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Radiotherapy for elder patients aged ≥80 with clinically localized prostate cancer – Brachytherapy enhanced late GU toxicity especially in elderly

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ABSTRACT

Background and purpose: Elongation of life expectancy had led to marked increase in number of elderly patients with localized prostate cancer. However, the standard treatment for such patients is not well determined because of a high prevalence of comorbidities and slow growth of prostate cancer. The aim of this study is to examine the feasibility of radiotherapy for elderly patients aged ≥80 years.
Materials and methods: We compared 96 patients aged ≥80 years and 2333 younger patients (aged 60–79 years) using multi-institutional data included cT1-T4N0M0 prostate cancer treated with 902 external beam radiotherapy (EBRT) and 1527 brachytherapy (BT).
Results: The 5-year biochemical failure-free survival rate was similar between elderly ≥80 years and younger control (91.3% vs. 85.9%, $p = 0.6171$) (100%, 92.9%, 82.4% and 96.3%, 93.7%, 89% for low, intermediate and high risk group), and for the prostate cancer-specific survival rate (100% and 99.3%, $p = 0.6171$). The accumulated incidence of late gastrointestinal (GI) at 5 years was also similar between elderly and younger patients (3.5% vs. 2.5%, $p = 0.6857$). Brachytherapy improved biochemical control rate and reduced GI toxicity compared with EBRT, however, enhanced late genitourinary (GU) toxicity, especially in elderly patients. Elderly received brachytherapy showed highest rate of late GU toxicity grade ≥2 of 22.1% than the younger counterparts of 12.7% at 5 years, whereas younger patients treated with EBRT had 2.4% and elderly EBRT had 2.7% ($p < 0.0001$).
Conclusion: Elderly patients aged ≥80 years showed equivalent biochemical control, prostate cancer-related survival, and gastrointestinal toxicity profiles to younger patients. Meticulous care should be required for brachytherapy enhanced late GU toxicity, especially in elderly patients aged ≥80 years.

1. Introduction

Prostate cancer has become one of the most frequently diagnosed cancers in developed countries, as a consequence of elongation in life expectancy [1,2]. Current standard treatments are radical prostatectomy and/ or radiotherapy with or without androgen deprivation therapy (ADT). However, in case of elderly patients [2,3], the treatment is not well determined because of the heterogeneous nature of the elderly population and slow growth of the disease. Then, conservative management would be the plausible option for fragile elderly patients with high prevalence of comorbidities who are afraid of untoward reactions caused by intervention, which affect the quality of life [2–4]. Furthermore, the incidence of prostate cancer death is not high in patients with clinically localized prostate cancer who were treated conservatively [4,5]. Recently, the prostate cancer-specific relative survival rate of clinically localized prostate cancer treatment has improved and reached nearly 100% in Japan [3,7].

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We have made a preceding comparison study for elderly patients aged ≥75 years and younger patients [6] and concluded that healthy elderly patients could tolerate aggressive treatment including brachytherapy, and the outcome is equivalent for both patient groups stratified by age. In Japan, however, the elderly population increased dramatically, and aged ≥80 years reached 11,250,000 (8.9% of total population) in 2019 [7], among which 4,050,000 (6.6%) are in men. Therefore, we conducted this large cohort study using multi-institutional data and included 2616 patients with locally prostate cancer to explore the characteristics of those patients aged ≥80 years. Thus, the aim of this study is to examine the clinical outcomes of elderly patients aged ≥80 years with a comparison to younger groups including brachytherapy.

2. Patients and methods

2.1. Patients

Our multi-institutional cohort included 2346 clinically localized prostate cancer patients who were treated with radiotherapy with a curative intent. Eligibility criteria were clinical (T1-4 and N0M0) TNM stage with histology-proven adenocarcinoma, radiotherapy treatment, availability and accessibility of data on pretreatment prostate-specific antigen (initial PSA = iPSA) level, Gleason score sum (GS), and T classification; which could determine clinical stage. Of those, we excluded patients aged ≤59 years and those with missing data. Then, we compared 96 elderly patients aged ≥80 years and 2333 younger patients aged 60–79 years (Table 1). For detailed comparison, we divided the patients into the following age groups: 60–69, 70–74, 75–79, and ≥ 80 years (Supplemental Table 1). Radiotherapy consisted of 1527 brachytherapy (BT) (1088 high-dose rate brachytherapy [HDR] with external beam radiotherapy [EBRT] and 439 low-dose rate brachytherapy [LDR] with or without EBRT) or 902 EBRT (2D, 3D-CRT, and image-guided intensity modulated radiotherapy [IMRT]). Patients' clinical characteristics are shown in Table 1 (Supplemental Table 1). Patients were staged according to the National Comprehensive Cancer Network (NCCN) 2015 risk classification as follows: low, T1-T2a and GS 2–6 and iPSA < 10 ng/ml; intermediate, T2b-T2c or GS 7 or PSA 10–20 ng/ml; high, T3a-T4 or GS 8–10 or PSA > 20 ng/ml [2]. PSA failure was defined using the Phoenix definition (nadir, +2 ng/ml) or as the start of salvage hormonal therapy. Common Terminology Criteria for Adverse Events version 4.0 Toxicity was applied to toxicity analysis. This study was conducted in accordance with the Declaration of Helsinki, and IRB permission from each institution.

