



Original Article

Oncological outcomes of patients with ductal adenocarcinoma of the prostate receiving radical prostatectomy or radiotherapy



Mengzhu Liu ^{a,1}, Kun Jin ^{a,1}, Shi Qiu ^{a,b,1}, Pengyong Xu ^c,
Mingming Zhang ^a, Wufeng Cai ^a, Xiaonan Zheng ^a, Lu Yang ^{a,*},
Qiang Wei ^{a,*}

^a Institute of Urology, Department of Urology, West China Hospital, Sichuan University, Chengdu, China

^b Center of Biomedical Big Data, West China Hospital, Sichuan University, Chengdu, China

^c Institute of Urology, Department of Urology, the First People's Hospital, Yantai, China

Received 24 July 2019; received in revised form 8 February 2020; accepted 15 April 2020

Available online 23 May 2020

KEYWORDS

Ductal adenocarcinoma of the prostate;
Cancer specific mortality;
Overall mortality;
Radical prostatectomy;
Radiotherapy

Abstract *Objective:* To evaluate the oncological outcomes of ductal adenocarcinoma of the prostate (DAC) managed with radical prostatectomy (RP) or radiotherapy (RT) and optimize the proper treatment modality to DAC comprehensively.

Methods: The cohorts included a total of 528 patients from the Surveillance, Epidemiology and End Results (SEER) database, 354 receiving RP and 174 receiving RT. Cox proportional hazards regressions were performed to assess cancer specific mortality (CSM) and overall mortality (OM) between treatment groups. A competing risk analysis was further conducted. Subgroup analyses by age and level of prostate-specific antigen (PSA) were performed. Propensity score matching was implemented.

Results: Patients managed with RP had lower risks of CSM and OM compared with RT (before matching: Hazard ratio [HR]=0.24, 95% confidence interval [CI] 0.13–0.47 and HR=0.26, 95% CI 0.17–0.40, respectively; after matching: HR=0.18, 95% CI 0.04–0.82 and HR=0.28, 95% CI 0.11–0.70, accordingly). Subgroup analyses demonstrated that patients in the middle tertile of the age or with lower tertile PSA level managed with RP took lower risks of OM significantly (HR=0.18, 95% CI 0.06–0.57, $p<0.01$ and HR=0.17, 95% CI 0.06–0.54, $p<0.01$).

Conclusion: Among patients with DAC, treatment with RP was associated with better survival outcomes in comparison with RT. Patients with DAC in the middle tertile of the age and with lower tertile PSA level benefited the most from RP.

* Corresponding author.

E-mail addresses: wycleflue@163.com (L. Yang), weiqiang163163@163.com (Q. Wei).

Peer review under responsibility of Second Military Medical University.

¹ These authors contributed equally as the first authors.

1. Introduction

Prostate cancer (PCa) was the most frequent cancer for men with estimated 1.6 million incident cases worldwide in 2015 and remained the leading cause of cancer deaths for men in some countries [1,2].

Ductal adenocarcinoma of the prostate (DAC), first described in 1967 [3], was a rare morphological variant of PCa, more frequently mixed with the conventional acinar subtype [4,5]. Considered as high Gleason grade cancer, DAC was managed with standard treatments of PCa: Radical prostatectomy (RP) and radiotherapy (RT) [6]. However, clinically, DAC had worse prognoses than conventional acinar adenocarcinoma of the prostate (AAC), usually presenting with advanced clinical stage in most studies [7–10]. Moreover, the differences in histology [11,12] and genomics [13,14] between DAC and AAC justified DAC as a unique clinical entity, instead of a merely high Gleason grade cancer. Thus, it is necessary to further investigate the outcomes of DAC treated with RP or RT. Only few studies reported the outcomes of DAC management with RP or RT with small sample sizes [15–21], but failed to compare the efficacy of the two treatments. In addition, most of these studies lacked robust adjustments of confounding factors. The ideal treatment modality to DAC has still been controversial.

Therefore, our study intends to evaluate the oncological outcomes of DAC managed with RP or RT and optimize the proper treatment comprehensively.

2. Methods

2.1. Patient selection

Data for this study were derived from the Surveillance, Epidemiology and End Results (SEER) database, composed of 18 cancer registries in America and accounting for 26% of the US population. We identified patients diagnosed with DAC (International Classification of Diseases-O-3 code: 8500/3) between 2004 and 2015 ($n=818$). DAC mixed with other types of PCa and all other histologic subtypes were excluded. The tumor-node-metastasis (TNM)-based staging was evaluated based on imaging manifestations, in accordance with the sixth edition of American Joint Committee on Cancer (AJCC) Cancer Staging Manual [22,23]. Patients who were not confirmed by histology examination ($n=2$) and whose primary treatment was neither RP nor RT ($n=288$) were excluded. Finally, 528 patients were included in this study and stratified into the two treatment groups: RP and RT.

