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Original Article

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Cancer-Specific Mortality among Korean Men with Localized or Locally Advanced Prostate Cancer Treated with Radical Prostatectomy Versus Radiotherapy: A Multi-center Study Using Propensity Scoring and Competing Risk Regression Analyses

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Purpose

Studies comparing radical prostatectomy (RP) outcomes with those of radiotherapy with or without androgen deprivation therapy (RT±ADT) for prostate cancer (PCa) have yielded conflicting results. Therefore, we used propensity score-matched analysis and competing risk regression analysis to compare cancer-specific mortality (CSM) and other-cause mortality (OCM) between these two treatments.

Materials and Methods

The multi-center, Severance Urological Oncology Group registry was utilized to identify 3,028 patients with clinically localized or locally advanced PCa treated by RP (n=2,521) or RT±ADT (n=507) between 2000 and 2016. RT±ADT cases (n=339) were matched with an equal number of RP cases by propensity scoring based on age, preoperative prostate-specific antigen, clinical tumor stage, biopsy Gleason score, and Charlson Comorbidity Index (CCI). CSM and OCM were co-primary endpoints.

Results

Median follow-up was 65.0 months. Five-year overall survival rates for patients treated with RP and RT±ADT were 94.7% and 92.0%, respectively (p=0.105). Cumulative incidence estimates revealed comparable CSM rates following both treatments within all National Comprehensive Cancer Network risk groups. Gleason score ≥ 8 was associated with higher risk of CSM (p=0.009). OCM rates were comparable between both groups in the low- and intermediate-risk categories (p=0.354 and p=0.643, respectively). For high-risk patients, RT±ADT resulted in higher OCM rates than RP (p=0.011). Predictors of OCM were age ≥ 75 years (p=0.002) and CCI ≥ 2 (p < 0.001).

Conclusion

RP and RT±ADT provide comparable CSM outcomes in patients with localized or locally advanced PCa. The risk of OCM may be higher for older high-risk patients with significant comorbidities.

Key words
Prostatic neoplasms, Prostatectomy, Radiotherapy, Treatment outcome

Introduction

The management of clinically localized and locally advanced prostate cancer (PCa) is controversial. Contemporary guidelines recommend that treatment decisions should be made on the basis of tumor features, baseline prostate-specific antigen (PSA) levels, patient age, comorbidity, life expectancy, and quality of life [1,2]. In general, radical prostatectomy (RP) and radiation therapy with or without androgen deprivation therapy (RT±ADT) are viable treatment options for patients with a life expectancy of more than 10 years [2].

Several studies have investigated the oncological outcomes of RP and RT±ADT in order to identify the population that would most benefit from a specific treatment and to determine which treatment is superior in terms of improving the length or quality of life [3-8]. However, most of these studies were retrospective in nature, and were limited by methodological biases arising from differences in pretreatment patient and cancer risk features between treatment cohorts [9,10]. Therefore, their results were inconclusive and yielded only weak evidence regarding which treatment was superior in terms of oncological outcome.

A randomized controlled trial is the ideal approach for comparing competing treatment modalities [11,12]. However, treatment options for PCa vary and decisions are largely based on patient preference and physicians' discretion. Compared to candidates for RP, patients who are offered RT generally tend to be older, have higher comorbidity scores, and have cancer-related risk features that are more aggressive, making a randomized trial impractical [9,13]. For instance, two large United States randomized trials comparing RP and RT were closed early because of poor accrual [14]. A feasible alternative is a propensity-score matched analysis, in which the possibility of patient selection bias can be minimized by adjusting for multiple preoperative confounders that may affect survival outcome, such as patient age, disease risk, and comorbidity [15]. The long lifespan of patients with subclinical PCa presents another hurdle in addressing the effect of a specific treatment on clinically relevant endpoints that truly represent the effect of a specific treatment, such as cancer-specific mortality (CSM) and other-cause mortality (OCM). Herein, a competing risks regression analysis can be used to better understand the magnitude and timeline in which a specific treatment might be expected to improve these survival endpoints.

