Intensity-modulated radiation therapy for elderly patients (aged ≥75 years) with localized prostate cancer: Comparison with younger patients (aged <75 years)

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Abstract. The aim of the present study was to evaluate the efficacy and safety of intensity-modulated radiation therapy (IMRT) for elderly patients with prostate cancer (age ≥75 years) compared with younger patients (<75 years). The numbers of patients enrolled into the elderly and younger groups were 238 and 853, respectively. More than half of the patients in the elderly group were high-risk, and the total risk of the elderly group was higher than that of younger group. The median follow-up periods for the elderly and younger groups were 42 (range, 2-108) and 49 (range, 2-120) months, respectively. All patients were treated with IMRT at a dose of 74-78 Gy with or without androgen-deprivation therapy. The biochemical failure-free rates (BFFRs) at 3-year follow-up for the elderly and younger groups were 93.3 and 95.7%, respectively; there was no significant difference between the 2 groups in regard to the BFFR. The clinical failure-free rates (CFFR) at 3-year follow-up for the elderly and younger groups was 95.8 and 98.5%, respectively; the 2 groups did not differ significantly in regard to the CFFR. The cumulative incidence rates of gastrointestinal toxicity (grade ≥2) and genitourinary toxicity (grade ≥2) at 3-year follow-up were 10.5 and 1.3%, respectively; there was no significant difference between the elderly and younger groups. It was concluded that in prostate cancer patients aged 75 years or older, IMRT has a treatment effect equivalent to that in patients <75 years old; adverse events are also comparable.

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Introduction

An estimated 1,095,000 men worldwide were diagnosed with prostate cancer in 2012, resulting in 307,000 deaths (1). In Japan, the incidence of prostate cancer was estimated of 86,100 cases in 2017 (2), and in 2015, 11,326 patients died of prostate cancer; the proportion of death from prostate cancer was larger in elderly patients (age 70 and over) (3).

There are several options to treat prostate cancer, such as surgery, external beam radiation therapy (EBRT), brachytherapy, and androgen-deprivation therapy (ADT), excluding active surveillance and watchful waiting. Patients may receive one or a combination of these treatments (4). Among them, EBRT is less invasive than surgery or brachytherapy and has curability. Intensity-modulated radiation therapy (IMRT), a technique of EBRT, is especially effective and has lower rates of gastrointestinal (GI) adverse events than conventional EBRT (5-9). The safety of IMRT also allows dose escalation, leading to better tumor control (10). However, elderly patients were more likely to receive ADT alone (11). A recent study with elderly patients reported that the conservative management with ADT alone does not improve the overall survival rate (OS) (12).

According to data collected in 2016, the life expectancy of 75- and 80-year-old Japanese men is 12.14 and 8.92 years, respectively (13).

This study aimed to evaluate the efficacy and safety of IMRT for elderly prostate cancer patients (age more than or equal to 75 years) compared with younger patients (age less than 75 years).

Materials and methods

Patients. From March 2006 to July 2014, 1,252 prostate cancer patients were treated with IMRT at our hospital. Exclusion criteria included presence of lymph node metastases or distant metastases; furthermore, patients whose prostate-specific antigen (PSA) levels were not measured at least once after IMRT were excluded. Histologically, all tumors were found to be adenocarcinomas. Among the 1,091 patients, 238 patients

Table I. Patient characteristics.

Characteristics	Age ≥75 years (n=238)	Age <75 years (n=853)	P-value
Median age (range), years	77 (75-87)	69 (39-74)	-
Median initial PSA (range), ng/ml	9.59 (4.09-356.00)	8.27 (2.65-370.00)	0.1520
Initial PSA ng/ml, n (%)			
<10	125 (52.5)	505 (59.2)	
≥10, ≤20	66 (27.7)	214 (25.1)	
>20	47 (19.7)	133 (15.6)	
T Stage, n (%)			0.0017
T1c	76 (31.9)	351 (41.1)	
T2a	69 (29.0)	262 (30.7)	
T2b	12 (9.7)	26 (3.0)	
T2c	33 (13.9)	92 (10.8)	
T3a	41 (17.2)	81 (9.5)	
T3b	4 (1.7)	35 (4.1)	
T4	3 (1.3)	6 (0.7)	
Gleason's score, n (%)			0.0815
≤6	56 (23.5)	260 (30.5)	
7	111 (46.6)	371 (43.5)	
8	36 (15.1)	139 (16.3)	
9	5 (2.1)	74 (8.7)	
10	14 (1.3)	9 (1.1)	
D'Amico classification, n (%)			0.0055
Low risk	31 (13.0)	174 (20.4)	
Intermediate risk	78 (32.8)	338 (39.6)	
High risk	129 (54.5)	341 (40.0)	
ADT use, n (%)			<0.0001
Yes	170 (71.4)	476 (55.8)	
No	68 (28.6)	377 (44.2)	