2.2. Statistical analysis

First, in the analysis of baseline characteristics, continuous variables were expressed as means with standard

deviations and medians with interquartile ranges, compared with a two-tail t -test, whereas categorical variables were presented as frequencies with its proportions and compared with a two-tailed χ^2 test (or Fisher exact test). Second, to compare the efficacy of the two treatments, we assessed cancer specific mortality (CSM) and overall mortality (OM) between treatment groups with the use of Cox proportional hazards regressions, including non-adjusted and multivariate adjusted models. A competing risk analysis was further conducted to verify the regression. Third, we tested the interactions of marital status, age, Gleason score (GS) and the level of prostate-specific antigen (PSA) and further conducted the subgroup analyses of age and level of PSA to investigate their influences on CSM and OM between treatments groups. Fourth, taken the definition of DAC from AUA (Graded as Gleason pattern 4, if pure, assigned as GS 4+4=8) into account, we performed subgroup analysis of biopsy GS 8. Fifth, propensity score matching (1:1 ratio, with nearest-neighbor matching or calliper width of 0.05) was used to control for confounding and emulate randomized cohort trial design [24]. Propensity scores were estimated with logistic regression, with treatment (RT and RP) as the outcome and age, PSA, TNM stages, biopsy GS and race as pretreatment, prognostic covariates. The matched baseline characteristics between the two groups were regarded as balanced while $p>0.05$.

All the analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation, X&Y Solutions, Boston, MA, USA) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc., Boston, MA, USA). A p -value <0.05 was considered statistically significant.

2.3. Compliance with ethical standards

Research data involving human participants and/or animals for this study were derived from SEER database.

3. Results

The cohorts included a total of 528 patients from SEER database, 354 receiving RP and 174 receiving RT. Table 1 presents the baseline characteristics of the patients treated with RP, compared with RT. The median follow-up time was 43 months (interquartile range [IQR], 20.0–77.5 months) for RT and 55 months (IQR, 23–85 months) for RP, respectively. Patients managed with RP were younger and had lower PSA level ($p<0.01$ and $p=0.01$, respectively). The TNM stages, the biopsy GS of the two groups differed with each other ($p<0.01$ and $p=0.01$, respectively), as well as the marital status ($p=0.03$), while the race of them showed as no differences ($p=0.52$).

Table 1 Baseline characteristics of patients with DAC.

	RT (n=174)	RP (n=354)	p-Value
Age, year			
mean±SD	71.51±8.26	63.64±8.26	<0.01
median (IQR)	72.50 (67.00–77.00)	63.00 (58.25–69.00)	
PSA level, ng/mL			
mean±SD	17.78±27.02	11.85±19.40	0.01
median (IQR)	6.75 (4.35–15.58)	6.10 (4.40–9.40)	
Time, month			
mean±SD	50.63±36.96	57.86±39.66	0.05
median (IQR)	43.00 (20.00–77.50)	55.00 (23.00–85.00)	
Marital status, n (%)			
Married	118 (67.82)	275 (77.69)	0.03
Single	12 (6.90)	27 (7.63)	
Divorced/widowed	30 (17.24)	32 (9.04)	
Unknown	14 (8.05)	20 (5.65)	
Race, n (%)			
Caucasian	131 (75.29)	278 (78.53)	0.52
African	26 (14.94)	44 (12.43)	
Other	15 (8.62)	31 (8.76)	
Unknown	2 (1.15)	1 (0.28)	
Clinical T stage, n (%)			
T1	75 (43.10)	2 (0.57)	<0.01
T2	55 (31.61)	166 (46.89)	
T3	24 (13.79)	157 (44.35)	
T4	15 (8.62)	29 (8.19)	
Unknown	5 (2.87)	0 (0.00)	
N stage, n (%)			
N0	157 (90.23)	326 (92.09)	0.01
N1	8 (4.60)	26 (7.35)	
Unknown	9 (5.17)	2 (0.57)	
M stage, n (%)			
M0	151 (86.78)	350 (98.87)	<0.01
M1	20 (11.49)	3 (0.85)	
Unknown	3 (1.72)	1 (0.28)	
Biopsy Gleason grade group, n (%)			
I	2 (1.15)	1 (0.28)	<0.01
II	19 (10.92)	68 (19.21)	
III	118 (67.82)	266 (75.14)	
IV	1 (0.57)	3 (0.85)	
Unknown	34 (19.54)	16 (4.52)	
Biopsy gleason score, n (%)			
6	20 (11.49)	37 (10.45)	0.01
7	9 (5.17)	50 (14.12)	
8	31 (17.82)	44 (12.43)	
Unknown	114 (65.52)	223 (62.99)	