To address these issues, we performed a propensity score-matched analysis followed by competing risk regression analyses to compare CSM and OCM outcomes between RP and RT±ADT in a multi-center cohort of Korean patients with localized or locally advanced PCa. We further stratified our analyses according to the National Comprehensive Cancer Network (NCCN) PCa risk category so that our results could aid clinical decision making.

Materials and Methods

1. Study population and data collection

A total of 3,082 consecutive Korean patients with localized or locally advanced PCa treated with curative intent were selected from the multi-center, Severance Urological Oncology Group PCa registry. Of these, 2,521 patients (81.8%) underwent RP and 561 patients (18.2%) received RT±ADT between 2000 and 2016. The decision to use RP or RT±ADT for treatment was based on surgeons' discretion and on patients' preference. Ninety-four patients (3.0%) with incomplete clinical information, 201 patients (6.5%) who were lost to follow-up, and 107 patients (3.5%) for both reasons were excluded from propensity-score calculation. This study was approved by the institutional ethics committee after review of the protocol and procedures employed (2014-0091-004).

2. Radical prostatectomy

RP was recommended for patients who either desired surgical treatment or were determined to be reasonable surgical candidates because of otherwise favorable clinical characteristics. Surgery was performed by the retropubic or robotic approach, with the extent of pelvic lymph node dissection being based upon the risk category of the patient.

3. Radiation therapy

Radio-oncologists of each participating institution confirmed that conventional or hypo-fractionated external beam RT was delivered to the prostate with pre-defined margins according to the guidelines of the European Organization for Research and Treatment of Cancer [16]. At Gangnam and Shinchon Severance Hospitals, RT consisted of 3D conformal radiation therapy (3DCRT) from 2000 to 2007 and intensity modulated external beam RT (IMRT) from 2007 to 2016. The median RT dose at Severance Hospitals was 7,000 cGy (interquartile range [IQR], 7,000 to 7,000 cGy). At Hallym University College Hospital, RT consisted of 3DCRT from 2000 to 2001 and IMRT from 2001 to 2016. The median RT dose at Hallym University College Hospital was 8,000 cGy (IQR, 8,000 to 8,000 cGy). At Ajou University Hospital, RT consisted of 3DCRT from 2000 to 2009 and IMRT from 2009 to 2016. The median RT dose at Ajou University Hospital was

Table 1. Clinicopathological characteristics of patients, by initial treatment modality

Characteristic	RP (n=339)	RT±ADT (n=339)	p-value
Propensity matched variable			
Age (yr)	70.0 (66.0-73.0)	70.1 (66.0-74.0)	0.629
PSA (ng/mL)	10.4 (6.7-20.7)	10.7 (7.0-21.5)	0.814
Biopsy Gleason score (%)			
≤ 6	78 (23.0)	78 (23.0)	> 0.99
7	133 (39.2)	133 (39.2)	
8-9	128 (37.8)	128 (37.8)	
Clinical T stage (%)			
cT1	79 (23.3)	79 (23.3)	> 0.99
cT2	140 (41.3)	140 (41.3)	
cT3	99 (29.2)	99 (29.2)	
cT4	21 (6.2)	21 (6.2)	
CCI			
0	224 (66.1)	224 (66.1)	> 0.99
1	82 (24.2)	82 (24.2)	
≥ 2	33 (9.7)	33 (9.7)	
Unmatched variable			
Clinical N stage (%)			
N0	322 (95.0)	322 (95.0)	> 0.99
N1	17 (5.0)	17 (5.0)	
Clinical M stage (%)			
M0	339 (100)	339 (100)	NS
M1	0	0	
Body mass index (kg/m^2)	23.7 (22.3-25.5)	23.6 (21.7-25.6)	0.948
NCCN risk criteria			
Low	23 (6.8)	22 (6.5)	0.985
Intermediate	107 (31.9)	108 (32.2)	
High	209 (61.3)	209 (61.3)	
Total follow-up period (mo)	69.0 (42.7-94.0)	60.5 (39.0-98.0)	0.789

Values are presented as median (interquartile range) and number (%). RP, radical prostatectomy; RT±ADT, radiotherapy with or without androgen deprivation therapy; PSA, prostate-specific antigen; CCI, Charlson comorbidity index; NS, not significant; NCCN, National Comprehensive Cancer Network.

