

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

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Research article

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Abstract

Background. Radical prostatectomy and radiotherapy are currently the main treatment options for localized prostate cancer. However, not yet a large cohort study of comparison between surgery and radiation has been investigated in Japan nor Asia. Objective of this study was to compare the survival outcome between surgery and radiotherapy among patients with clinically localized prostate cancer and in the elderly and young patients.

Methods. We retrospectively evaluated survival outcomes of localized prostate cancer patients (age at diagnosis ≤ 79 years, cT1-3) initially treated with surgery or radiotherapy. Data were collected from the population-based cancer registry of Kanagawa Prefecture, Japan. A 1:1 coarsened exact matching of age at diagnosis, clinical T stage, and cancer differentiation was made between the two treatment groups. Patients were also categorized into two groups by age at a cut-off of 70 years for analysis.

Results. The cohort comprised 4,810 patients aged 50-79 years. No significant difference in CSS was observed between the two groups ($p=0.612$), but the surgery group had significantly better prognosis in OS ($p=0.004$). When stratified for age, similar tendencies were seen in the elderly group (aged 70-79 years) ($p=0.961$ and $p=0.007$, respectively). By contrast, no significant difference in either CSS or OS was found 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 in those undergoing surgery (69.3% vs 78.2%, $p=0.128$).

Conclusions. Our data suggests that surgery provided significantly better OS than radiotherapy, particularly among the elderly. However, radiotherapy may be more appropriate in elderly patients due to less invasiveness of the procedure. Prospective trials evaluating these therapies are warranted.

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]. The incidence of prostate cancer has been particularly increasing in northeast Asian countries [2]. In Japan, prostate cancer had the highest morbidity rate among all cancers in men in 2015 [3]. 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 has remained 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 [4]. However, the prostate cancer cases in this trial mostly had a Gleason score of 6 (77%), cT1c (21%), and PSA less than 10 $\mu\text{g/L}$ (median PSA, 5.8 $\mu\text{g/L}$) [5]. Given that most patients had low risk cancer, the survival outcomes differed from those of previous studies that used real-world data mostly showing survival benefit mainly in high risk prostate cancer.[6–11].

Furthermore, the ProtecT trial included only patients aged 50–69 years, while prostate cancer is commonly detected in the elderly (i.e. those aged 70 years or older). The number of elderly cancer patients has been increasing [12]. Japan is anticipated to become a super-aging society by 2030, with one in every three people turning 65+ years and one in five people reaching 75+ years [13]. 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.

Besides, previous studies indicated that hormonal therapy is relatively more sensitive and safer in Japanese patients than in Caucasian men [14,15]. Nevertheless, no large cohort study on Japanese or Asian patients has ever investigated the survival of local treatments.

For the reasons above, this present study was carried out with two objectives: 1) to compare the effectiveness between surgery and radiotherapy for clinically localized prostate cancer using data from a Japanese regional population-based prostate cancer database; and 2) to compare the effectiveness of these two treatment modalities between the elderly group and the younger patient group. In order to fulfil these objectives, we conducted a coarsened exact matching of cancer features, and patients were also categorized by age at a cut-off 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 Kanagawa Prefecture, Japan. The inclusion criteria were localized prostate cancer (cT1–3N0M0), adenocarcinoma, age range of 50–79 years, an observation period of ≥ 2 years, and either having surgery or radiotherapy as the main treatment. Patients with missing data were excluded. For those treated with both treatment modalities, surgery was considered as the main one. The reason for this is that salvage radiotherapy is common in prostate cancer recurrence after surgery, while salvage prostatectomy after radiotherapy is rare [16]. As we used secondary data, the requirement to obtain the informed consent was waived.

The primary endpoint of this study was CSS and OS. The patients were also categorized by the age cut-off of 70 years (i.e. 50–69 years vs 70–79 years). Moreover, 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 Kanagawa Cancer Center.

Data source

Data were collected from a population-based regional cancer registry of 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 of 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 survival confirmed. 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.

A Kaplan-Meier method and univariate comparisons using log-rank test and unadjusted Cox models were performed to estimate CSS and OS. A 2-tailed *p* value of <0.05 was considered statistically significant. All statistical analyses were carried out with the IBM SPSS Statistics v25 (IBM Corp, Armonk, NY). 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) [17].

