Comparative effectiveness of surgery and radiotherapy for survival of patients with clinically localized prostate cancer: A population-based coarsened exact matching retrospective cohort study

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Abstract. Radical prostatectomy and radiotherapy are currently the main treatment options for localized prostate cancer. However, no large cohort study comparing surgery and radiation has been performed in Japan or Asia. The objective of the current study was to compare the survival outcomes of patients with clinically localized prostate cancer and in elderly and young patients receiving surgery and radiotherapy. The survival outcomes of patients with localized prostate cancer (age at diagnosis ≤79 years, clinical T1-3) initially treated with surgery or radiotherapy were retrospectively analyzed. Data were collected from the population-based cancer registry of the Kanagawa Prefecture, Japan. A 1:1 coarsened exact matching of age at diagnosis, clinical T stage and cancer differentiation was performed between the two treatment groups. Patients were also categorized into two subgroups by age using a cutoff of 70 years for analysis. The cohort comprised 4,810 patients aged 50-79 years. No significant difference in cancer-specific survival (CSS) was observed between the two groups (P=0.612). However, the surgery group had significantly better overall survival (OS; P=0.004). When stratified for age, similar tendencies were observed in the elderly group (aged 70-79 years; CSS, P=0.961 and OS, P=0.007). No significant difference in either CSS or OS was identified in the younger group (P=0.550 and P=0.408, respectively). Intrinsic deaths were more likely to occur in elderly patients treated with radiotherapy than those undergoing surgery (69.3 vs. 78.2%; P=0.128). The results indicated that surgery provided significantly better OS than radiotherapy, particularly among the elderly. However, no significant difference was observed in CSS. These results should be interpreted with caution, given that some important factors were unavailable in the present study, such as prostate-specific antigen values and Gleason scores. Prospective trials evaluating these therapies are warranted.

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Abbreviations: CSS, cancer-specific survival; OS, overall survival; PSA, prostate-specific antigen; ProtecT, Prostate Testing for Cancer and Treatment; HR, hazard ratio; CI, confidence interval; IMRT, intensity-modulated radiotherapy

Key words: prostate cancer, surgery, radiotherapy, overall survival, cancer-specific survival, exact matching

Introduction

Prostate cancer is now one of the most commonly diagnosed cancers, with more than 1,100,000 newly diagnosed cases worldwide in 2012 (1), and the incidence of prostate cancer has been particularly increasing in northeast Asian countries (2). The increase in prostate cancer incidence primarily results from early diagnosis following the widespread use of prostate-specific antigen (PSA) screening. This indicates that the management of localized prostate cancer plays an important role in its treatment.

The effectiveness of surgery, radiotherapy, and active monitoring for localized prostate cancer remains controversial. The first randomized trial, the Prostate Testing for Cancer and Treatment (ProtecT) trial, indicated no significant differences in cancer-specific survival (CSS) and overall survival (OS) among the three treatment modalities (3). However, the prostate cancer cases in this trial mostly had a Gleason score of 6 (77%), cT1c (21%), and PSA <10 μg/l (median PSA, 5.8 μg/l) (4). Given that most patients had low-risk cancer, the survival outcomes differed from those of previous studies that used real-world data, which generally showed a survival benefit in patients with high-risk prostate cancer (5-10). Furthermore, the ProtecT trial included only patients aged 50-69 years, whereas prostate cancer is commonly detected in the elderly (those aged 70 years or older). The number of elderly cancer patients has been increasing (11). Japan is anticipated to become a super-aging society by 2030, with one in every three people being 65+ years and one in five people being 75+ years (12). Therefore, treatments for elderly patients will be crucial, and clinical trials or large cohort studies for survival outcomes of elderly patients are needed for treatment selection.

Previous studies indicated that hormonal therapy is relatively more efficacious and safer in Japanese men than in Caucasian men (13,14). Nevertheless, no large cohort study on Japanese or Asian patients has ever investigated survival after local treatments.

For the reasons above, the present study was carried out with two objectives: i) To compare the efficacy between surgery and radiotherapy for clinically localized prostate cancer using data from a Japanese regional population-based prostate cancer database; and ii) to compare the efficacy of these two treatment modalities between elderly and younger patients. In order to fulfill these objectives, we conducted a coarsened exact matching of cancer features, and patients were also categorized by age using a cutoff point of 70 years.