2.2. Treatment planning

2.2.1. Brachytherapy (BT)

BT contained 439 LDR with or without EBRT and 1088 HDR with EBRT.

LDR was performed by intraoperative permanent I-125 implantation (The OncoSeed model 6711; General Electric Healthcare, Barrington, IL) used with Inter-Plan version 3.4 (ELEKTA, Stockholm, Sweden). The prescription dose for the clinical target volume (prostate) was 145 Gy (LDR-BT alone) or 110 Gy (LDR-BT with EBRT) at University Hospital Kyoto Prefectural University of Medicine (n = 383) [8]. We added EBRT (40 Gy in 20 fractions with 3D-CRT) for case with T3a or Gleason score sum ≤8 or LDR-BT for cases with Gleason score sum 7 (4 + 3) (not for cases with Gleason score sum 7 [3 + 4]) (n = 56).

Data of HDR + EBRT were obtained from freely accessible database [9]. The detailed method of HDR was described elsewhere [10]. A total of 1088 patients were treated with a combination of HDR and EBRT at various fractionations (Supplemental Table 2). The median dose of HDR was 31.5 Gy (10.5–31.5 Gy), and that of EBRT was 39 Gy (30–51 Gy) in median fraction number of 5 (1–5) in HDR and 10 (10–23) in EBRT. Regarding hormonal therapy, 1185 patients (77.6%) received androgen-deprivation therapy (1038/1088 = 95.4% in HDR, 147/439 = 33.5% in LDR).

2.3. External beam radiotherapy (EBRT)

EBRT included 421 three-dimensional conformal radiotherapy (3D-CRT) and 481 intensity-modulated radiotherapy (IMRT)

Table 1
Characteristics and treatment factors of patients.

Variables	Strata	Elder age 80-		Younger age 60–79		*p*-value
		n = 96		n = 2333		
		No. or Median (range)	(%)	No. or Median (range)	(%)	
Age		81 (80–89)		70 (60–79)		–
T category	1	21	(22%)	628	(27%)	0.74
	2	39	(41%)	894	(38%)	
	3	35	(36%)	783	(33%)	
	4	1	(1%)	28	(1%)	
iPSA	ng/ml	16.2 (3.3-155)		11.22 (1.4-1454)		**0.0022**
Gleason score	−6	20	(21%)	469	(20%)	0.5529
	7	39	(41%)	1073	(46%)	
	8-	36	(38%)	791	(34%)	
NCCN risk classification	Low	4	(4%)	246	(10%)	**0.008**
	Intermediate	19	(20%)	668	(28%)	
	High	73	(76%)	1419	(60%)	
Modality	EBRT	61	(64%)	841	(36%)	**<0.0001**
	Brachythrapy	35	(36%)	1492	(64%)	
	HDR + EBRT	*29*	*(30%)*	*1059*	*(45%)*	
	LDR ± EBRT	*6*	*(6%)*	*433*	*(18%)*	
Hormonal therapy	Yes	85	(89%)	1832	(78%)	**0.0184**
Neoadjuvant	months	10 (3–89)		9 (1–92)		
Adjuvant	months	36 (2–37)		36 (1–134)		
	No	11	(11%)	501	(21%)	
Follow-up	Months	60 (2–136)		72 (4–177)		**0.0008**

*Bold values indicate statistically significance, NA; not available.
HDR = high dose rate brachytherapy, LDR = low-dose-rate brachytherapy, EBRT = external beam radiotherapy

(Supplemental Table 2). Part of EBRT data were obtained from freely accessible dataset (n = 643) [9], and image-guided IMRT using helical tomotherapy was performed at the Department of Radiology, Ujitakeda Hospital (n = 259). The technique of image-guided IMRT using helical tomotherapy has been described elsewhere [11]. Dose prescriptions were D95 (95% of PTV received at least the prescribed dose) of 74.8 Gy/34 fractions (2.2 Gy/fraction, n = 98) for intermediate- and high-risk patients and 72.6 Gy/ 33 fractions (n = 22) low-risk patients between June 2007 to 2009. We modified the prescribed dose, reduced to 74 Gy/37 fractions (2 Gy/fraction, n = 115) for the high- and intermediate-risk groups and 72 Gy in 36 fractions (n = 24) for the low-risk group from June 2009 to September 2013. The EBRT group consisted of 421 patients who received three-dimensional conformal RT (3D-CRT) and 481 who received intensity modulated RT (IMRT, Supplemental Table 1). The median dose of EBRT was 72 Gy (62–80 Gy) in 36 (20–40) fractions, 732 patients received androgen-deprivation therapy (81.1%) in EBRT group.