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 1). One half of these patients had surgery as the main treatment, while the other half 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 patients (6.3 %) died of prostate cancer and other causes, respectively.

Survival benefit, by treatment modality

In the surgery group, prostate cancer was the main cause of death to 23 patients (1.0%), whereas 142 patients died of other reasons (5.9%). The 5- and 10-year CSS were 99.6% and 98.4%, while 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 reasons. The 5-year CSS was 99.8%, and the 10-year CSS was 98.1%. Meanwhile, the figures for OS were 97.2% and 84.3%, correspondingly.

The Kaplan-Meier curves are shown in Figure 1. There was no significant difference in CSS between the two groups (surgery vs radiotherapy: HR, 0.852; 95% CI 0.459–1.582; $p = 0.612$); however, the surgery group had significantly better prognosis in OS than did the radiotherapy group (HR, 0.732; 95% CI 0.591–0.905; $p = 0.004$).

Subgroup analyses showed no significant interactions in CSS (Figure 2a). With respect to OS, the magnitude of the association between surgery and improved survival was greater for patients diagnosed until 2009 (vs 2010 onwards; p value for interaction <0.001 ; Figure 2b).

Comparison of efficacy between the 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 70–79) comprised 2,286 patients, as opposed to 2,524 patients in the younger group (aged 50–69 years) (Table 2). The Kaplan-Meier curves are shown in Figure 3. In the elderly group, there was no significant difference in CSS (HR, 0.976; 95% CI 0.374–2.546; $p = 0.961$) (Figure 3a). However, those who underwent surgery had significantly better prognosis in OS (HR, 0.691; 95% CI 0.529–0.902; $p = 0.007$) (Figure 3b). By contrast, in the younger group, there were no significant differences in either CSS (HR, 0.782; 95% CI 0.348–1.755; $p = 0.550$) (Figure 3a) or OS (HR, 0.860; 95% CI 0.602–1.229; $p = 0.408$) (Figure 3b).

In order to investigate what factors might lead to the difference in overall survival among the elderly group, we analyzed the causes of death. The surgery group had 101 dead cases, of whom 70 (69.3%) died from intrinsic disease. Meanwhile, the radiotherapy group had 124 dead cases, including 97 (78.2%) ones due to intrinsic diseases. 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 3).

Discussion

The question of whether surgery is more efficacious (i.e. having better survival outcomes) than radiotherapy has remained inconsistently answered. Most previous studies showed that surgery yielded better prognosis than radiotherapy [6–11]. 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 [6]. A population-based study of 68,665 patients conducted between 1992 and 2005 by Abdollah F et al. pointed out an association between radiotherapy and less favorable CSS all risk levels of prostate cancer ($p < 0.001$) [7]. However, in our study, both treatment modalities offered good CSS, and no significant difference in CSS was observed between surgery and radiotherapy. This result was similar to that from the ProtecT trial. Besides, the latest nationwide population-based study of 41,503 patients in Sweden showed a lower difference in CSS between surgery and radiotherapy than that 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) [18].

Unlike in the younger group, the difference in OS was found significant in the elderly group, leading to that same tendency in the all-age cohort. This result may come from the bias of treatment selection; the reason for treatment selection was not indicated in the database. However, based on the result relating to the causes of death in the elderly patients, more intrinsic deaths were seen in those treated with radiotherapy. We could predict that patients with heavy comorbidities and low performance status had a tendency to be treated with radiotherapy. Thus, considering that there was no significant difference in CSS, we could expect that radiotherapy to be a good treatment selection for the elderly patients because of its less invasiveness.

Interestingly, the forest-plot sub-analysis showed a significant interaction among treatments with respect to OS on the date of diagnosis. This might result from advances in radiotherapy modalities, for example the intensity-modulated radiotherapy (IMRT), which have lower adverse events than does three-dimensional conformal radiotherapy [19–21]. Also, the combination of IMRT and

brachytherapy has been shown to achieve a good cancer control rate and lesser toxicity [22, 23]. Moreover, as combination androgen deprivation therapy has been proved to improve survival, particularly in intermediate- and high-risk localized prostate cancer [24,25], combination hormonal therapy has become widely used worldwide. Finally, these improvements in survival might have led patients with good general condition to choose radiotherapy, probably before 2010, thereby contributing to better OS in this treatment.