Patients and methods

Study population and study design. In this study, we accessed the data of 58,894 patients diagnosed with prostate cancer between 1970 and 2014 from the population-based cancer registry of the Kanagawa Prefecture, Japan. The inclusion criteria were localized prostate cancer (cT1-3N0M0), adenocarcinoma, age 50-79 years, an observation period of ≥2 years, and either surgery or radiotherapy as the main treatment. Patients with missing data were excluded. For those treated with both treatment modalities, surgery was considered the main treatment. The reason for this is that salvage radiotherapy is common in patients with prostate cancer recurrence after surgery, whereas salvage prostatectomy after radiotherapy is rare (15). As we used secondary data, the requirement to obtain informed consent was waived.

The primary endpoints of this study were CSS and OS. The patients were also categorized by the age cutoff of 70 years (i.e., 50-69 vs. 70-79 years), and the effectiveness of treatment in either group was analyzed in terms of survival outcomes.

This study was conducted in accordance with the ethical standards of the Helsinki Declaration and was approved by the institutional review board of the Kanagawa Cancer Center.

Data source. Data were collected from a population-based regional cancer registry of the Kanagawa Prefecture. The registry stores medical data obtained from hospitals and survival information from the regional public health center. The primary information includes the date of birth, age at cancer diagnosis, cancer differentiation (well, moderate, poor and undifferentiated), clinical and pathological stages, diagnostic methods, the main treatment modality (surgery, laparoscopic surgery, endoscopic surgery, radiotherapy, hormonal therapy, chemotherapy and immunotherapy), initial symptoms, the hospital where the patient was treated, cause of death, and date of death or the latest date of confirmed survival. However, no information on PSA was provided.

Statistical analysis. Cancer stages were classified using the 2017 TNM classification, and survival time was calculated from the date of diagnosis. To analyze the patients' characteristics, we used the Mann-Whitney U test for continuous variables and Pearson's chi-squared tests for categorical variables. Continuous measurements were used for analysis of age at diagnosis. To precisely assess treatment efficacy, a 1:1 coarsened exact matching of age at diagnosis, clinical T stage, and cancer differentiation was made between the surgery and radiotherapy groups. Exact matching was conducted via propensity score matching with a caliper width of 0. The covariate balance between the two groups was assessed using the Mann-Whitney U test and Pearson's Chi-squared tests.

The Kaplan-Meier method and univariate comparisons using log-rank test and unadjusted Cox models were performed to estimate CSS and OS. A two-tailed P-value of <0.05 was considered statistically significant. All statistical analyses were carried out with the IBM SPSS Statistics v25 (IBM Corp.). In addition, interaction in the forest plot study was analyzed using the statistical software 'EZR' (version _1.36_; Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (version 3.4.1; The R Foundation for Statistical Computing, Vienna, Austria) (16).

Results

Patient characteristics. The cohort included 6,805 patients, of whom 3,610 underwent surgery and 3,195 received radiotherapy as the main treatment. After exact matching for age, clinical T stage, and cancer differentiation, we analyzed data of 4,810 patients (Table I), 2,405 of whom underwent surgery as the main treatment and 2,405 who received radiotherapy. The median observation period was 6.3 years (range, 2.0-18.7 years). Out of 4,810 patients, 43 (0.9%) and 305 (6.3%) patients died of prostate cancer and other causes, respectively.

Survival based on treatment modality. In the surgery group, prostate cancer was the main cause of death in 23 patients (1.0%), whereas 142 patients died of other causes (5.9%). The 5- and 10-year CSS were 99.6 and 98.4%, respectively, and the 5- and 10-year OS were 96.8 and 89.6%, respectively. In the radiotherapy group, there were 20 deaths due to prostate cancer (0.8%), compared to 163 patients (6.8%) who died of other causes. The 5-year CSS was 99.8%, and the 10-year CSS was 98.1%. The 5- and 10-year OS were 97.2 and 84.3%, respectively.

