with the LDR group ($P = 0.003$, Figure-1A). The 5- and 8-year cRFS rates were 94.2% in the RP group, and 95.1% and 93.7% in the LDR group, respectively (Figure-1B). The 5- and 8-year CSS rates were 99.2% in the RP group, and 98.9% in the LDR group (Figure-1C). The 5- and 8-year OS rates were 98.6% and 97.0% in the RP group, and 97.7% and 95.4.5% in the LDR group, respectively (Figure-1D). The log-rank test were not significant for cRFS, CSS or OS rates between RP and LDR groups (cRFS: $P = 0.404$, Figure-1B; CSS: $P = 0.774$, Figure-1C; OS: $P = 0.951$, Figure-1D).

3.2.1 bRFS curves between LDR and RP

Comparison of bRFS curves between LDR and RP groups under the condition of different variables is shown in Table 2. Log-rank test was used to compare the bRFS curves between LDR and RP in terms of different variables according to pretreatment characteristics. Risk of BF was significantly higher with RP compared with LDR in the patients with GS 7 (3 + 4: $P = 0.027$; 4 + 3: $P = 0.001$), prostate volume > 30ml ($P < 0.001$), iPSA ≤ 10 ng/ml ($P = 0.007$), clinical T stage with T1c-T2a ($P = 0.016$), any PPBC ($\leq 50\%$: $P = 0.043$; $>50\%$: $P = 0.003$) or unfavorable IRPC ($P = 0.003$). However, survival of LDR patients was not statistically different from RP patients at any age, GS 6, prostate volume ≤ 30 ml, iPSA > 10 ng/ml, clinical T stage with T2b-T2c or favorable IRPC.

3.2.2 Prognostic Factors

Cox proportional-hazard models were constructed to identify factors associated with bRFS, and results are shown in Table 3. With univariate analysis of the entire cohort, treatment with RP ($P = 0.004$), age < 70 years old ($P = 0.001$), clinical T stage with T2b-T2c ($P = 0.005$), prostate volume ≤ 30 ml ($P < 0.001$) and PPBC > 50% ($P < 0.001$) were associated with significantly worse bRFS. With multivariate analysis of the entire cohort, prostate volume ≤ 30 ml ($P < 0.001$) and PPBC > 50% ($P < 0.001$) were associated with significantly worse bRFS, other factors such as the duration of ADT application, fail to demonstrate a positive result in multivariate analysis.

4. Discussion

Currently the guidelines of the American Urological Association, the European Association of Urology and the NCCN endorse RP, LDR and EBRT therapy as appropriate treatment options for IRPC. No differences have been observed in OS or CSS among the three approaches in the recent studies [14, 15]. However, treatment options for Pca are diverse, and therapeutic decisions are largely based on the condition of

each medical institution, the preference of doctors and the cognition of patients [14]. The comparison of the oncological outcomes of RP and LDR treatments remains a challenge, due to differential definitions for recurrence and methodological biases arising from the differences in baseline characteristics, including age, comorbidity and cancer risk features [14, 16–18]. A randomized controlled trial is the ideal approach for comparing competing treatment modalities [19]. However, most of the previously reported literatures comparing the efficacy of LDR and RP are retrospective studies [14, 20]. Compared with candidates for RP, patients who are offered LDR generally tend to be older and have higher comorbidity scores, therefore, a random trial is impractical [17, 18].

We retrospectively analyzed data from 361 IRPC patients treated in our hospital. Our results showed there were no statistically significant differences in the cRFS, CSS and OS between the two therapeutic groups. This result was consistent with recent publications in the literature, though they were not supported by randomized prospective studies [21–23]. Hamdy *et al*/reported 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer, and there were no significant difference in cRFS, CSS and OS between treatments of surgery and radiotherapy [15]. However, his study included patients of all risk categories, and thus we cannot make any conclusions regarding IRPC. Goy *et al*/statistically analyzed 1503 IRPC patients who underwent treatment from 2004 to 2007. There were no significant differences in cRFS or CSS. The 10-year bRFS was 80.2% for LDR vs 57.1% for RP vs 57.0% for EBRT, which showed improved bRFS with LDR, $P = 0.0003$ [24]. But LDR patients had a significantly smaller proportion number compared with RP (7.3% Vs 54.5%) in his study, which might cause some bias in the results. In our study, the proportion of patients in both groups was more balanced than that in Goy's study. Consistent with Goy's results, in the present study, the 5- and 8-year bRFS rates were 70.2% and 63.1% in the RP group, and 83.2% and 68.9% in the LDR group, respectively. The log-rank test showed the bRFS for RP was significantly lower than LDR. However, in terms of the pretreatment characteristics, patients treated with LDR were older, experienced longer follow-up time, and had a higher preponderance of combined ADT treatment. In previous studies using models adjusted for risk, ADT was not shown to be an independent predictor [18, 25], which met our results. In our present study both multivariate and univariate analysis indicated that ADT application has little impact on the prognosis of IRPC. In a word, our study supports the use of LDR as a reasonable treatment option for IRPC.