2.3.1. Statistical analysis

StatView 5.0 statistical software and R stat package [12] were used for statistical analyses. R stat package was used only to calculate the propensity score and inverse probability treatment weighting (IPTW) method.

StatView 5.0 statistical software was used for statistical analyses. Percentages were analyzed using the chi-square test, and Student's *t*-test was used for normally distributed data. The Mann-Whitney *U* test for skewed data was used to compare means or medians. The Kaplan-Meier method was used to analyze biochemical control rate, survival and accumulated toxicity, and comparisons were made using the log-rank test. Cox's proportional hazard model was used for multivariate analyses, and $p < 0.05$ was considered as statistically significant.

Because the included patients were not randomized, unbalanced baseline characteristics could have led to ineligible bias. The propensity score is defined here as the probability of being assigned to patients aged ≥80 years or patients aged <80 years given the patients characteristics. In the calculation of the propensity scores, the logistic regression model was used considering the baseline covariates shown in Table 2 (T classification, Gleason score, pretreatment PSA, and hormonal therapy). IPTW values were calculated from the propensity scores and represented the inverse probability of an age group based on their characteristics. The treatment effects were recalculated using the IPTW with a Cox model. We weighted survival analysis using the inverse probability treatment weighting (IPTW) method, i. e., weighting patients aged ≥80 years by 1/propensity score, whereas patients aged <80 years were weighted by 1/(1–propensity score).

3. Results

3.1. Patients characteristics

The median follow-up for the entire cohort was 71.4 (ranging from 2 to 177) months. A comparison of the patients' backgrounds is shown in Table 1. Elderly group ≥80 years showed advanced diseases (higher iPSA and higher ratio of intermediate-high risk groups in NCCN) with more cases with hormonal therapy than younger control.

3.2. Biochemical control, prostate cancer-specific survival rate, and overall survival rate between elderly and younger patients

In the elderly group ≥0 years, 11 (11.4%) patients developed biochemical failure, compared with 269 (11.5%) in the control group ($p = 0.9828$). The actuarial 5-year biochemical failure-free survival rate (bNED) was 91.3% (95% confidential interval = 95% CI: 90.1–92.4%) and 85.9% (95% CI: 77.4%-94.3%, $p = 0.6171$, Fig. 1) in elderly and control (Hazard ratio = HR 1.003; 95% CI = 0.5343–1.882, $p = 0.993$ in IPTW), respectively; bNED was 96.3% (100% for elderly and 96.3% for control, $p = 0.611$) for the low-risk group, 93.7% (92.9% and 93.7%, $p = 0.5693$) for the intermediate-risk group (HR 1.236; 95% CI = 0.3002–5.088, $p = 0.769$ in IPTW), and 88.8% (82.4% and 89.0%, $p = 0.8711$) for the high-risk group (HR 1.009; 95% CI = 0.5063–2.009, $p = 0.981$ in IPTW). There is a significant difference in the biochemical control rate among those three risk groups ($p < 0.0001$). As shown in Table 2, the predictors of biochemical control on multivariate analysis included T classification (T1-2 vs. T3-4), Gleason score sum (≤7 vs. 8 ≤), a higher baseline PSA (<20 vs. 20≤), and treatment modality (EBRT vs. BT ± EBRT). Age was not a statistically significant prognostic factor for biochemical control (hazard risk = 0.994, 95% CI: 0.543–1.820, $p = 0.9838$).

By subdividing them into age groups (60–79, 70–74, 75–79, and ≥80 years), bNED was 90.5%, 92.8%, 90.3%, and 85.9% (Supplemental Fig. 1, p = 0.3763), respectively; bNED was 94.2%, 97.8%, 100%, and 100% ($p = 0.772$) for the low-risk group, 92.6%, 93.8%, 96.3%, and 92.8% ($p = 0.2365$) for the intermediate-risk group, and 88.3% (85.8%-91.2%), 91.3%, 86.4%, and 82.4% for the high-risk group ($p = 0.4001$).

The overall five-year survival rate was 97.8% (95% CI: 94.8%-100.7%) and 96.4% (95.6%-97.1%, $p = 0.4202$, Supplemental Fig. 2) in elderly and control, respectively, while it was 100% (100% and 100%, respectively, $p = 0.738$) for the low-risk group, 98.5% (100% and 98.2%, respectively, $p = 0.3978$) for the intermediate-risk group, and 96.3% (86.2% and 97.0%, respectively, $p = 0.3183$) for

Table 2
Multi-variate analysis for biochemical control rate using Cox proportional hazards model.