The Kaplan-Meier curves are shown in Fig. 1. There was no significant difference in CSS between the two groups [surgery vs. radiotherapy: Hazard ratio (HR), 0.852; 95% confidence interval (CI) 0.459-1.582; P=0.612]; however, the surgery group had significantly better OS than the radiotherapy group (HR, 0.732; 95% CI 0.591-0.905; P=0.004).

Subgroup analyses showed no significant interactions in terms of CSS (Fig. 2A). With respect to OS, the magnitude of the association between surgery and improved survival was greater for patients diagnosed through 2009 (vs. 2010 onwards; P-value for interaction <0.001; Fig. 2B).

Comparison of efficacy between elderly and younger patients. For the secondary goal, we categorized the adjusted cohort into two groups by age at a cutoff of 70 years. The elderly group (aged

Table I. Characteristics of the entire cohort and after matching age, clinical T stage and differentiation.

	Entire cohort				After matching			
Characteristics	Total (n=6,805)	Surgery (n=3,610)	Radiation (n=3,195)	P-value	Total (n=4,810)	Surgery (n=2,405)	Radiation (n=2,405)	P-value
Age, median years (range)	69 (50-79)	68 (50-79)	71 (50-79)	<0.001[a]	69 (50-79)	69 (50-79)	69 (50-79)	>0.999[a]
Age				<0.001[b]				>0.999[b]
50-69, n (%)	3,519 (51.7)	1,487 (41.2)	1,396 (43.7)		2,524 (52.5)	1,262 (52.5)	1,262 (52.5)	
70-79, n (%)	3,286 (48.3)	2,123 (58.8)	1,799 (56.3)		2,286 (47.5)	1,143 (47.5)	1,143 (47.5)	
Clinical T stage, n (%)				<0.001[b]				>0.999[b]
T1	3,083 (45.3)	1,653 (45.8)	1,430 (44.8)		2,386 (49.6)	1,193 (49.6)	1,193 (49.6)	
T2	3,014 (44.3)	1,727 (47.8)	1,287 (40.3)		2,040 (42.4)	1,020 (42.4)	1,020 (42.4)	
T3	708 (10.4)	230 (6.4)	478 (15.0)		384 (8.0)	192 (8.0)	192 (8.0)	
Differentiation, n (%)				0.047[b]				>0.999[b]
Well	948 (13.9)	481 (13.3)	467 (14.6)		738 (15.3)	369 (15.3)	369 (15.3)	
Moderate	2,662 (39.1)	1,459 (40.4)	1,203 (37.7)		2,024 (42.1)	1,012 (42.1)	1,012 (42.1)	
Poor/undifferentiated	3,195 (47.0)	1,670 (46.3)	1,525 (47.7)		2,048 (42.6)	1,024 (42.6)	1,024 (42.6)	
Date of diagnosis				<0.001[b]				<0.001[b]
<2009	1,965 (28.9)	1,127(31.2)	838 (26.2)		1,766 (36.7)	1,029 (42.8)	737 (30.6)	
>2010	4,840 (71.1)	2,483 (68.8)	2,357 (73.8)		3,044 (63.3)	1,376 (57.2)	1,668 (69.4)	

[a]P-values were determined using a Wilcoxon-Mann-Whitney test; [b]P-values were determined using a Pearson's Chi-squared test.

Table II. Patient characteristics in the elderly and younger group.

	Elderly group				Younger group			
Characteristics	Total (n=2,286)	Surgery (n=1,143)	Radiation (n=1,143)	P-value	Total (n=2,524)	Surgery (n=1,262)	Radiation (n=1,262)	P-value
Age, median years (range)	73 (70-79)	73 (70-79)	73 (70-79)	1.000[a]	65 (50-69)	65 (50-69)	65 (50-69)	>0.999[a]
Clinical T stage, n (%)				1.000[b]				>0.999[b]
T1	1,074 (47.0)	537 (47.0)	537 (47.0)		1,312 (52.0)	656 (52.0)	656 (52.0)	
T2	1,050 (45.9)	525 (45.9)	525 (45.9)		990 (39.2)	495 (39.2)	495 (39.2)	
T3	162 (7.1)	81 (7.1)	81 (7.1)		222 (8.8)	111 (8.8)	111 (8.8)	
Differentiation, n (%)				1.000[b]				>0.999[b]
Well	298 (13.0)	149 (13.0)	149 (13.0)		440 (17.4)	220 (17.4)	220 (17.4)	
Moderate	958 (41.9)	479 (41.9)	479 (41.9)		1,066 (42.2)	533 (42.2)	533 (42.2)	
Poor/undifferentiated	1,030 (45.1)	515 (45.1)	515 (45.1)		1,018 (40.3)	509 (40.3)	509 (40.3)	
Date of diagnosis				0.024[b]				<0.001[b]
<2009	779 (34.1)	415 (36.3)	364 (31.8)		987 (39.1)	614 (48.7)	373 (29.6)	
>2010	1,507 (65.9)	728 (63.7)	779 (68.2)		1,537 (60.9)	648 (51.3)	889 (70.4)	