Neither treatment modality has proven superior to the other with respect to RP and LDR; therefore, the optimal treatment for different risk categories in Pca remains a matter of debate. Although our median follow-up time of 54 months was sufficient to capture a considerable number of systemic failure events, it may still be too short to achieve mortality results. Therefore, we chose bRFS as the main evaluation criterion of curative effect. We observed that bRFS was significantly higher with LDR than RP in patients with GS 7, prostate volume > 30ml, iPSA ≤ 10 ng/ml, clinical T stage with T1c-T2a, any PPBC or unfavorable IRPC. Supported by the results of our study, LDR may be a better option than RP in patients with the above conditions. In our experience, a subgroup analysis of unfavorable IRPC had improved bRFS with LDR compared to RP. These results showed that LDR was also a good option for those with unfavorable IRPC. Taussky *et al*/reported RP and LDR treatment did not result in significantly different outcomes at four years post-treatment in patients with low- and low-intermediate- risk Pca [26]. However,

Ferreira *et al* found the 5-year bRFS of patients with early Pca who had undergone LDR was significantly higher than those who had undergone surgery [27]. Furthermore, Ciezki *et al* reported high-risk Pca treated with EBRT, LDR, or RP yields efficacy with better bRFS for LDR and EBRT compared with RP [21]. It should be noted that these studies were obviously heterogeneous, because different centers adopted different LDR technologies, and different methods were used to compare the results between RP and LDR [28].

As the previously studies reported, there were many factors affecting the prognosis of Pca, including general situation, tumor stage, tumor grade, iPSA, age and bone scintigraphy [29–31]. Ciezki *et al* found clinical stage T3, GS 8 to 10, higher iPSA and more frequent PSA testing after therapy were all associated with a significantly worse bRFS [21]. Taussky *et al* reported younger age, higher percentage of positive biopsies, and PSA at diagnosis were predictive of BF [26]. On univariate analysis of the entire cohort in the present study, treatment with RP, age < 70 years old, clinical T stage with T2b-T2c, prostate volume \leq 30ml and PPBC > 50% were associated with significantly worse bRFS. Previous studies had reported that clinical stage was the most dangerous factor influencing Pca prognosis [32, 33]. On multivariate analysis of the entire cohort, prostate volume \leq 30ml and PPBC > 50% were associated with significantly worse bRFS. Therefore, they were important independent prognostic factors. Goy *et al* also reported in their study that PPBC > 50% had significant impact on cRFS and CSS[26]. On the other hand, after searching multiple online libraries, we still couldn't find a reasonable explanation for why prostate volume < 30ml was associated with worse bRFS. Therefore, we expect to see a multi-center population based prospective study in the future to investigate the relationship between prostate volume and the prognosis of Pca.

The limitations of this study include the following: (1) Baseline characteristics of the two groups did not completely match, which was inevitable due to random grouping in a retrospective study. Therefore, a prospective study comparing eligible patients is needed to make a more accurate conclusion. (2) The aim of our study was to provide a guide to aid clinical decision making at diagnosis. Thus, duration of ADT following initial treatment, which may contribute to survival, was not adjusted. However, in previous studies using models adjusted for risk, ADT was not shown to be an independent predictor [18, 25]. (3) The definition of BF is different for the RP versus LDR groups. Although this definition is commonly used in the world [15, 23, 24], there might be some bias in interpretation of the results. (4) There were fewer deaths in this study; therefore, whether higher bRFS rates observed in patients could translate into superior oncological endpoints is still undetermined. A longer observational period is needed for a meaningful comparison of overall survival. (5) Due to its respective nature, co-morbidities of participants in each group was not compared in present study, we are now following up these included patients to collect relevant clinical data to improve our study in the future.

5. Conclusion

In summary, LDR, with or without androgen deprivation, is as good a treatment option for IRPC patients, producing equivalent rates of cRFS, CSS and OS compared with RP. Despite the difference in BF definitions, LDR improved bRFS compared with RP. Prostate volume \leq 30ml ($P < 0.001$) and PPBC > 50%

($P < 0.001$) were independent predictors for worse bRFS. A longer follow-up may be necessary to detect a difference in OS between these two treatments.