PSA, prostate-specific antigen; ADT, androgen-deprivation therapy.

were aged 75 years or older, the younger group comprised 853 patients. Patient characteristics are listed in Table I. This study was approved by the Ethics Committee of Kizawa Memorial Hospital. All patients provided written informed consent before receiving radiotherapy.

According to the classification of D'Amico *et al* (14), patients were stratified into three risk groups. More than half of the patients in the elder group were high-risk, and the total risk of the elder group was higher than that of the younger group. The rate of ADT use administration was higher in the elder group than in the younger group. The median follow-up periods of the elder and younger groups were 42 (range, 2-108) and 49 (range, 2-120) months, respectively.

Treatment planning. One hour after urine collection, each patients was positioned supine with the immobilization devices and computed tomography (CT) scanning was performed. Axial CT scans of 2.5-mm thick sections were obtained from the superior border of the sacroiliac joint to 5 cm below the ischial tuberosity. TomoTherapy Treatment Planning System (TomoTherapy Inc., Madison, WI, USA) is a radiation delivery system that combines dynamic IMRT with an image-guided radiation therapy system. IMRT involving helical tomotherapy (HT) was planned using an inverse-planning approach. For T1-T3a cancer patients, the clinical target volume (CTV) was defined as the prostate and proximal portions of the seminal vesicles. For T3b cancer patients, the CTV included the prostate and entire seminal vesicles. The planning target volume (PTV) was set by expanding the CTV by 5 mm in all directions. Patients at low- and intermediate-risk with biopsy-positive core rate ≤50% were irradiated with 74 Gy in 37 fractions. Patients at intermediate-risk with biopsy-positive core rate >50% were irradiated with 76 Gy in 38 fractions. For high-risk patients, the prescribed dose was 78 Gy in 39 fractions. Radiation therapy was administered five times a week. The dose limits for PTV were as follows: the volume of PTV receiving 95% of the prescribed dose (V95) was >90% (preferably >95%); the volume of the PTV receiving at least 90% of the prescribed dose (V90) was >96% (preferably >98%); and maximum dose to the PTV was <110% of the prescribed dose. The rectum was delineated from 15 mm superior to 15 mm inferior to the PTV. Rectal wall thickness and bladder wall

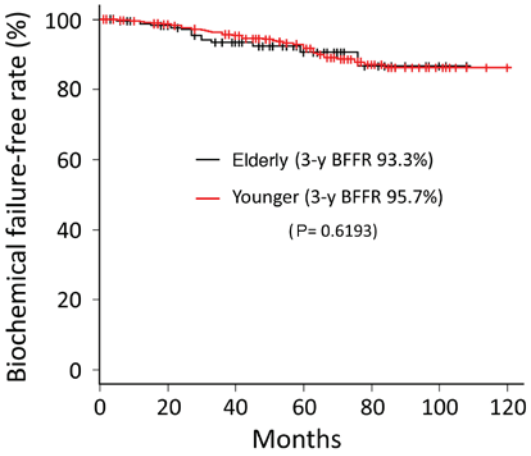

Figure 1. Biochemical failure-free rate for the elderly and younger groups. BFFR, biochemical failure-free rate; y, year.

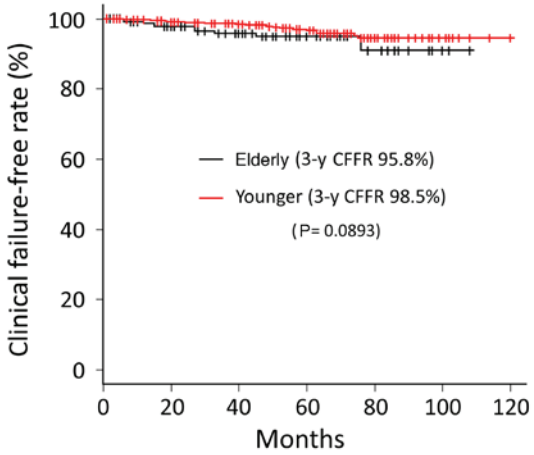

Figure 2. Clinical failure-free rate for the elderly and younger groups. CFFR, clinical failure-free rate; y, year.

thickness, both of 3 mm, were created. The dose constrains for the rectum were V40<60%, V60<30%, V70<20% and V78<1%. The dose constrains for the bladder were V40<60% and V70<30%. Vx was defined as the percentage of structure volume receiving at least one dose of 'x' Gy. Megavoltage CT image-guided verification was carried out every day prior to each treatment. A 6-MV photon beam was used for treatment.