Variable	Strata	Multivariate analysis		
		HR	95% CI	*p*
Age, years	≤79	1	(referent)	
	80≤	0.994	0.543–1.820	0.9838
T classification	1–2	1	(referent)	–
	3–4	1.91	1.440–2.533	**<0.0001**
Gleason score	≤7	1	(referent)	–
	8≤	1.684	1.321–2.162	**<0.0001**
Pretreatment PSA (ng/mL)	≤20	1	(referent)	–
	20<	1.362	1.036–1.791	**0.0267**
Hormonal therapy	Yes	1	(referent)	–
	No	1.317	0.913–1.899	0.1409
Treatment modalities	BT ± EBRT	1	(referent)	
	EBRT	2.539	1.9893.243	**<0.0001**

Bold values indicate statistically significance.
CI = confidence interval; HR = hazard ratio.

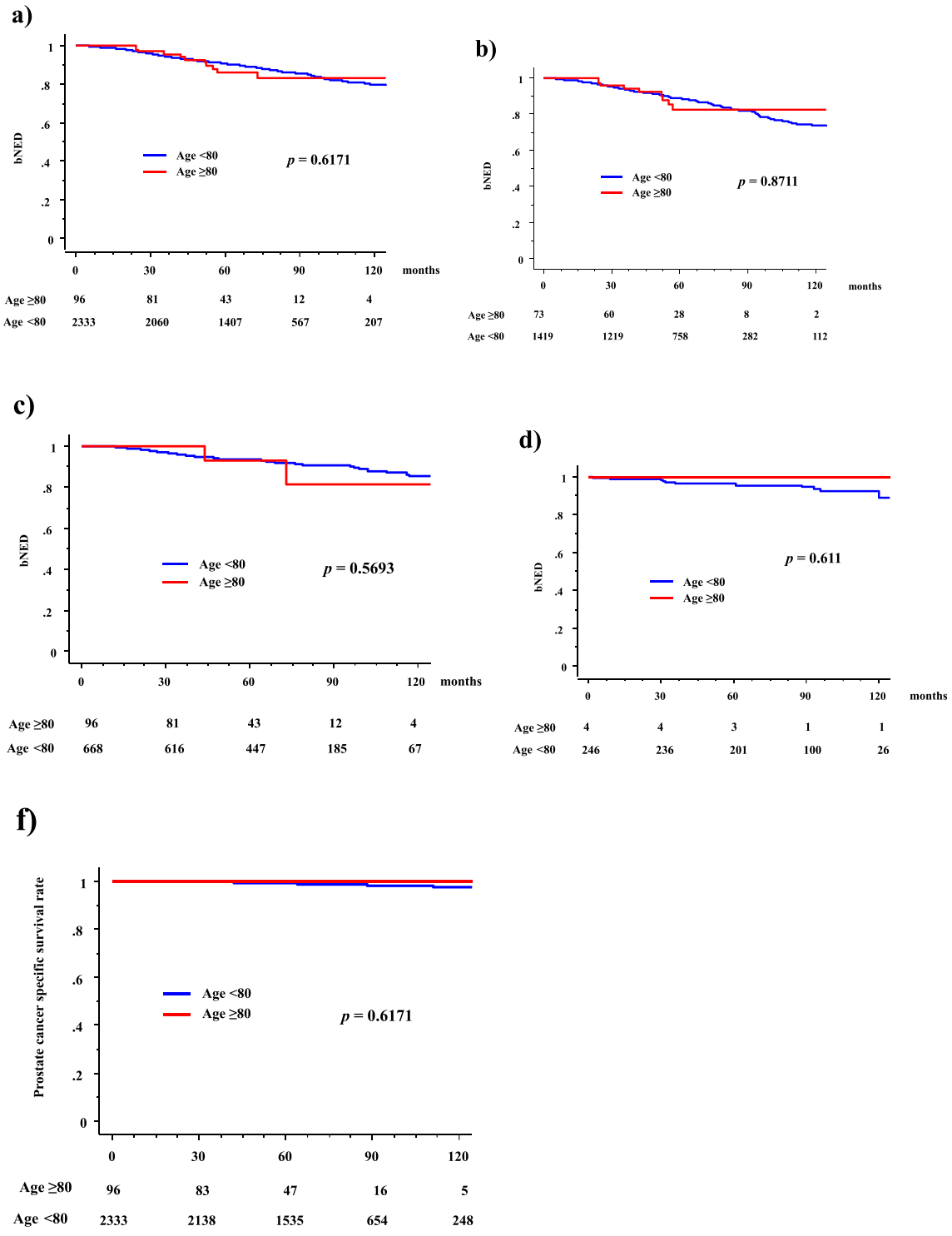

Fig. 1. Biochemical control rates and Overall survival rates between elderly (age ≥ 80) and younger control. (a) Total population. (b) High risk group. (c) Intermediate risk group. (d) Low risk group. (e) Prostate cancer specific survival rate between elderly (age ≥ 80) and younger control. bNED = no biochemical evidence of disease.

the high-risk group. The overall survival rate was significantly different among the three risk groups (p = 0.0002).