This study also has some limitations that need to be considered when interpreting the results. First, there was a lack of several clinicopathological data related to prostate cancer. Particularly, 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. Besides, no Gleason scores were available although they play an important role in evaluating the prognosis of men with prostate cancer. 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; thus, patient selection bias could not be eliminated. Fourth, the database contained no data on timing of treatment after cancer diagnosis and the conduct of combination hormonal therapy. Therefore, our study included patients treated with surgery or radiotherapy after active monitoring. Finally, the biological effective dose (BED), which could strongly affect oncological outcomes, was unavailable in patients treated with radiotherapy.

Conclusion

Our study showed no significant difference in CSS between surgery and radiotherapy, but surgery yields 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. Besides, the study found no significant difference in terms of both CSS and OS among younger patients, but better tendency of survival in patients treated after 2010. This implied that radiotherapy was less invasive, and therefore, it may 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 and Asian countries. Furthermore, to our best knowledge, this is the very first study to compare treatment modalities using the coarsened exact matching method. Our study results provided important data relating to Asian patients, particularly in Japanese patients. They could inform the selection of the appropriate treatment for localized prostate cancer.

Declarations

Ethics approval and consent to participate: This 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 (IRB number: EKI–048)

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests: The authors declare no competing interests.

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Authors' contributions MY and MS contributed to the conception and design of the study; acquisition, analysis, and interpretation of data; and drafting the manuscript. RJ, ST, TT, GN, SU, KK contributed to the conception and design of the study and revision and approval of the manuscript. HU contributed of drafting and critical revision of the manuscript. HN and TK supervised the study.

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Tables

Table 1. Patient characteristics of the entire cohort and after exact matching of age, clinical T stage, and differentiation

Characteristics	<i>Entire cohort</i>			<i>P</i>	<i>After matching</i>			<i>P</i>
	Total (n=6805)	Surgery (n=3610)	Radiation (n=3195)		Total (n=4810)	Surgery (n=2405)	Radiation (n=2405)	
Age, median (range)	69 (50-79)	68 (50-79)	71 (50-79)	<0.001*	69 (50-79)	69 (50-79)	69 (50-79)	1.000*
Age				<0.001 [†]				1.000 [†]
50-69, n (%)	3519 (51.7%)	1487 (41.2%)	1396 (43.7%)		2524 (52.5%)	1262 (52.5%)	1262 (52.5%)	
70-79, n (%)	3286 (48.3%)	2123 (58.8%)	1799 (56.3%)		2286 (47.5%)	1143 (47.5%)	1143 (47.5%)	
Clinical T stage, n (%)				<0.001 [‡]				1.000 [†]
T1	3083 (45.3%)	1653 (45.8%)	1430 (44.8%)		2386 (49.6%)	1193 (49.6%)	1193 (49.6%)	
T2	3014 (44.3%)	1727(47.8%)	1287 (40.3%)		2040 (42.4%)	1020 (42.4%)	1020 (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 [†]				1.000 [†]
Well	948 (13.9%)	481 (13.3%)	467 (14.6%)		738 (15.3%)	369 (15.3%)	369 (15.3%)	
Moderate	2662 (39.1%)	1459 (40.4%)	1203 (37.7%)		2024 (42.1%)	1012 (42.1%)	1012 (42.1%)	
Poor/Undifferentiated	3195 (47.0%)	1670 (46.3%)	1525 (47.7%)		2048 (42.6%)	1024 (42.6%)	1024 (42.6%)	
Date of diagnosis				<0.001 [†]				<0.001 [†]
-2009	1965 (28.9%)	1127(31.2%)	838 (26.2%)		1766 (36.7%)	1029 (42.8%)	737 (30.6%)	
2010-	4840 (71.1%)	2483 (68.8%)	2357 (73.8%)		3044 (63.3%)	1376 (57.2%)	1668 (69.4%)	