DAC, ductal adenocarcinoma of the prostate; RT, radiotherapy; RP, radical prostatectomy; SD, standard deviations; IQR, interquartile range; PSA, prostate-specific antigen.

In the multivariate regression model, patients managed with RP had lower risks of CSM and OM (hazard ratio [HR] = 0.24, 95% confidence interval [CI] 0.13–0.47 and HR = 0.26, 95% CI 0.17–0.40, respectively) (Table 2). After adjusting relevant covariates including marital status, age, race, TNM stage, biopsy GS and PSA level, HRs of CSM and OM are 0.41 (95% CI 0.17–0.99) and 0.50 (95% CI 0.28–0.90), respectively, which changed slightly, also indicating that patients could receive survival benefit from RP (Table 2, Figs. 1–2). To overcome the effects of all the

non-cancer-specific death, our competing risk analysis showed that patients receiving RP is superior to RT (sub-distribution HR = 0.25, 95% CI 0.13–0.48).

Significant interactions were observed in the age and the level of the PSA between the treatments and OM (p for interaction = 0.001 and p for interaction = 0.05, respectively). Subgroup analyses demonstrated that patients in the middle tertile of the age managed with RP took lower risks of both CSM and OM significantly (HR = 0.08, 95% CI 0.01–0.71, p = 0.02 and HR = 0.18, 95% CI 0.06–0.57,

Table 2 Cox proportional hazards regression models of CSM and OM.

	CSM		OM	
	HR (95% CI)	<i>p</i> -Value	HR (95% CI)	<i>p</i> -Value
Non-adjusted (<i>n</i> =528)				
RT	1		1	
RP vs. RT	0.24 (0.13, 0.47)	<0.01	0.26 (0.17, 0.40)	<0.01
Adjusted (<i>n</i> =487) ^a				
RT	1		1	
RP vs. RT	0.41 (0.17, 0.99)	0.05	0.50 (0.28, 0.90)	0.02

CSM, cancer-specific mortality; OM, overall mortality; HR, Hazard ratio; CI, confidence interval; RT, radiotherapy; RP, radical prostatectomy; PSA, prostate-specific antigen.

^a This model adjusted for marital status, age, race, TNM stage, biopsy Gleason score and PSA level.

$p < 0.01$); for patients in the lower tertile of PSA level treated with RP, the risks of OM was reduced significantly (HR=0.17, 95% CI 0.06–0.54, $p < 0.01$), while the reduction of CSM was not significant ($p = 0.08$) (Table 3).

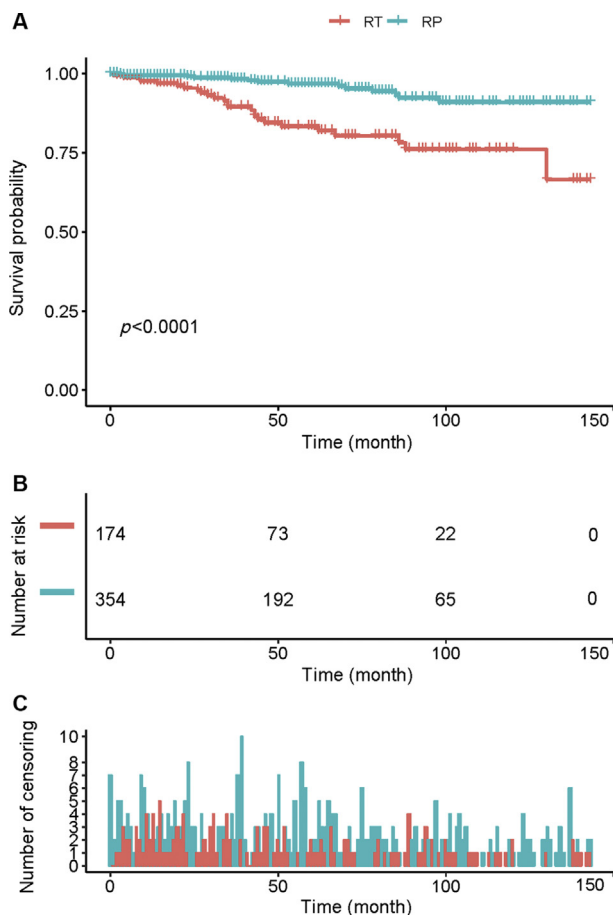


Figure 1 Kaplan-Meier analyses depicting cancer-specific mortality rates. (A) Survival curves; (B) Number at risk at different times; (C) Number of censoring at different times. RT, radiotherapy; RP, radical prostatectomy.