[a]P-values were determined using a Wilcoxon-Mann-Whitney test; [b]P-values were determined using a Pearson's Chi-squared test.

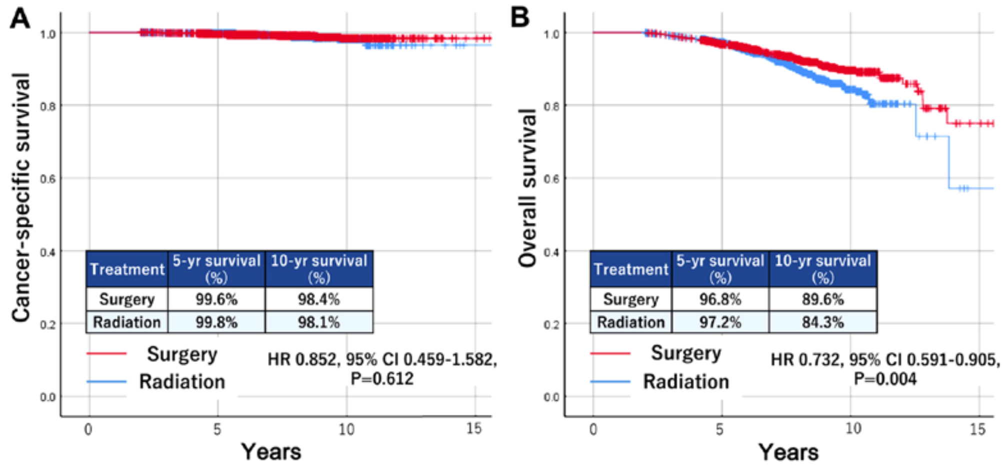

Figure 1. Kaplan-Meier curves for survival after exact matching stratified by treatment type. Kaplan-Meier curves for (A) cancer-specific survival and (B) overall survival stratified by treatment type. HR, hazard ratio; CI, confidence interval.