*p values correspond to Wilcoxon-Mann-Whitney test

[†]p values correspond to Pearson's Chi-squared test

Table 2. Patient characteristics in the elderly and younger group

Characteristics	Elderly group			<i>p</i>	Younger group			<i>p</i>
	Total (n=2286)	Surgery (n=1143)	Radiation (n=1143)		Total (n=2524)	Surgery (n=1262)	Radiation (n=1262)	
Age, median (range)	73 (70-79)	73 (70-79)	73 (70-79)	1.000*	65 (50-69)	65 (50-69)	65 (50-69)	1.000*
Clinical T stage, n (%)				1.000 ⁺				1.000 ⁺
T1	1074 (47.0%)	537 (47.0%)	537 (47.0%)		1312 (52.0%)	656 (52.0%)	656 (52.0%)	
T2	1050 (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 ⁺				1.000 ⁺
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%)		1066 (42.2%)	533 (42.2%)	533 (42.2%)	
Poor/Undifferentiated	1030 (45.1%)	515 (45.1%)	515 (45.1%)		1018 (40.3%)	509 (40.3%)	509 (40.3%)	
Date of diagnosis				0.024 ⁺				<0.001 ⁺
-2009	779 (34.1%)	415 (36.3%)	364 (31.8%)		987 (39.1%)	614 (48.7%)	373 (29.6%)	
2010-	1507 (65.9%)	728 (63.7%)	779 (68.2%)		1537 (60.9%)	648(51.3%)	889 (70.4%)	

**p* values correspond to Wilcoxon-Mann-Whitney test

⁺*p* values correspond to Pearson's Chi-squared test

Table 3. Cause of death in the elderly group

	Total (n=225)	Surgery (n=101)	Radiation (n=124)	<i>P</i>
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 correspond to Pearson's Chi-squared test

Figures

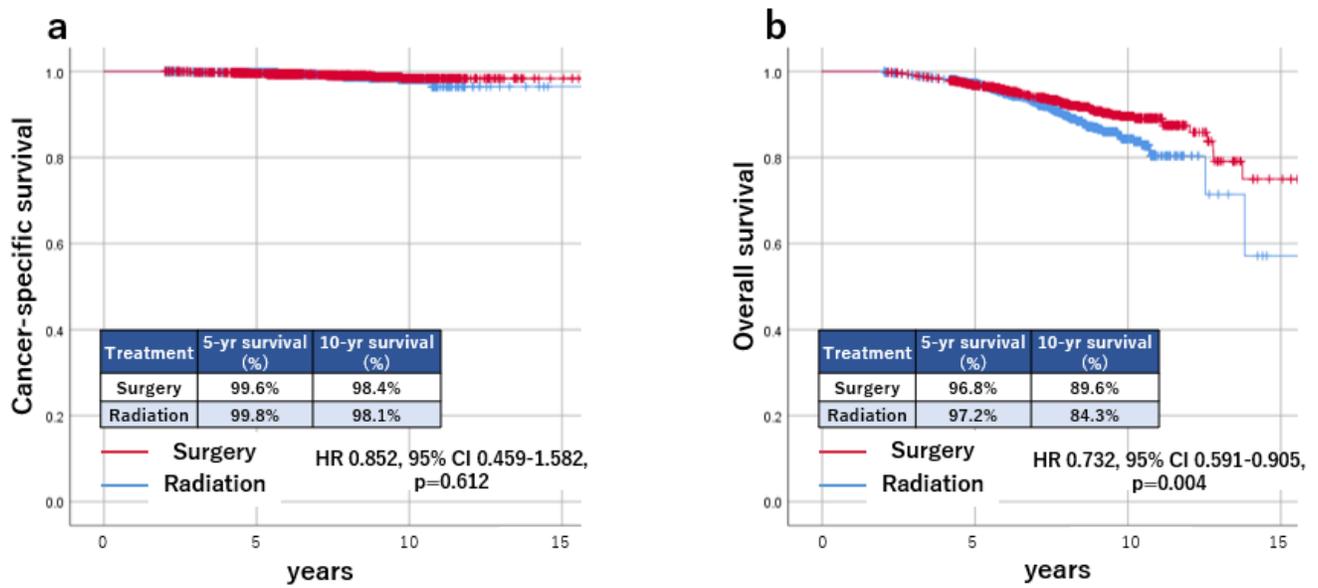


Figure 1

Kaplan-Meier curves for (a) cancer-specific survival and (b) overall survival stratified by treatments