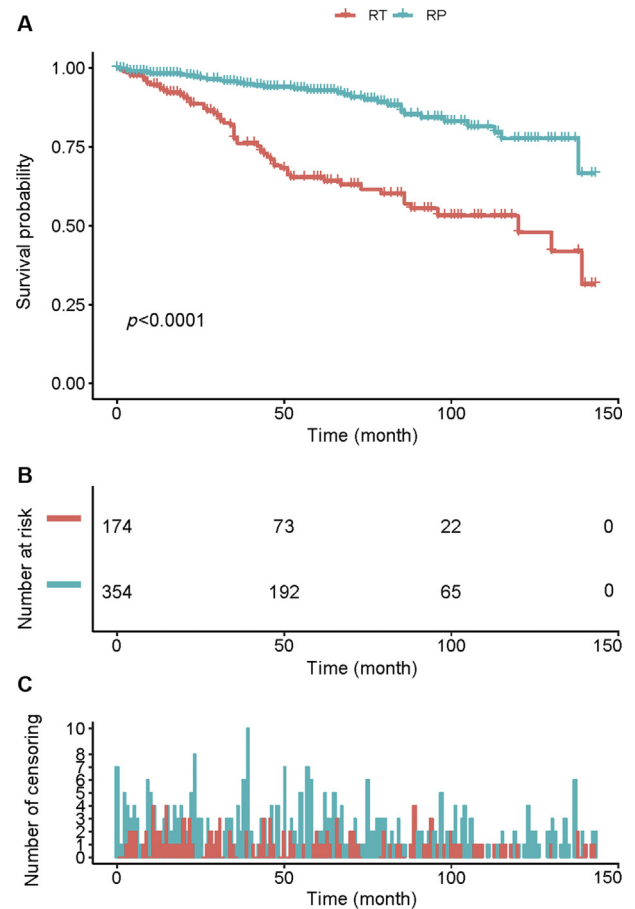


Figure 2 Kaplan-Meier analyses depicting overall mortality rates. (A) Survival curves; (B) Number at risk at different times; (C) Number of censoring at different times. RT, radiotherapy; RP, radical prostatectomy.

Considering the definition of DAC from AUA website, we sought to further illustrate whether a superior benefit from RP could be identified within the biopsy GS 8 cohort versus others. However, due to the small sample sizes of biopsy GS 8 cohort ($n = 31$), the subgroup analysis could not be performed.

A total of 148 patients were selected with propensity score matching (1:1 ratio). The T stage and biopsy Gleason grade were still unbalanced after matching (Table 4). In the matched cohort, HR of CSM and OM for RP versus RT was 0.18 (95% CI 0.04–0.82, $p = 0.03$) and 0.28 (95% CI 0.11–0.70, $p = 0.01$), respectively (Table 5, Figs. 3–4).

4. Discussion

In this study, we compared the efficacy of RP and RT to DAC with a cohort of 528 patients. The results showed RP was associated with lower rates of CSM and OM, in comparison with RT. Due to the rarity of the DAC with an incidence ranging from 0.49% to 3.2% of the PCa [4,5], DAC was used to be only considered as high Gleason grade PCa and treatment for DAC has merely been described in small

Table 3 Subgroup analyses by age and PSA level.

	CSM		OM	
	HR (95% CI), RP vs. RT	<i>p</i> -Value	HR (95% CI), RP vs. RT	<i>p</i> -Value
Age ^a				
Low (<i>n</i> =157)	0.10 (0.00, 37.88)	0.44	0.10 (0.00, 37.88)	0.44
Middle (<i>n</i> =180)	0.08 (0.01, 0.71)	0.02	0.18 (0.06, 0.57)	<0.01
High (<i>n</i> =191)	0.52 (0.12, 2.16)	0.36	0.61 (0.28, 1.31)	0.20
PSA level ^b				
Low (<i>n</i> =161)	0.16 (0.02, 1.21)	0.08	0.17 (0.06, 0.54)	<0.01
Middle (<i>n</i> =158)	0.07 (0.00, 1.58)	0.09	1.16 (0.32, 4.27)	0.82
High (<i>n</i> =168)	0.79 (0.21, 2.92)	0.72	0.67 (0.26, 1.76)	0.42

CSM, cancer-specific mortality; OM, overall mortality; HR, Hazard ratio; CI, confidence interval; RT, radiotherapy; RP, radical prostatectomy; PSA, prostate-specific antigen.