By dividing detailed age group (age 60–79, 70–74, 75–79, and ≥80 years), overall survival rate was 98.8%, 96.9%, 95%, and 97.8% (Supplemental Fig. 2, p = 0.0034) at 5 years, respectively; overall survival rate was 100, 100%, 100%, and 100% (p = 0.779) for the low-risk group, 99.7%, 98.9%, 94.6%, and 100% (p = 0.028) for the intermediate-risk group, and 98%, 95.3%, 94.5%, and 97.1% for the high-risk group (p = 0.0229).

In assessment of prostate cancer-specific survival rate, no patients died of prostate cancer during follow-up periods in elderly group, whereas 26 high risk patients (1.07%) died of prostate cancer in the control group (p = 0.254). The actuarial 5-year prostate cancer-specific survival rate was 100% and 99.3% (98.7%-99.9%, p = 0.6171, Fig. 1) in elderly and control, respectively; 5-year prostate cancer-specific survival rate was 100% for elderly and 94.7% for younger control (p = 0.4771) in the high-risk group (Supplemental Fig. 2). By dividing detailed age group (60–79, 70–74, 75–79, and

≥80 years), prostate cancer-specific survival rate was 98.7%, 99.2%, 98.5%, and 100% (p = 0.812), respectively; it was 98.7%, 99.2%, 98.5%, and 100% (p = 0.794) for the high-risk group.

3.3. Toxicity

Table 3 shows the incidence of maximal toxicity. In acute phase, grade ≥2 gastrointestinal (GI) toxicities occurred in 2 (2%) patients in elderly ≥80 years and 14 (1%) in younger control, respectively (p = 0.1892). Acute genitourinary (GU) toxicity grade ≥2 occurred in 9 (9%) in elderly and in 343 (14.3%), patients in control (p = 0.2552), respectively. In detailed analysis, (Supplemental Table 3) each age group (60–69, 70–74, 75–79, and ≥80 years) showed equivalent toxicity rate in acute phase (Supplemental Fig 3).

In late phase toxicity, the maximal late GI toxicity grade ≥2 occurred in 3 (3%) patients in elderly and 71 (3.4%) patients in younger control, respectively (Table 3, p = 0.9515). The accumulated incidence for GI toxicity grade ≥2 was 3.5% (95% CI: 0–7.42%) at 5 years in elderly and 2.5% (95% CI: 1.912–3.088% p = 0.6857) in younger control (Fig. 2). In detailed analysis, (Supplemental Table 3) each age group (60–69, 70–74, 75–79, and ≥80 years) showed equivalent GI toxicity rate in late phase (Supplemental Fig 3).

Multivariate analysis revealed that a predictor of late GI toxicity grade ≥2 on multivariate analysis was treatment modality (EBRT vs. BT ± EBRT: Hazard risk 0.426, 95% CI: 0.265–0.687, p = 0.0005) (Table 4). EBRT elevated GI toxicity if compared to BT ± EBRT group. Accumulated incidence of GI toxicity grade ≥2 was 1.6% at 5 years (95% CI: 2.72–5.47%) in BT ± EBRT group, which is lower than that of 4.1% (95% CI: 2.72–5.47%, p = 0.001, Fig. 2) in EBRT group.

Late GU toxicity grade ≥2 occurred in 11 (13%) patients in elderly and 264 (12%) patients in control (Table 3. p = 0.1855), respectively. In detailed analysis dividing by age and modality in brachytherapy group (Table 5), the elderly group (≥80 years) showed higher incidence of late GU toxicity of 31% than other age groups (16% 60–69 years, 16% in 70–74 years, and 15% in 75–79 years) only in brachytherapy group (p = 0.0015).

Accumulated incidence for GU toxicity grade ≥2 was 9.9% at 5 years (95% CI: 3.236–16.564%) for elderly and 9.4% (95% CI: 8.028–10.772%, p = 0.3323) for younger control (Fig. 2).