7,400 cGy (IQR, 7,010 to 7,400 cGy). The complete conversion from 3DCRT to IMRT at all participating institutions took place in 2011 along with the National Health Insurance Service reimbursement coverage. In overall, 216 (63.7%) and 123 (36.3%) patients received of 3DCRT and IMRT, respectively. The median total radiation dose was 70 Gy (IQR, 70 to 74 Gy) in 33.5 fractions (IQR, 28 to 37 fractions), in which 295 patients (87.0%) received greater than 7,600 cGy.

Pelvic lymph nodes were included if the patient had regional lymphadenopathies. Neoadjuvant, concomitant, and/or adjuvant ADT was performed in 13/22 (59.1%), 69/108 (63.9%), and 186/209 (88.9%) of low-, intermediate-, and high-risk patients, respectively.

4. Study endpoints

CSM and OCM were the co-primary endpoints. For all patients, the status of survival and cause of death were investigated using institutional electronic medical records, the National Cancer Registry Database, or the Social Security Death Index. Death was attributed to PCa if evidence of progressive metastatic castration-resistant PCa (CRPC) was present, PCa was listed on the death certificate as the cause of death, or if the patient died of complications of PCa treatment. Secondary endpoints were biochemical recurrence-free survival (BCRFS), adjuvant therapy following recurrence, metastasis-free survival, and progression to CRPC-free survival. All patients received standard care according to contemporary guidelines until death or last follow-up.

Table 2. Causes of death and 5-year survival rates stratified by risk category and initial treatment modality

Variable	RP (n=339)	RT±ADT (n=339)	p-value
Deaths, n (%)	29 (8.6)	46 (13.6)	0.038
PCa	6 (1.7)	4 (1.2)	0.530
Other cause	23 (6.8)	42 (12.4)	0.013
Second primary malignancy	7 (2.1)	13 (3.8)	0.758
Cardiopulmonary disease	3 (0.9)	7 (2.1)	0.645
Unknown	13 (3.8)	22 (6.5)	0.532
5-Year survival rate (%)			
Cancer-specific	98.8	99.5	0.576
Low risk	100	100	NS
Intermediate risk	100	100	0.994
High risk	98	99.2	0.399
Other-cause	95.3	93.0	0.051
Low risk	100	100	NS
Intermediate risk	94.2	90.5	0.863
High risk	95.2	92.9	0.011
Overall	94.7	92.0	0.105
Low risk	100	100	NS
Intermediate risk	94.2	90.5	0.871
High risk	93.3	92.1	0.047

RP, radical prostatectomy; RT±ADT, radiotherapy with or without androgen deprivation therapy; PCa, prostate cancer; NS, not significant.

Table 3. Oncological outcomes, by initial treatment modality

Variable	RP (n=339)	RT±ADT (n=339)	p-value
BCR			
No. (%)	108 (31.9)	57 (16.8)	< 0.001
Time to BCR (mo)	17.0 (7.0-34.5)	40.0 (15.0-57.5)	< 0.001
5-Year BCRFS (%)	3.7	22.8	< 0.001
Adjuvant therapy following BCR			
Observation	16 (4.7)	11 (3.2)	0.103
Salvage RT	18 (5.3)	2 (0.6)	
ADT	44 (13.0)	40 (11.8)	
Salvage RT plus ADT	30 (8.8)	4 (1.2)	
CRPC (%)			
No. (%)	16 (4.7)	14 (4.1)	0.721
Time to CRPC progression (mo)	35.5 (22.5-56.8)	60.5 (52.3-70.3)	0.013
CRPC progression-free survival (%)	18.8	42.9	0.071
Chemotherapy	7 (2.1)	9 (2.7)	0.603
Metastasis			
No. (%)	12 (3.5)	12 (3.5)	> 0.99
Time to metastasis (mo)	45.0 (26.0-71.3)	54.5 (24.5-68.0)	0.839
Metastasis-free survival rate (%)	33.3	41.7	0.778