^a This model adjusted for marital status, race, T stage, N stage, M stage, Gleason score and PSA level.

^b This model adjusted for marital status, age, race, T stage, N stage, M stage and Gleason score.

Table 4 Baseline characteristics of patients with DAC after propensity score matching.

	RT (<i>n</i> =74)	RP (<i>n</i> =74)	<i>p</i> -Value
Age, year			
mean±SD	68.70±7.99	67.28±10.65	0.36
median (IQR)	70.00 (65.00–74.00)	69.00 (62.25–74.00)	
PSA level, ng/mL			
mean±SD	16.11±24.42	15.36±25.29	0.86
median (IQR)	7.25 (4.40–14.88)	5.80 (3.38–13.73)	
Time, month			
mean±SD	56.81±39.52	55.49±39.43	0.84
median (IQR)	47.00 (23.00–87.50)	46.50 (23.25–89.00)	
Marital status, <i>n</i> (%)			
Married	52 (70.27)	53 (71.62)	0.49
Single	6 (8.11)	4 (5.41)	
Divorced/widowed	13 (17.57)	10 (13.51)	
Unknown	3 (4.05)	7 (9.46)	
Race, <i>n</i> (%)			
Caucasian	53 (71.62)	59 (79.73)	0.39
African	14 (18.92)	8 (10.81)	
Other	7 (9.46)	6 (8.11)	
Unknown	0 (0.00)	1 (1.35)	
Clinical T stage, <i>n</i> (%)			
T1	16 (21.62)	2 (2.70)	<0.01
T2	28 (37.84)	42 (56.76)	
T3	20 (27.03)	26 (35.14)	
T4	10 (13.51)	4 (5.41)	
N stage, <i>n</i> (%)			
N0	70 (94.59)	69 (93.24)	0.73
N1	4 (5.41)	5 (6.76)	
M stage, <i>n</i> (%)			
M0	72 (97.30)	73 (98.65)	0.56
M1	2 (2.70)	1 (1.35)	
Biopsy Gleason grade group, <i>n</i> (%)			
I	1 (1.35)	0 (0.00)	<0.01
II	7 (9.46)	16 (21.62)	
III	54 (72.97)	56 (75.68)	
Unknown	12 (16.22)	2 (2.70)	
Biopsy Gleason score			
6	8 (10.81)	7 (9.46)	0.90
7	6 (8.11)	7 (9.46)	
8	14 (18.92)	11 (14.86)	
Unknown	46 (62.16)	49 (66.22)	

DAC, ductal adenocarcinoma of the prostate; RT, radiotherapy; RP, radical prostatectomy; SD, standard deviations; IQR, interquartile range; PSA, prostate-specific antigen.

series before. The optimal management modality has been controversial. Previous population-based studies solely made a comparison of clinicopathologic characteristics and survival outcomes of DAC and AAC [7–10], and one of them illustrated RP was an independent prognostic factor of better survival outcomes in DAC [8]. In a single-armed study, Bergamin et al. [15] just reported 27 patients of DAC receiving RT with four local failures and five distant failures after the median time of 57 months. He only demonstrated that dose escalation to the prostate and

Table 5 Cox proportional hazards regression models of CSM and OM after propensity score matching.

	CSM		OM	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
RT	1		1	
RP vs. RT	0.18 (0.04, 0.82)	0.03	0.28 (0.11, 0.70)	0.01

CSM, cancer-specific mortality; OM, overall mortality; HR, Hazard ratio; CI, confidence interval; RT, radiotherapy; RP, radical prostatectomy.