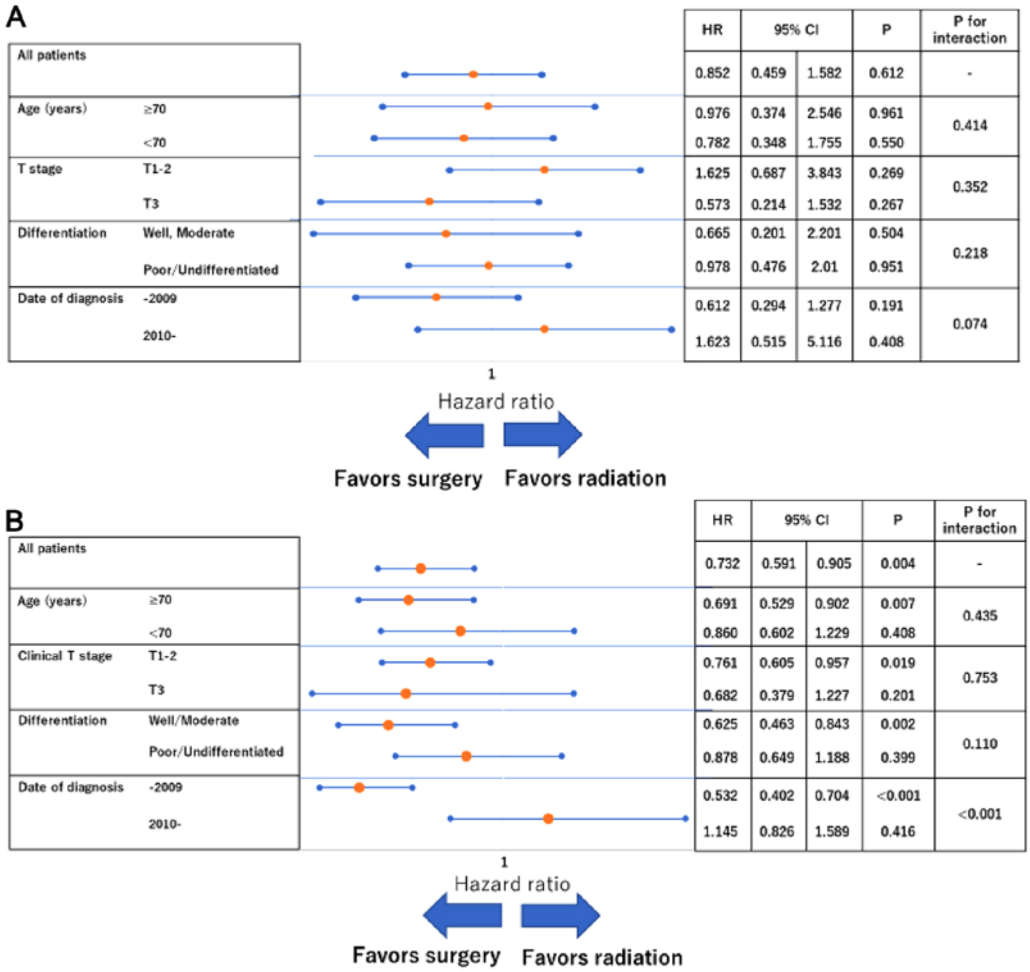

Figure 2. Association between treatment type and survival. (A) Cancer-specific survival. (B) Overall survival. HR, hazard ratio; CI, confidence interval.

70-79 years) comprised 2,286 patients, and the younger group (aged 50-69 years) comprised 2,524 patients (Table II). The Kaplan-Meier curves are shown in Fig. 3. In the elderly group, there was no significant difference in CSS based on treatment modality (HR, 0.976; 95% CI 0.374-2.546; P=0.961) (Fig. 3A). However, those who underwent surgery had significantly better OS (HR, 0.691; 95% CI 0.529-0.902; P=0.007) (Fig. 3B). By contrast, in the younger group, there were no significant differences in either CSS (HR, 0.782; 95% CI 0.348-1.755; P=0.550) (Fig. 3C) or OS (HR, 0.860; 95% CI 0.602-1.229; P=0.408) based on treatment modality (Fig. 3D).

In order to investigate which factors might lead to the difference in OS among the elderly group, we analyzed the causes of death. The surgery group had 101 deaths, of whom

Table III. Cause of death in the elderly group.

Cause of death	Total (n=225)	Surgery (n=101)	Radiation (n=124)	P-value
Prostate cancer death, n (%)	19 (8.4)	11 (10.9)	8 (6.5)	0.234
Intrinsic death, n (%)	167 (74.2)	70 (69.3)	97 (78.2)	0.128
Extrinsic death, n (%)	5 (2.2)	2 (2.0)	3 (2.4)	0.824
Unknown death, n (%)	34 (15.1)	18 (17.8)	16 (12.9)	0.306

P-values were calculated using a Pearson's Chi-squared test.