Values are presented as number (%) or median (interquartile range), unless otherwise indicated. RP, radical prostatectomy; RT±ADT, radiotherapy with or without androgen deprivation therapy; BCR, biochemical recurrence; BCRFS, BCR-free survival; CRPC, castration-resistant prostate cancer.

5. Statistical analysis

The chi-square test and ANOVA were used to compare two or more variables, and the Mann-Whitney U test was used for the analysis of continuous variables. To address imbalances in the distribution of covariates among treatment groups, we calculated propensity scores for each subject by using multivariable logistic regression based on patient age, preoperative PSA, biopsy Gleason score, clinical tumor stage, and Charlson Comorbidity Index (CCI). Fine and Gray competing risk regression analysis was used to evaluate the association of clinical covariates with CSM and OCM. Survival endpoints were estimated and compared using the Kaplan-Meier method and a log-rank test. Statistical analyses were performed using R ver. 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, with a statistical significance set at $p < 0.05$.

Results

1. Patient characteristics

Propensity matching yielded 339 RT±ADT cases matched to an equal number of RP cases. Clinicopathological characteristics of the two groups for matched and unmatched variables are presented in Table 1. Variables used for propensity-score matching did not differ significantly between the two groups; this finding was confirmed by the comparable distribution of the NCCN risk criteria subgroups between the two groups. The median follow-up period of the overall cohort was 65.0 months (IQR, 40.0 to 95.0 months), with no significant differences between the two treatment groups (p=0.789).

2. Causes of death

The causes of death according to treatment modality are presented in Table 2. The causes of death were attributed to PCa and other causes in 10/678 (1.5%) and 65/678 (9.6%) patients, respectively. The overall mortality (OM) rate in the RT±ADT group was significantly higher than that in the RP group (13.6% vs. 8.6%, p=0.038) because of a higher rate of OCM in the RT±ADT group (p=0.013). The most common

Table 4. Pretreatment predictors of cancer-specific mortality in patients with clinically localized or locally advanced prostate cancer

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)				
< 70	1 (reference)		-	
≥ 70	0.288 (0.060-1.391)	0.121	-	-
Body mass index	0.953 (0.753-1.206)	0.687	-	-
Pretreatment PSA	1.012 (0.973-1.054)	0.545	-	-
Biopsy Gleason score				
≤ 7	1 (reference)		1 (reference)	
≥ 8	7.974 (1.649-38.56)	0.010	8.107 (1.676-39.21)	0.009
Clinical T stage				
≤ T2	1 (reference)		-	
≥ T3	1.311 (0.323-5.316)	0.704	-	-
CCI				
≤ 1	1 (reference)		-	
≥ 2	2.688 (0.719-10.05)	0.142	-	-
Initial treatment modality				
RP	1 (reference)		-	
RT±ADT	0.686 (0.182-2.588)	0.578	-	-

HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; CCI, Charlson comorbidity index; RP, radical prostatectomy; RT±ADT, radiotherapy with or without androgen deprivation therapy.

Table 5. Pretreatment predictors of other-cause mortality in patients with clinically localized or locally advanced prostate cancer

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)				
< 70	1 (reference)		1 (reference)	
≥ 70	1.684 (0.992-2.860)	0.053	1.894 (1.105-3.249)	0.020
Body mass index	0.895 (0.816-0.982)	0.019	0.924 (0.842-1.013)	0.091
Pretreatment PSA	1.010 (0.995-1.025)	0.207	-	-
Biopsy Gleason score				
≤ 7	1 (reference)		-	
≥ 8	0.976 (0.572-1.665)	0.929	-	-
Clinical T stage				
≤ T2	1 (reference)		-	
≥ T3	1.222 (0.718-2.078)	0.460	-	-
CCI				
≤ 1	1 (reference)		1 (reference)	
≥ 2	2.837 (1.532-5.252)	0.001	2.853 (1.536-5.301)	0.001
Initial treatment modality				
RP	1 (reference)		1 (reference)	
RT±ADT	1.684 (0.992-2.860)	0.053	1.672 (0.978-2.858)	0.061

HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; CCI, Charlson comorbidity index; RP, radical prostatectomy; RT±ADT, radiotherapy with or without androgen deprivation therapy.

cause of OCM was second primary malignancy, followed by cardiopulmonary disease.

3. Survival outcome

Cumulative incidence estimates of CSM and OCM according to treatment modality are presented in Table 2. Both treatments resulted in comparable CSM in all NCCN risk groups (p=0.576). However, the OCM rate in the RT±ADT group was marginally higher than that in the RP group (p=0.051). This could be attributed to a significantly higher rate of OCM in high-risk patients who received RT±ADT (p=0.011). Accordingly, a higher rate of OM was observed in high-risk patients in the RT±ADT group (p=0.047).

Outcomes of secondary study endpoints are described in Table 3. Patients who received RT±ADT had higher BCRFS rates than those who underwent RP (p < 0.001). However, this did not translate into superior oncological outcomes in terms of rates of adjuvant therapy, CRPC progression-free survival, or metastasis-free survival.

4. Predictors of cancer-specific mortality and OCM

A multivariate competing risks regression model was used to identify pretreatment predictors of CSM and OCM. Gleason score ≥ 8 was significantly associated with a higher risk of CSM (Table 4). Age ≥ 75 years and CCI ≥ 2 were independent predictors of a higher risk of OCM (Table 5).

Discussion

Our results compare favorably with those of two randomized trials reported in the literature, which compared survival outcomes of RP with those of RT [17,18]. Akakura et al. [17] reported no significant differences in CSM or overall survival according to treatment modality in patients with T2b-3N0M0 PCa. The recently published ProtecT study also revealed no difference in CSM between the RP and RT groups [18]. However, the limitation of this study was that men who received RP were younger and had lower PSA compared to the RT group. Moreover, CCI was not accounted for. In contrast, several observational studies have reported that OM, CSM, and/or metastatic progression associated with RP are better than those associated with RT, which contradicts the findings of the present study [5-8, 19,20]. Albertsen et al. [7] reported that the CSM associated with RP was lower than that associated with RT during a

13-year follow-up. Although PCa risk and comorbidity were adjusted for, their study did not reflect the current standard of care because it was conducted during the early PSA era [7]. Tewari et al. [19] used propensity risk scoring and reported that CSM and OM in patients with high grade PCa treated with RP were lower than those in patients treated with EBRT. Zelefsky et al. [6] and Merglen et al. [5] reported that CSM in men treated with RT was higher than that in men who underwent RP. However, patients treated with RT tended to be older, with higher PSA and Gleason scores, precluding a meaningful comparison. Furthermore, no adjustments were made for comorbidity [5,6]. The superiority of RP observed in these studies may be attributed to the improved ability to interpret early post-treatment PSA changes and to deliver timely and effective adjuvant therapy by enabling a pathologic assessment of the primary tumor [20]. Moreover, patients for whom RP was deemed appropriate may have been better screened for second primary malignancies or comorbidities such as cardiopulmonary disease, which contributes to OCM. Nevertheless, the most reliable quantitative exploratory analyses, including the aforementioned observational studies, concluded that the differences in 10-year CSM are less than 1%, and that the unadjusted survival curves and unaccounted-for confounders in these studies preclude a definitive conclusion that RP results in superior survival compared to RT±ADT [21].