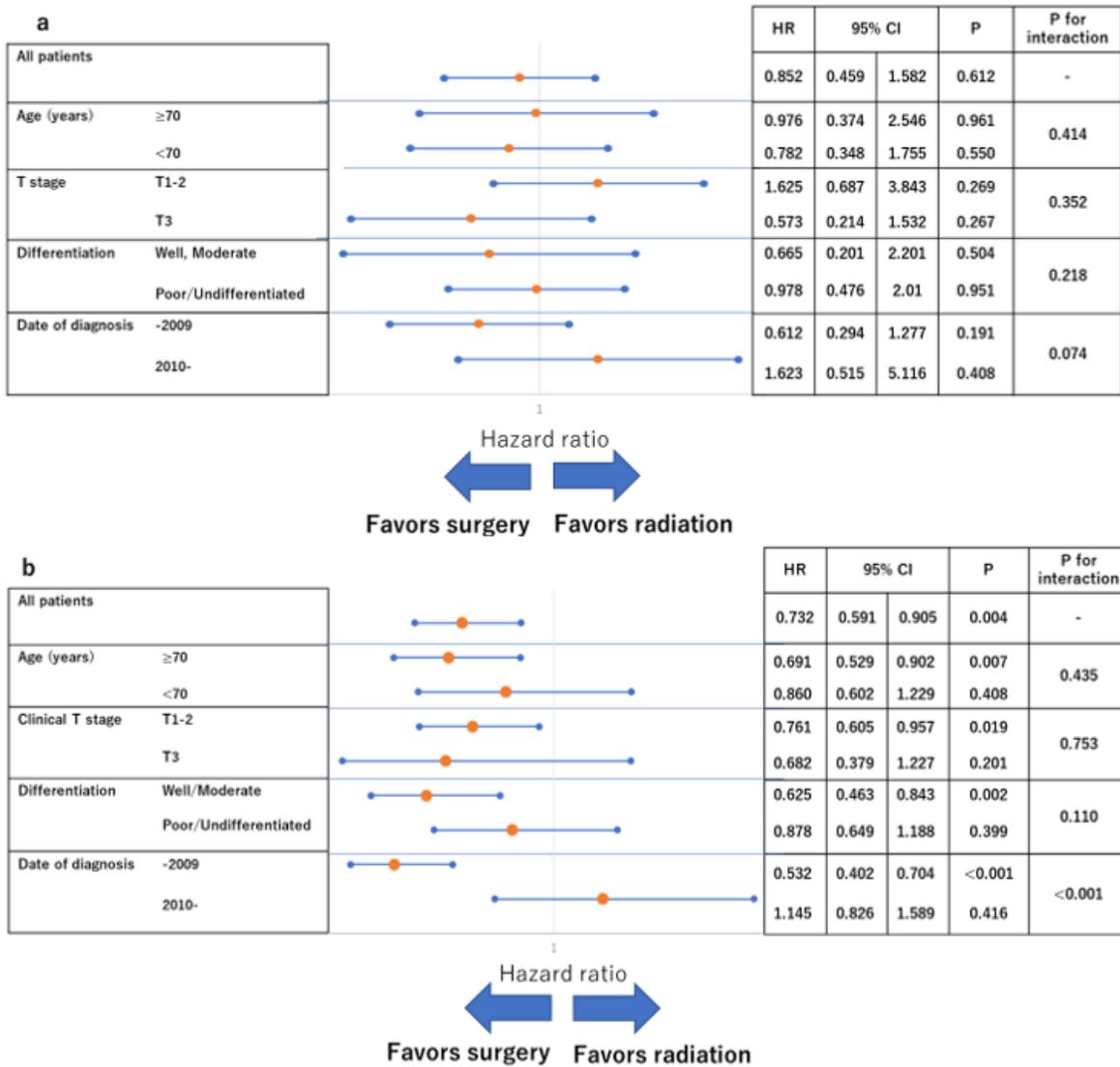


Figure 2

Association between treatments and survival (a) Cancer-specific survival; (b) overall survival