Multivariate analysis revealed that age ≥80 years (hazard risk = 2.023, 95% CI: 1.069–3.830, p = 0.0304) and treatment modality (EBRT vs. BT ± EBRT, Hazard risk 5.601, 95% CI: 3.703–8.470, p < 0.0001; Table 4) were predictors of late GU toxicity grade ≥2. The accumulated incidence of GU toxicity grade ≥2 was 13.4% (95% CI: 11.6–15.2%) at 5 years in the BT group, which was higher than that in the EBRT group (2.4%; 95% CI: 1.22–3.57%, p < 0.0001, Fig 3). If dividing by age and modality, elderly received brachytherapy showed highest rate of late GU toxicity grade ≥2 of 22.1% (95% CI: 5.83–38.3%) than the younger counterparts of 12.7% (95% CI: 10.9–14.46%) at 5 years, whereas younger patients treated with EBRT had 2.4% (95% CI: 1.224%-3.576%) and elderly EBRT had 2.7% (95% CI: 0%-7.99%) (p < 0.0001 among 4 groups, p = 0.0111 between aged ≥80 and younger counterpart in BT group, Fig. 2). This trend of higher incidence of accumulated GU toxicity grade ≥2 is only found in patients aged ≥80 treated with brachytherapy but not in age 60–69, 70–74, and 75–79 (Supplementary Fig 3). IPTW correction also revealed that elderly showed higher GU toxicity grade ≥2 than younger counterpart (p = 0.0431, with HR 2.12; 95% CI 1.012–4.035) in patients treated with brachytherapy.

4. Discussion

In this study, we described clinical characteristics of elderly patients aged ≥80 years with localized prostate cancer. Our findings indicated that elderly patients aged ≥80 years could tolerate treatment and achieved equivalent efficacy compatible to the younger population after radiotherapy. However, toxicity profiles were different between elderly and younger counterparts in GU toxicity. Strength of our study is that we used large population of more than 2000 patients.

In Japan, of the 89,717 patients diagnosed for the first time with prostate cancer in 2016, 22,380 (24.9%) were aged ≥80 years [7]. In our cohort, only 3.6% patients were classified in the ≥80 years age group, which reflects the situation that elderly ≥80 years population did not receive RT than younger counterparts. Peterson et al. reported that only 0.17% of patients received RT among patients aged ≥80 years in Sweden in the population-based analysis [13]. It is natural that the increased age correlated with decreased use of active intervention.

Table 3
Comparisons of toxicities among age groups.

Toxicities	Grade	Elder age 80-		Younger age 60–79		p-value
		n = 96		n = 2333		
		No.	(%)	No.	(%)	
(a) Acute toxicity.						
Gastrointestinal	0	83	(86%)	1948	(83%)	0.1892
	1	11	(11%)	371	(16%)	
	2	2	(2%)	13	(1%)	
	3	0	(0%)	1	(0%)	
Genitourinary	0	43	(45%)	842	(36%)	0.2552
	1	44	(46%)	1148	(49%)	
	2	9	(9%)	336	(14%)	
	3	0	(0%)	7	(0.3%)	
(b) Late toxicity.						
Gastrointestinal	0	79	(82%)	1952	(84%)	0.9515
	1	14	(15%)	310	(13%)	
	2	3	(3%)	60	(3%)	
	3	0	(0%)	10	(0.4%)	
	4	0	(0%)	1	(0.04%)	
Genitourinary	0	64	(67%)	1366	(59%)	0.1855
	1	19	(20%)	703	(30%)	
	2	9	(9%)	191	(8%)	
	3	4	(4%)	73	(3%)	