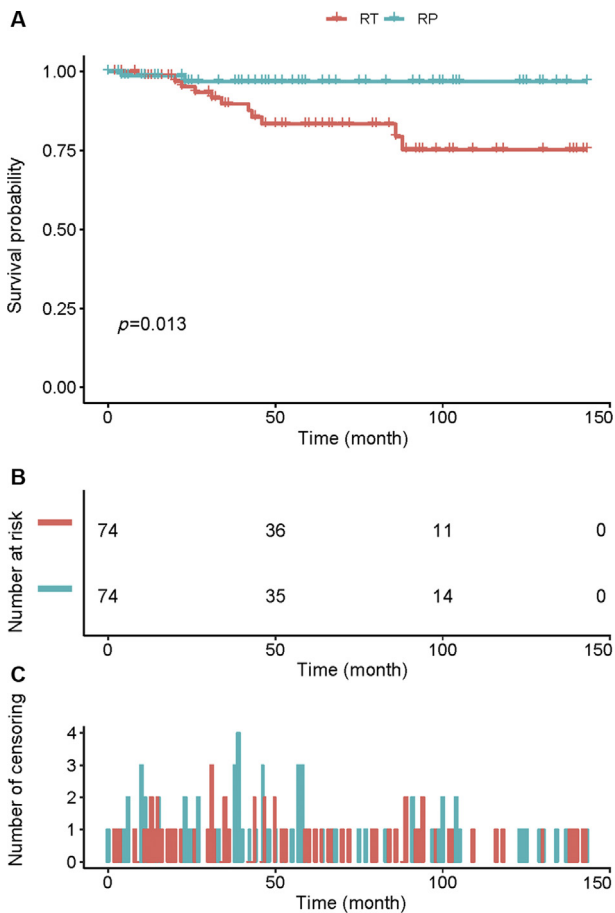


Figure 3 Kaplan-Meier analyses depicting cancer-specific mortality rates after propensity score matching. (A) Survival curves; (B) Number at risk at different times; (C) Number of censoring at different times. RT, radiotherapy; RP, radical prostatectomy.

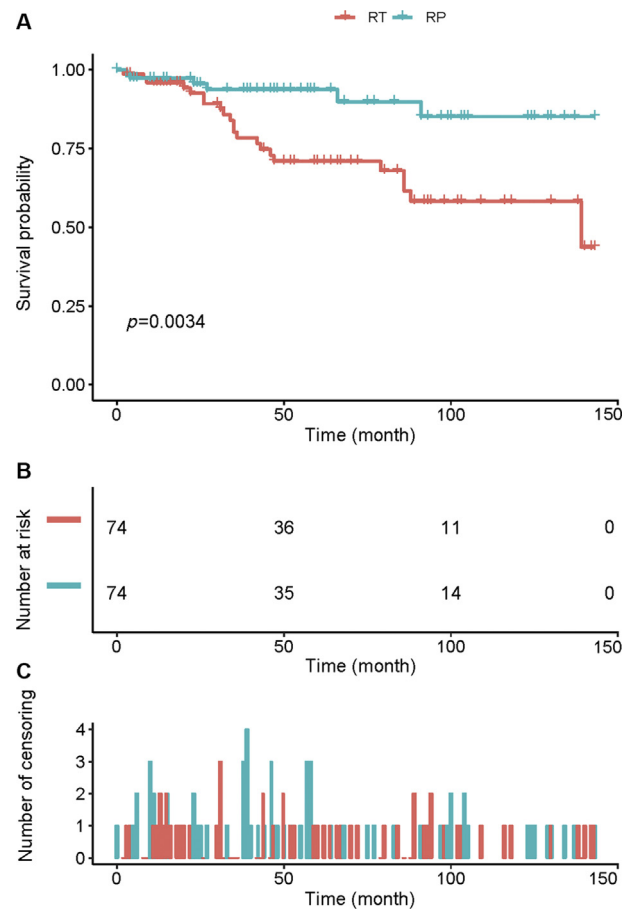


Figure 4 Kaplan-Meier analyses depicting overall mortality rates after propensity score matching. (A) Survival curves; (B) Number at risk at different times; (C) Number of censoring at different times. RT, radiotherapy; RP, radical prostatectomy.

seminal vesicles could improve the local control, without comparison with RP. Sha et al. [16] sorely reminded RP could improve the outcomes of DAC with seven patients with no comparison of RT neither. Nevertheless, two of four patients receiving RP in Kan’s study had biochemical recurrence 1–2 years post-operation [17], partly related to delayed diagnosis which meant DAC was more aggressive. Four retrospective studies evaluating the outcomes managed with RP or RT showed conflicting results, with 108, 17, 31 and 41 patients, respectively [18–21]. Only one study showed patients of DAC could get longer survival from RP, especially for pure DAC, while the other three series indicated RT could improve the outcome of DAC in terms of biochemical recurrence. However, none of the four studies compared the two treatments directly with control of confounding due to the small sample sizes.