Patients treated with RT±ADT exhibited higher BCRFS rates than those who underwent RP. However, this finding did not translate into improvement in consequent oncological outcomes during our observational period. The high rate of ADT administration in our patients treated with RT may have contributed to this result. Overall, 78% of the patients who received RT in the current analysis also received neoadjuvant, concomitant, and/or adjuvant ADT. This proportion is markedly higher than the 51% to 56% reported in previous studies [6]. This may be, in part, due to the higher proportion of high-risk patients in our cohort who received ADT, a practice based on evidence that RT with ADT results in better survival than that for RT alone [2]. Indeed, the use of ADT in the RT group is a potential confounding factor for comparisons between RP and RT. Nevertheless, we did not adjust for the use of ADT in the present study for several reasons. First, the use of ADT is associated with disease risk, such that higher risk patients are more likely to receive ADT. The impact of ADT is usually reflected in the risk adjustment. In previous studies using models adjusted for risk, ADT was not proven to be an independent predictor [13,22]. Second, BCRFS which may be affected by the use of ADT, was not the primary endpoint of our study. Biochemical recurrence is known to antedate clinical progression by a median of 5 to 7 years [23]. However, considering the protracted natural history of PCa, biochemical recurrence is an imprecise proxy for CSM or OM.

A noteworthy finding in the present study was that the OCM rate in patients who received RT±ADT was higher than that in patients who underwent RP. Although propensity-score matching was utilized to adjust for confounding comorbidities that might have increased OCM, unobserved and unaccounted disparities between the groups may have existed. CCI has been suggested to predict the risk of OCM unreliably, and adequate adjustments are best applied when populations are more homogeneous, such as those with a CCI of 0 [8,21]. To account for this issue, we compared survival outcomes within patients with a CCI of 0. Interestingly, no differences in OCM were observed within this subgroup (data not shown). This observation implies that CCI may fail to ensure adequate adjustments for OCM in patients with at least one or more significant comorbidity. The administration of ADT is another potential risk factor contributing to cardiopulmonary disease as the cause of OCM. Studies have suggested increased risk of cardiopulmonary disease with long term ADT [24,25]. However at the same time, there equal levels of evidences that oppose this observation [26,27]. The jury is still out whether lower levels of testosterone has caused more cardiopulmonary disease and have contributed to higher OCM rates in our patients who received RT+ADT.

The present study has a few noteworthy limitations. (1) Although we utilized a propensity-score matched analysis, unobserved and unaccounted disparities between cohorts may have existed, as evidenced by our subset analysis of patients without any comorbidities. (2) The aim of our study was to provide a guide to aid clinical decision making at diagnosis. Thus, no adjustments were made for confounders that may contribute to survival following initial treatment, namely, salvage therapy, duration of ADT, or administration of chemotherapy or androgen receptor-targeted therapy. Although studies comparing RP and RT have reported that adjustment for salvage therapy had no impact on survival outcomes [6], it is difficult to preclude the effect of salvage therapy considering multidisciplinary treatment strategies and the prolonged natural history of PCa. (3) Treatments are constantly evolving and advances in radiation delivery may have some impact of survival. Randomized trials have demonstrated dose-escalated RTx (74-90 Gy) to improve BCRFS compared to conventional RTx (64-70 Gy) [28]. However, we did not account for this confounder because none have demonstrated improvement in CSM or OM with higher doses or variations in technique, such as intensity modulation [29,30]. Moreover, no differences in BCRFS or CSM were noted according to radiation dose subgroups (data not shown). (4) A limited number of cases of CSM occurred in the low-risk group, which limited our ability to draw statistically significant conclusions. (5) The follow-up period was relatively short compared to previous similar studies.

Although higher BCRFS rates observed in patients treated with RT±ADT did not translate into superior oncological endpoints, a longer observational period would be needed for a meaningful comparison of overall survival. (6) We did not investigate the differences in adverse events and quality of life, which are meaningful clinical endpoints.

RP and RT±ADT yield comparable CSM outcomes in Korean patients with localized or locally advanced PCa. Our results imply that the risk of OCM may be higher for older high-risk patients with significant comorbidities. Future investigations focusing on long-term cancer control as well as functional and patient satisfaction outcomes will be necessary for a more definitive conclusion.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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