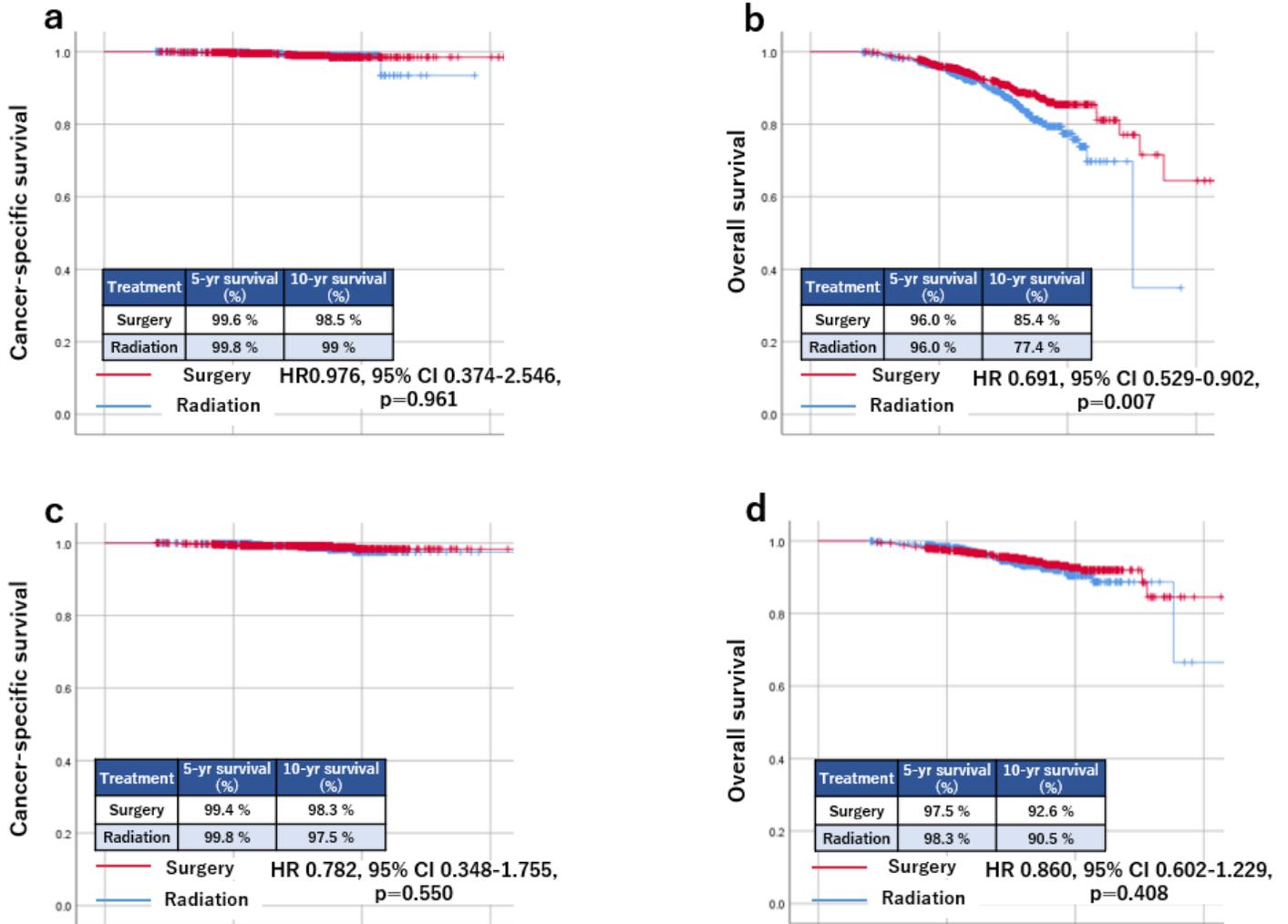


Figure 3

Kaplan-Meier curve for cancer-specific survival and overall survival stratified by treatments. (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