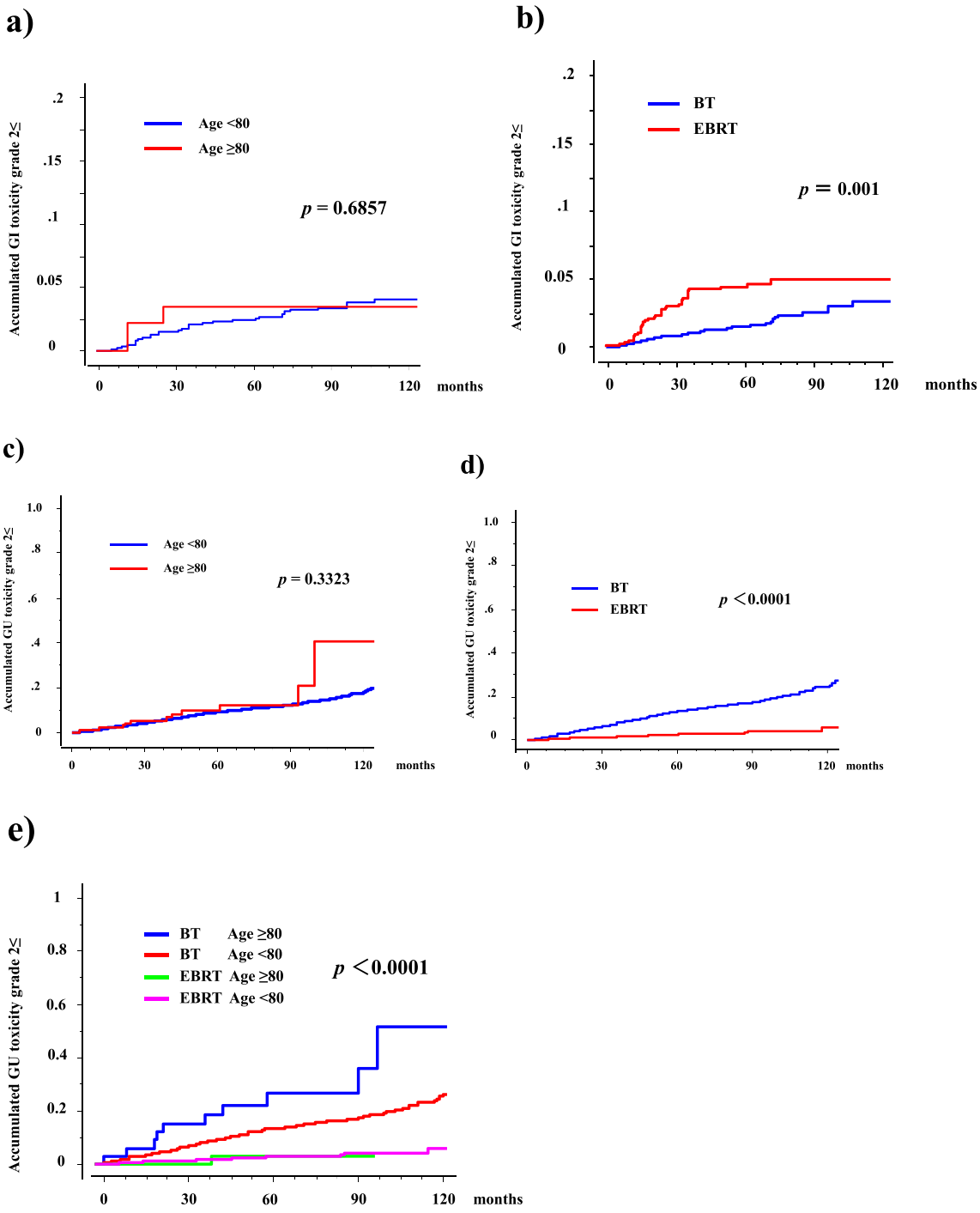

Fig. 2. Accumulated incidence of grade ≥ 2 toxicity according to age and modality. (a) Accumulated incidence of gastrointestinal toxicity grade ≥2 between elderly and younger control. (b) Accumulated incidence of gastrointestinal toxicity grade ≥2 between BT and EBRT. (c) Accumulated incidence of genitourinary toxicity grade ≥2 between elderly and younger counterpart. (d) Accumulated incidence of genitourinary toxicity grade ≥2 between BT and EBRT. (e) Accumulated incidence of genitourinary toxicity grade ≥2 divided by age and modality.

Elderly patients would not die of prostate cancer because of increasing other causes of mortality, concurred with our data [2,3]. No patient aged ≥80 years died of prostate cancer in our cohort. In this scenario, observation could be a sensible choice in avoiding unnecessary treatments (overtreatment), which will increase the adverse events and the medical cost. Several randomized controlled trials and population-based studies have already proven no survival benefit with active intervention such as surgery and radiotherapy for patient with low-risk prostate cancer [3–5] compared with conservative management. Therefore, in recent guidelines, conservative management is recommended for patients with low-risk prostate cancer with a life expectancy of <10 years [2,3]. However, Gorin et al. reported that only 36% of patients with low-risk prostate cancer were provided with an active surveillance option by the physicians [14]. There is a tendency to hesitate choosing conservative management for several reasons. One of the reasons was that the patients' anxiety regarding not treating the cancer [15]. They received active treatment for fear of cancer

Table 4
Multi-variate analysis for late toxicity grade ≥ 2 using Cox proportional hazards model.

Variable	Strata	GI toxicity grade ≥ 2			GU toxicity grade ≥ 2		
		HR	95% CI	*p*	HR	95% CI	*p*
Age, years	≤79	1	(referent)		1	(referent)	
	80≤	1.259	0.391–4.052	0.6994	2.023	1.069–3.830	**0.0304**
T classification	1–2	1	(referent)	–	1	(referent)	–
	3–4	1.014	0.584–1.761	0.9604	0.961	0.722–1.279	0.7851
Gleason score	≤7	1	(referent)	–	1	(referent)	–
	8≤	1.316	0.791–2.188	0.2909	1.179	0.906–1.533	0.2203
Pretreatment PSA (ng/mL)	≤20	1	(referent)	–	1	(referent)	–
	20<	1.115	0.644–1.932	0.6965	0.904	0.677–1.208	0.4952
Hormonal therapy	No	1	(referent)	–	1	(referent)	–
	Yes	0.974	0.495–1.918	0.94	0.897	0.644–1.248	0.5178
Treatment modalities	BT ± EBRT	1	(referent)		1	(referent)	
	EBRT	0.426	0.265–0.687	**0.0005**	5.601	3.703–8.470	**<0.0001**

Bold values indicate statistically significance.
CI = confidence interval; HR = hazard ratio,
EBRT = external beam radiothrapy, BT = brachytherapy, GI = gastrointestinal, GU = genitourinary.