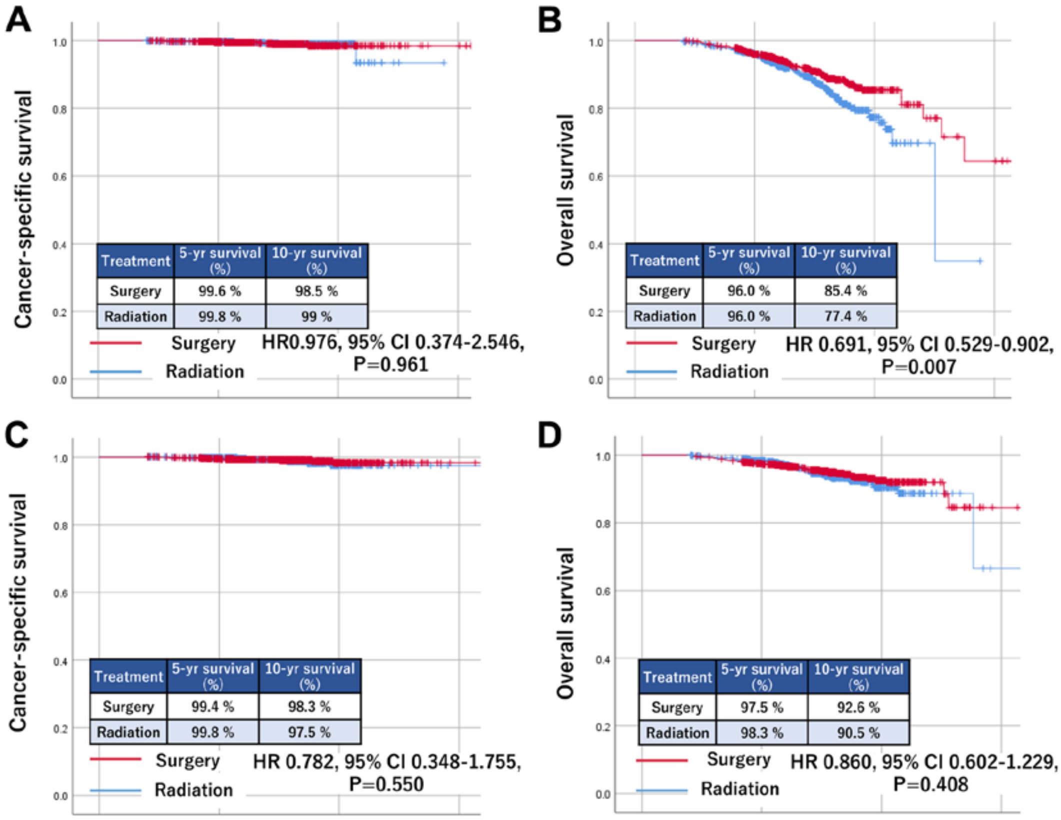

Figure 3. Kaplan-Meier curve for cancer-specific survival and overall survival stratified by treatment type. (A) Cancer-specific survival in the elderly group. (B) Overall survival in the elderly group. (C) Cancer-specific survival in the younger group. (D) Overall survival in the younger group. HR, hazard ratio; CI, confidence interval.

70 (69.3%) died from intrinsic disease. Meanwhile, the radiotherapy group had 124 deaths, including 97 (78.2%) due to intrinsic disease. Relatively, more intrinsic deaths were seen in the radiotherapy group than in the surgery group (P=0.128); however, no significant difference was observed (Table III).

Discussion

The question of whether surgery is more efficacious (i.e., having better survival outcomes) than radiotherapy for localized prostate cancer has remained inconsistently answered. Most previous studies showed that surgery yielded better prognosis than radiotherapy (5-10). According to a meta-analysis of 19 studies with 118,830 patients, those treated with radiotherapy were at higher risk of overall mortality (HR, 1,63; 95% CI, 1.54-1.73; P<0.001) and cancer-specific mortality (HR, 2.08; 95% CI, 1.76-2.47; P<0.001) than those undergoing surgery (5). A population-based study of 68,665 patients conducted between 1992 and 2005 by Abdollah *et al* pointed out an association between radiotherapy and decreased CSS at all risk levels of prostate cancer (P<0.001) (6). However, in our study, both treatment modalities offered good CSS, and no significant difference in CSS was observed between patients undergoing surgery and radiotherapy. This result was similar to that from the ProtecT trial. Further, the latest nationwide population-based study of 41,503 patients in Sweden showed a lower difference in CSS between patients undergoing surgery and radiotherapy than those in previous studies (radiotherapy vs. surgery: Low- and intermediate-risk: HR, 1.24; 95% CI, 0.97-1.58; high-risk: HR, 1.03; 95% CI, 0.81-1.31) (17).