Abbreviations

ADT: androgen deprivation therapy

BF: biochemical failure

bRFS: biochemical relapse-free survival

CI: confidence interval

cRFS: clinical relapse-free survival

CSS: cancer-specific survival

EBRT: external beam radiation therapy

GS: Gleason score

HR: hazard ratio

iPSA: initial prostate-specific antigen

IRPC: intermediate-risk prostate cancer

LDR: low-dose-rate brachytherapy

NCCN: The National Comprehensive Cancer Network

OS: overall survival

Pca: Prostate cancer

PPBC: Percentage positive biopsy cores

PSA: prostate-specific antigen

RP: Radical prostatectomy

Declarations

Disclosures

Not applicable.

Acknowledgements

Not applicable.

Author contributions Statements

ZEZ, ZL, YZ, and WY Conception and design. ZEZ and YZ Administrative support. ZBZ and XW Provision of study materials or patients. WY, FZ, ZJ, HL Collection and assembly of data. ZEZ and WY Data analysis and interpretation. Manuscript writing: All authors. Final approval of manuscript: All authors.

Funding

No funding was received.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board (IRB) of Peking Union Medical College Hospital (PUMCH). The present study was approved by the Institutional Review Board of Peking Union Medical College Hospital. Informed consent was obtained from all individual participants included in the study. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Accordance

The study protocol was approved and performed in agreement with the provisions of the Declaration of Helsinki

Contribution to the Field Statement

In this study, we compared the efficacy of radical prostatectomy vs low-dose-rate prostate brachytherapy for 361 patients with intermediate-risk prostate cancer, who underwent treatment from January 2010 and August 2019. We found low-dose-rate brachytherapy using Iodine-125, used alone or in combination with androgen deprivation therapy, is a reasonable treatment option for intermediate-risk prostate cancer patients, yielding improved biochemical relapse-free survival and equivalent rates of clinical relapse-free survival, cancer-specific survival and overall survival compared with radical prostatectomy. Prostate volume ≤ 30 ml and percentage positive biopsy cores $>50\%$ were independent predictors for lower biochemical relapse-free survival rate in intermediate-risk prostate cancer patients.

Consent to publish

Not applicable

Availability of data and materials section:

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Tables

TABLE 1 Patient cohort characteristics

Parameters	RP(n=160)	LDR(n=201)	P value
Age(years)			<0.001
Median	66	74	
Range	48-78	50-84	
Clinical Stage			0.002
T1c	15(9.4%)	42	
T2a	40(25.0%)	36	
T2b	41(25.6%)	32	
T2c	64	91	
Gleason Score			0.086
6(3+3)	75()	79	
7(3+4)	54	63	
7(4+3)	31	59	
Prostate volume[ml]			0.172
≤30	76()	110	
>30	84	91	
Initial PSA (ng/ml)			0.891
Median	12	12.5	
Range	4.2-20	0.8-19.9	
Risk			0.172
Favorable	45	44	
Unfavorable	115	157	
PPBC			0.734
≤50%	125	154	
>50%	35	47	
Follow-up, months			<0.001
Median	54	69	
Range	17-114	26-117	
Duration ADT, months			<0.001

0	110	11
1-6	25	94
≥6	25	96

TABLE 2 Comparison of the bRFS curves between LDR and RP groups, according to different variables using a log-rank test.

Variables	P value
Age, years	
<70	0.328
≥70	0.117
Gleason score	
6(3+3)	0.667
7(3+4)	0.027
7(4+3)	0.001
Prostate volume, ml	
≤30	0.953
>30	<0.001
iPSA, ng/ml	
≤10	0.007
10.1-20	0.085
Clinical T Stage	
T1c, T2a	0.016
T2b, T2c	0.065
PPBC	
≤50%	0.043
>50%	0.003
Risk	
Favorable	0.342
Unfavorable	0.003

TABLE 3 Univariate and multivariable analyses of prognostic factors

Factor	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Treatment				
RP		1		1
LDR	0.004	0.533 (0.349-0.814)	<u>0.067</u>	<u>0.503 (0.241-1.051)</u>
Age, years				
<70		1		1
≥70	0.001	0.497 (0.325-0.761)	<u>0.287</u>	<u>0.724 (0.400-1.312)</u>
Clinical T stage				
T1c, T2a		1		1
T2b, T2c	0.005	1.988 (1.225-3.226)	<u>0.426</u>	<u>1.286 (0.692-2.391)</u>
iPSA, ng/ml				
≤10		1	-	-
10.1-20	0.151	0.726 (0.468-1.124)	-	-
Gleason score				
6(3+3)		1	-	-
7(3+4)	0.523	0.856 (0.531-1.380)	-	-
7(4+3)	0.095	0.615 (0.347-1.088)	-	-
Prostate volume, ml				
≤30		1		1
>30	<0.001	0.349 (0.218-0.560)	<u><0.001</u>	<u>0.325 (0.176-0.602)</u>
PPBC				
≤50%		1		1
>50%	<0.001	2.826 (1.846-4.327)	<u><0.001</u>	<u>1.192 (1.712-5.952)</u>
Duration ADT, months				
0		1	-	-
<u>1-6</u>	<u>0.254</u>	<u>0.724(0.645-1.285)</u>	<u>0.106</u>	<u>2.607(0.872-4.134)</u>
<u>>6</u>	<u>0.177</u>	<u>0.593(0.512-0.712)</u>	<u>0.426</u>	<u>0.634(0.618-3.129)</u>