ADT was started before IMRT and was continued during IMRT for patients in the intermediate-, and high-risk groups. Neoadjuvant ADT was initiated 3-6 months before IMRT. For high-risk patients, adjuvant ADT was continued for up to 2 years.

Evaluation. Biochemical failure was defined as PSA nadir plus 2 ng/ml according to the Phoenix criteria (15). In patients suspected of having local recurrence, magnetic resonance imaging (MRI) was performed and any MRI positive lesions were diagnosed using. A clinical failure was defined as the presence of local recurrence or metastases, and was confirmed by imaging, such as CT, MRI, or bone scintigraphy, in addition to checking PSA elevation. The examination was repeatedly conducted in patients with biochemical failure at appropriate timing, such as upon further elevation of PSA or appearance of symptom. Failure-free rates and survival rates were calculated from the completion date of IMRT to the occurrence of any event. We calculated the biochemical failure-free rate (BFFR), clinical failure-free rate (CFFR), and OS rates using the Kaplan-Meier method. Comparisons between the groups were conducted using the log-rank test. Using the Kaplan-Meier method, the cumulative incidence rate of grade ≥2 GI and genitourinary (GU) toxicities were calculated according to the Common Terminology Criteria for Adverse Events (v4.0) (16). At our hospital, a radiation oncologist and urologist interviewed the patient regarding presence or absence of rectal bleeding upon each visit after IMRT. Moreover, a urologist performed digital rectal examination at every visit. When rectal bleeding is present, patients are required to undergo colonoscopy.

Comparison between clinical factors of the two groups was performed using the chi-square test and R 2.13.0 software (www.r-project.org/). P<0.05 was considered to indicate a statistically significant difference.

Results

Biochemical failure was observed in 15 (6.3%) patients in the elder group. The BFFRs at 3-year follow-up for elder and younger groups were 93.3 and 95.7%, respectively. There was no significant difference between the two groups in BFFR (P=0.6193) (Fig. 1).

Ten (4.2%) cases of clinical failure were observed in the elder group. The first failure sites were pelvic node, bone, and lungs in five, four, and one patient, respectively. Local failure was not observed in the elder group during the follow-up period. Conversely, the sites of first failure in the younger group were local (prostate), pelvic node, para-aortic node, and bone in eight, five, one, and nine patients, respectively. The CFFR at 3-year follow-up for elder and younger groups were 95.8 and 98.5%, respectively. No significant difference was observed between the two groups (P=0.0893) (Fig. 2).

Five (2.1%) patients in the elder group died during the follow-up period. Among them, two died due to prostate cancer, two died due to another cancer, and one died due to pneumonia. The OS rates at 3-year follow-up for elder and younger groups were 98.9 and 99.5%, respectively; the difference between the two groups was statistically significant (P=0.0302) (Fig. 3). We compared the OS rates of elderly and younger patients in each group. There were no significant differences between elderly and younger patients in the intermediate-, high-, and very high-risk groups (P=0.236, 0.841, and 0.215, respectively). In the low-risk group, the OS rate of elderly group was significantly lower than that of younger group (P=0.00169). Meanwhile, there was no significant difference between elderly and young patients in CFFR, even in the low-risk group (P=0.443).

Grade ≥2 GI toxicity was observed in 23 (9.7%) cases in the elder group. Among them, six (2.5%) cases were grade 3. No cases of grade 4 GI toxicity were observed. The cumulative incidence rates of GI toxicity (grade ≥2) at 3-year follow-up were 10.5 and 9.6% for elder and younger groups, respectively; no significant difference between the two groups was founded (P=0.4143) (Fig. 4). Grade ≥2 GU toxicity was observed in nine (3.8%) cases in the elder group. No cases with grade ≥3 GU toxicity were noted. The cumulative incidence

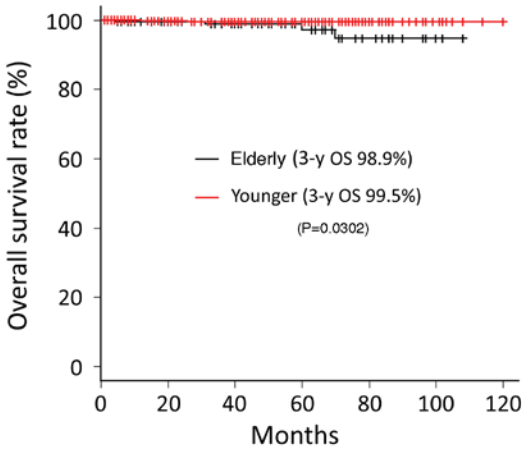

Figure 3. Overall survival rate for the elderly and younger groups. OS, overall survival; y, year.