Unlike in the younger group, there was a significant difference in OS based on the treatment modality in the elderly group, leading to that same tendency in the entire cohort. This result may come from a bias in treatment selection; the reason for treatment selection was not indicated in the database. More intrinsic deaths were seen among elderly patients treated with radiotherapy than those treated with surgery. We could predict that patients with heavy comorbidities and low performance status had a tendency to be treated with radiotherapy. Therefore, considering that there was no significant difference in CSS, we could expect radiotherapy to be a good treatment selection for elderly patients because of its lower invasiveness.

Interestingly, the forest-plot subanalysis showed a significant interaction among treatment type with respect to OS based on the date of diagnosis. This might result from advances in radiotherapy modalities, such as intensity-modulated radiotherapy (IMRT), which have lower adverse events than three-dimensional conformal radiotherapy (18-20). Additionally, the combination of IMRT and brachytherapy has been shown to achieve a good cancer control rate with lower toxicity (21,22). Moreover, as combination androgen deprivation therapy has been proved to improve survival, particularly in intermediate- and high-risk localized prostate cancer (23,24), combination hormonal therapy has become widely used worldwide. Finally, these improvements in survival might have led patients with good general condition to choose radiotherapy, particularly after 2010, thereby contributing to better OS in this group.

This study also has some limitations that need to be considered when interpreting the results. First, there was a lack of clinicopathological data related to prostate cancer. In particular, PSA values, which are crucial to determine the risk of localized prostate cancer, were unavailable in the database, making it impossible for us to stratify the patients by risk group. Gleason scores, which play an important role in evaluating the prognosis of men with prostate cancer, were also unavailable. Only a limited number of factors were included in our analyses; this enabled us to analyze exactly matched data in a relatively large cohort. However, PSA value and Gleason scores are needed for a more accurate analysis. Second, the median observation period was relatively short for localized prostate cancer. To have more precise survival outcome data for the sake of comparison, the observation should have lasted 15-20 years. Third, as previously mentioned, neither the performance status nor the comorbidity was known; therefore, patient selection bias could not be eliminated. Fourth, the database contained no data on the timing of treatment after cancer diagnosis and the administration of combination hormonal therapy. Therefore, our study included patients treated with surgery or radiotherapy after active monitoring. Fifth, the prognosis of patients receiving combination therapy could not be evaluated in this study. We categorized patients who underwent both surgery and radiotherapy into the surgery group because salvage radiotherapy is a common treatment for patients with biochemical recurrence after surgery in clinical practice, as mentioned in the Methods section. Although it would have been better to compare the results between combination therapy and surgery because surgery and adjuvant radiotherapy could yield better outcomes than surgery alone, the precise timing of each therapy in this study is unknown. Further, we could not determine whether the patients were treated with adjuvant or salvage radiotherapy. As such, other combination therapies, such as surgery and hormone deprivation or surgery and chemotherapy, could not be evaluated. Finally, the biological effective dose, which could strongly affect oncological outcomes, was unavailable in patients treated with radiotherapy.

In conclusion, our study showed no significant difference in CSS between surgery and radiotherapy, but surgery yielded significantly better OS, particularly in elderly patients. However, as mentioned, the study results should be interpreted with caution, given that some important factors were unavailable in this study. Further, the study found no significant difference in terms of both CSS and OS among younger patients, although we did observe a tendency toward improved survival in patients treated with radiotherapy after 2010. This implied that radiotherapy was less invasive, and it should therefore be considered for use in elderly patients.

As the registration of prostate cancer data in the National Cancer Database was initiated in April 2018, these limitations are expected to be overcome. Despite the limitations, our study has hitherto been the largest cohort study in Japan or any Asian country. Furthermore, to our best knowledge, this is the very first study to compare treatment modalities using the coarsened exact matching method. Our study results provide important data relating to Asian patients, particularly Japanese patients. They could inform the selection of the appropriate treatment for localized prostate cancer.

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Availability of data and materials

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

Authors' contributions

MY, MS, HN and TK conceived and designed the current study, acquired, analyzed and interpreseted the data, and drafted the manuscript. RJ, ST, TT, GN, SU, KK and HU contributed to the conception and design of the present study, and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the ethical standards of the Helsinki Declaration and was approved by the Institutional Review Board of Kanagawa Cancer Center (approval no. EKI-048).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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