Figures

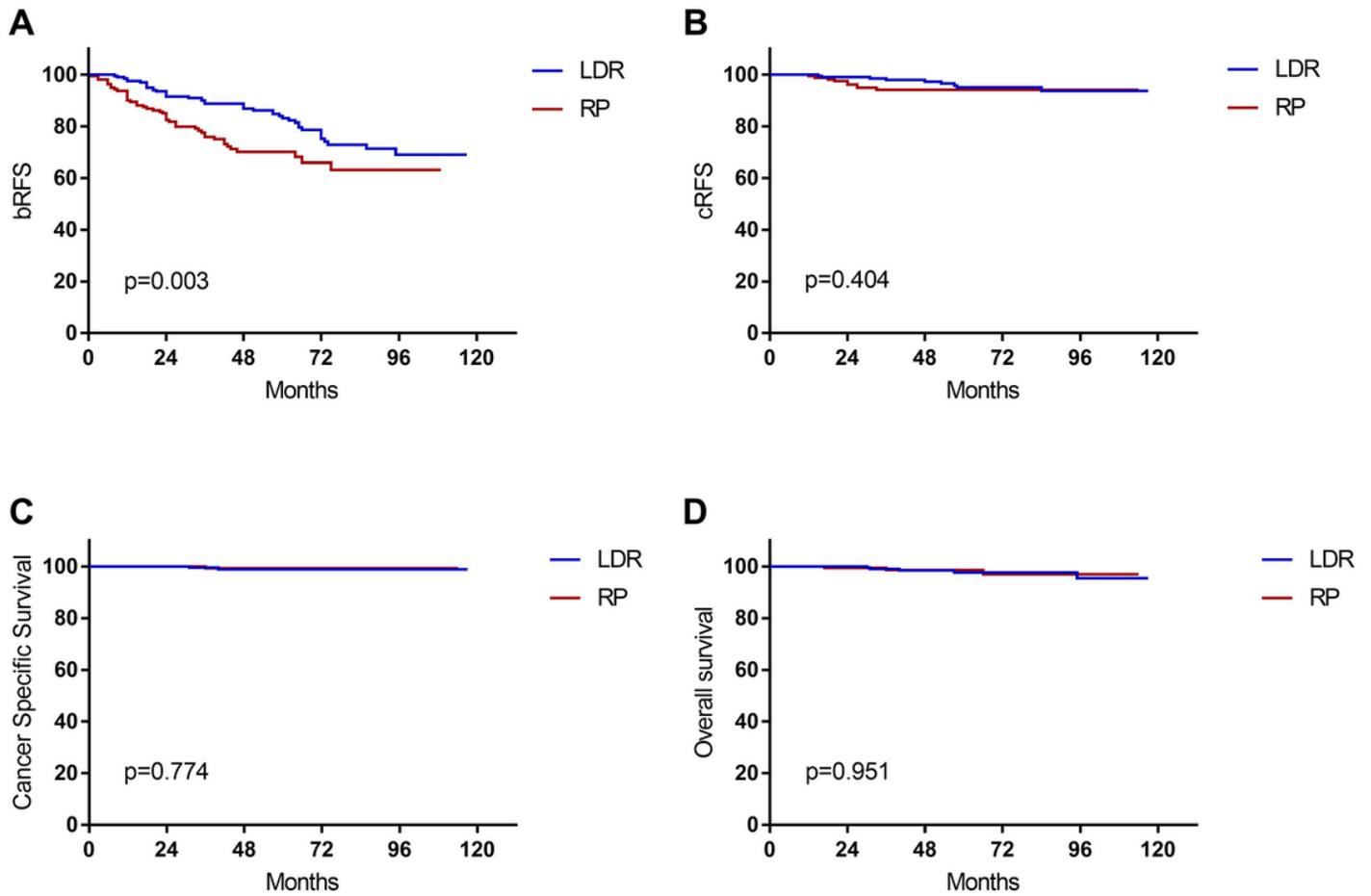


Figure 1

Kaplan-Meier survival curves of bRFS (A), cRFS (B), CSS (C) and OS (D) in patients with IRPC treated with LDR vs RP. bRFS biochemical relapse-free survival; cRFS clinical relapse-free survival; CSS cancer specific survival; OS overall survival; IRPC intermediate-risk prostate cancer; LDR low-dose-rate brachytherapy; RP radical prostatectomy.