Table 5
Detailed Comparisons of late GU toxicities among age group divided by BT ± EBRT and EBRT only.

Toxicities		Grade	Elder age 80-		Younger age 60–69		Younger age 70–74		Younger age 74–79		*p*-value
			N = (EBRT:BT) 61:35		n = 306:701		n = 302:542		n = 233:249		
			No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Genitourinary	EBRT	0	54	(89%)	264	(86%)	262	(87%)	187	(80%)	0.7864
		1	5	(8%)	31	(10%)	30	(10%)	35	(15%)	
		2	2	(3%)	9	(3%)	8	(3%)	9	(4%)	
		3	0	(0%)	2	(1%)	2	(1%)	2	(1%)	
	BT	0	10	(29%)	326	(47%)	240	(44%)	87	(35%)	**0.0015**
		1	14	(40%)	264	(38%)	220	(41%)	123	(49%)	
		2	7	(20%)	81	(12%)	63	(12%)	21	(8%)	
		3	4	(11%)	30	(4%)	19	(4%)	18	(7%)	

*Bold values indicate statistically significance.
GU = genitourinary, BT = brachytherapy, EBRT = external beam radiotherapy.

progression even with the awareness of the possibility of significant adverse effects. Another reason is insufficient information offered by physicians and academic societies. Davison et al. reported a passive role in treatment decision making of men aged >70 years [16]. Then, physician recommendations in the choice of treatment play an important role in the patients' decision [16]. Furthermore, Mitsuzuka et al. found that active surveillance was not used in 26.9% of urologists in Japan in large sample (2133 urologist survey) [16]. Urologists tend to have anxieties about repeat biopsies (60.3%), inadequate inclusion criteria (49.9%), psychological burden for patients (43.7%), unexpected progression (41.1%) and unknown long-term outcomes (40.6%), which were considered major problems of active surveillance [17]. Robust evidence can alleviate the patients' and physicians' anxiety over cancer progression and provide accurate information to support shared decision making.

In contrast, healthy elderly patients with a locally advanced prostate cancer who can endure aggressive standard treatment are increasing, at the same time they are often undertreated, i.e. ADT alone. Lunardi et al. reported a 16% undertreatment rate in older patients >75 years without any significant comorbidity [18]. After a careful evaluation of the nature of the cancer and comorbidity, international recommendations are that fit elderly patients >70 should be managed according to their individual health status but not according to their ages [3].

Until now, toxicity analysis showed that age does not always increase acute or late urinary or bowel toxicity by EBRT, in which our data concur to a previous study [19,20]. However, here we presented that BT elevated late GU toxicity than EBRT and especially higher in elderly aged ≥80 than younger, which is the first report as far as we are concerned. In general, urinary symptom increased by age. For instance, urinary incontinence is a common health problem, and its prevalence and severity increase with age [21]. Wilson et al. reported that patient-reported bladder bother was slightly higher in the group aged ≥75 years than the group aged <75 years after treatment of conventional and hypofractionated Radiation Therapy [22], which imply the need for meticulous care for elderly patients aged ≥75 years. Our data may reflect the fragility of urinary tract of patients aged ≥80 years. Our data could provide useful information to choose radiotherapy especially brachytherapy for both physicians and patients to decide whether radiotherapy or other treatment including observation should be selected.

We recognize several limitations of this study, the retrospective nature of this study of a multi-institutional data collection, inevitably involve intrinsic bias. Longer follow-up with larger number of patients or randomized controlled trial is essential before reaching concrete conclusion if possible. Next, because there was no defined follow up schedule, timing of follow up and examinations among the hospitals were heterogeneous. Therefore, "soft" end points such as biochemical control might be ambiguous. Third, because various treatment schedules were used at each hospital, the results reported in this paper can vary, depending on treatment schedules. Additionally, important parameters are not considered in our study which makes the interpretation of the results (DVH parameters for the bladder/Urethra, volume of the prostate, comorbidities and previous treatments like TUR-B). Comorbidity analysis is important because comorbidities are common in elderly patients. Several

studies indicated that comorbidity is an important factor to choose modality for curative treatment in elderly population and is also a prognostic factor. [3,19]. Then, our results could not free from the possibility that patients (>80 years) with more aggressive tumors received BT in order to apply a higher dose, although IPTW and multivariate analysis could help mitigating this confounding risk partially. Future study is warranted for meticulous and better patient selection criteria for patients aged ≥80 years.

In conclusion, elderly patients aged ≥80 years showed equivalent biochemical control, prostate cancer-related survival, and GI toxicity profiles to younger patients. However, elderly patients who receiving brachytherapy showed higher late GU toxicity rate than EBRT group and even younger group who were receiving brachytherapy.

Conflict of interest disclosure

The authors made no disclosure.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2020.09.008.

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