That RP was superior to RT in the primary management of DAC was a novel finding. Given the high possibility for DAC of extra-prostatic extension (ranging from 66.7% to 93.0%) and positive surgical margins (ranging from 31.9% to 47.0%) [25,26], RT has been considered as a better option [15]. However, we confirmed RP possessed better clinical outcomes than RT in DAC through various and robust

analyses, which calling for paying doctors' attention to RP in clinical management to DAC.

We additionally found that patients of DAC in the middle tertile of the age and with lower tertile of PSA level benefited the most from RP. The latter might be explained by the previous studies which indicated the PSA level began to rise when DAC became extra-prostatic extension [15,27], so the status of aggression might influence the survival outcomes, which need further studies. More solid studies were needed to verify this finding and to ensure the accurate cut-off.

There were several strengths that distinguish our work from previous researches. We made a direct comparison of RP and RT based on the large sample database. In addition, we used the most contemporary population and therefore the conclusion could be applicable to current clinical practice.

However, some limitations in this study required highlighting. First, the data gathered retrospectively might result in certain selection biases, which could not be overcome entirely through statistical analyses. Second, there was not a consensus on the definition of DAC, and high interobserver variability of DAC diagnosis was also reported [28], likely resulting in inaccurate assessment in our study. Third, DAC was diagnosed on biopsy in this study, which might lead to biases. Third, we merely included pure DAC, whereas DAC was more frequently mixed with AAC and the percentage of DAC relative to AAC might hold prognostic value [18,27]. More studies including pure and mixed form were needed. Fourth, our study was based on the SEER database and diagnoses on transurethral resection of the prostate (TURP), details in treatments, androgen deprivation therapy and comorbidities were not available.

5. Conclusions

Among patients with DAC, treatment with RP was associated with better survival outcomes in comparison with RT. Patients of DAC in the middle tertile of the age and with lower tertile of PSA level benefited the most from RP.

Author contributions

Study concept and design: Mengzhu Liu, Kun Jin, Shi Qiu, Xiaonan Zheng, Mingming Zhang, Wufeng Cai, Lu Yang, Qiang Wei.

Data acquisition: Mengzhu Liu, Kun Jin.

Data analysis: Mengzhu Liu, Kun Jin, Shi Qiu, Xiaonan Zheng.

Drafting of manuscript: Mengzhu Liu, Kun Jin, Shi Qiu, Xiaonan Zheng.

Chart making: Mingming Zhang, Wufeng Cai, Pengyong Xu.

Critical revision of the manuscript: Mengzhu Liu, Kun Jin, Shi Qiu, Pengyong Xu, Lu Yang, Qiang Wei.

Conflicts of interest

The authors have no conflict of interest to declare.

Acknowledgements

The authors acknowledge Ian Charles Tobias for reviewing the manuscript. This work was supported by the National Key Research and Development Program of China (Grant No. SQ2017YFC0908003), National Natural Science Foundation of China (Grant No.81702536, 81770756), the Sichuan Science and Technology Program (2017HH0063), China Postdoctoral Science Foundation (2017M612971), Post-Doctor Research Project, West China Hospital, Sichuan University (2018HXBH085), and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Z2018C01).

References

- [1] Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncol* 2017;3:524–48.
- [2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7–30.
- [3] Melicow MM, Pachter MR. Endometrial carcinoma of prostatic utricle (uterus masculinus). *Cancer* 1967;20:1715–22.
- [4] Marcus DM, Goodman M, Jani AB, Osunkoya AO, Rossi PJ. A comprehensive review of incidence and survival in patients with rare histological variants of prostate cancer in the United States from 1973 to 2008. *Prostate Cancer Prostatic Dis* 2012; 15:283–8.
- [5] Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs—Part B: prostate and bladder tumours. *Eur Urol* 2016;70:106–19.
- [6] Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71:618–29.
- [7] Meeks JJ, Zhao LC, Cashy J, Kundu S. Incidence and outcomes of ductal carcinoma of the prostate in the USA: analysis of data from the Surveillance, Epidemiology, and End Results program. *BJU Int* 2012;109:831–4.
- [8] Wu YP, Chen SH, Wang ST, Li XD, Hai C, Lin YZ, et al. Prognostic values of clinicopathological characteristics and survival outcomes in prostate infiltrating ductal carcinoma: a population-based study. *Oncotarget* 2017;8:29048–55.
- [9] Knipper S, Preisser F, Mazzone E, Mistretta FA, Tian Z, Briganti A, et al. Contemporary comparison of clinicopathologic characteristics and survival outcomes of prostate ductal carcinoma and acinar adenocarcinoma: a population-based study. *Clin Genitourin Canc* 2019;17:231–7.
- [10] Packiam VT, Patel SG, Pariser JJ, Richards KA, Weiner AB, Paner GP, et al. Contemporary population-based comparison of localized ductal adenocarcinoma and high-risk acinar adenocarcinoma of the prostate. *Urology* 2015;86:777–82.
- [11] Seipel AH, Delahunt B, Samarasinghe H, Egevad L. Ductal adenocarcinoma of the prostate: histogenesis, biology and clinicopathological features. *Pathology* 2016;48:398–405.
- [12] Epstein JI, Allsbrook Jr WC, Amin MB, Egevad LL, ISUP Grading Committee. The 2005 International Society of Urological

- Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol* 2005;29:1228–42.
- [13] Jeong SU, Kekatpure AK, Park JM, Han M, Hwang HS, Jeong HJ, et al. Diverse immunoprofile of ductal adenocarcinoma of the prostate with an emphasis on the prognostic factors. *J Pathol Transl Med* 2017;51:471–81.
- [14] Gillard M, Lack J, Pontier A, Gandla D, Hatcher D, Adam GS, et al. Integrative genomic analysis of coincident cancer foci implicates CTNNB1 and PTEN alterations in ductal prostate cancer. *Eur Urol Focus* 2019;5:433–42.
- [15] Bergamin S, Eade T, Kneebone A, Kench JG, Sved P, Biset JF, et al. Ductal carcinoma of the prostate: an uncommon entity with atypical behaviour. *Clin Oncol* 2019;31:108–14.
- [16] Sha JJ, Bo J, Pan JJ, Zhang LH, Xuan HQ, Chen W, et al. Ductal adenocarcinoma of the prostate: immunohistochemical findings and clinical significance. *Onco Targets Ther* 2013;6:1501–6.
- [17] Kan RW, Kan CF, Wong JH, Fu KK, Ng CF, Chan SW. Ductal adenocarcinoma of the prostate: a Hong Kong case series. *Int Urol Nephrol* 2014;46:2133–7.
- [18] Tu SM, Lopez A, Leibovici D, Bilen MA, Evliyaoglu F, Aparicio A, et al. Ductal adenocarcinoma of the prostate: clinical features and implications after local therapy. *Cancer* 2009;115:2872–80.
- [19] Orihuela E, Green JM. Ductal prostate cancer: contemporary management and outcomes. *Urol Oncol* 2008;26:368–71.
- [20] İğdem S, Spiegel DY, Efstathiou J, Miller RC, Poortmans PM, Koca S, et al. Prostatic duct adenocarcinoma: clinical characteristics, treatment options, and outcomes—a Rare Cancer Network study. *Onkologie* 2010;33:169–73.
- [21] Nakamura K, Terada N, Kobayashi T, Sugino Y, Yamasaki T, Matsui Y, et al. Clinical characteristics of prostate ductal adenocarcinoma in Kyoto University Hospital. *Hinyokika Kyo* 2015;61:487–91.
- [22] Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al. *AJCC cancer staging manual*. ed. 6. New York, NY: Springer Verlag; 2002. p. 301–47.
- [23] Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC cancer staging manual*. ed. 7. New York, NY: Springer Verlag; 2009. p. 457–68.
- [24] Benedetto U, Head SJ, Angelini GD, Blackstone EH. Statistical primer: propensity score matching and its alternatives. *Eur J Cardio Thorac Surg* 2018;53:1112–7.
- [25] Seipel AH, Wiklund F, Wiklund NP, Egevad L. Histopathological features of ductal adenocarcinoma of the prostate in 1,051 radical prostatectomy specimens. *Virchows Arch* 2013;462:429–36.
- [26] Christensen WN, Steinberg G, Walsh PC, Epstein JI. Prostatic duct adenocarcinoma. Findings at radical prostatectomy. *Cancer* 1991;67:2118–24.
- [27] Samaratunga H, Duffy D, Yaxley J, Delahunt B. Any proportion of ductal adenocarcinoma in radical prostatectomy specimens predicts extraprostatic extension. *Hum Pathol* 2010;41:281–5.
- [28] Seipel AH, Delahunt B, Samaratunga H, Amin M, Barton J, Berney DM, et al. Diagnostic criteria for ductal adenocarcinoma of the prostate: interobserver variability among 20 expert uropathologists. *Histopathology* 2014;65:216–27.