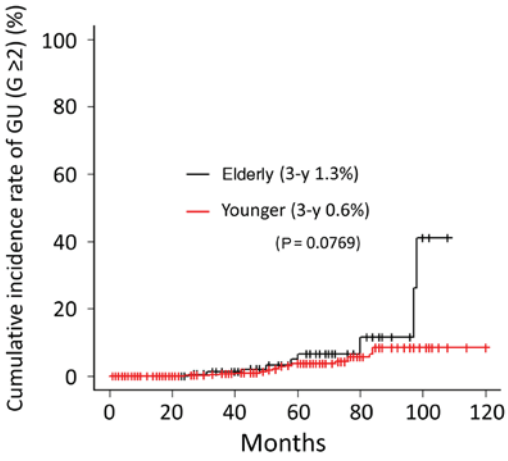

Figure 5. Cumulative incidence rate of Grade ≥2 genitourinary adverse events. OS, overall survival; y, year.

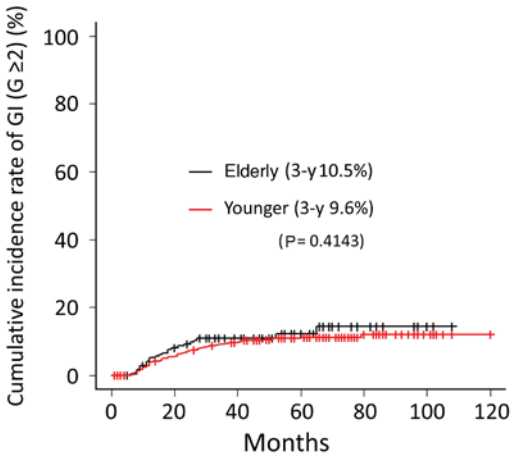

Figure 4. Cumulative incidence rate of Grade ≥2 gastrointestinal adverse events. OS, overall survival; y, year.

rates of GU toxicity (grade ≥2) at 3-year follow-up were 1.3 and 0.6% in the elder and younger groups, respectively; no significant difference was observed between the two groups (P=0.0769) (Fig. 5). There were no significant differences in the incidence rates of GI or GU ≥ grade 2 overall, or in elderly patients only, due to differences in prescription dose or risk classification.

Discussion

IMRT has been widely used for EBRT of localized prostate cancer. The outcome of IMRT is comparable to other treatment modalities, such as prostatectomy or brachytherapy (17). Although each modality has advantages and disadvantages, the incidence rate of adverse events in every modality is within acceptable range (18). However, IMRT is the least invasive choice among curable treatment options. To treat cancer in the elderly, the treatment is chosen with consideration of age, life expectancy, general condition, and comorbidity. Elderly patients with prostate cancer were more likely to receive ADT alone (11); however, a study in elderly patients reported that conservative management with ADT alone does not improve the OS rate (12). The life expectancy of the elderly is increasing, and a curable approach should be considered for patients in good general condition independent of age. IMRT would be the most promising modality among curable treatment choices due to its lower invasiveness. During treatment of elderly cancer patients, a higher frequency and degree of adverse events may be observed (19). It is worthwhile to note that in our study, the IMRT for prostate cancer in the elderly was comparable to that in younger patients. Although no significant difference between elderly and the young patient groups was founded in regard to GU rates, it is necessary to attend to the fact that the incidence rate of GU was higher in the elder group (1.3% compared to 0.6% in elder and younger groups, respectively).

In our study, the elder group had a higher overall risk than the younger group. This result is in agreement with the report of Shao *et al* showing increased proportion of higher risk prostate cancer with increased age at the time of diagnosis (20). Despite the large proportion of high-risk patients, the BFFR and CFFR of the elder group did not significantly differ from those of the younger group. This result may be partly due to the high ADT usage in the elder group; however, the reason for the high usage of ADT was the high proportion of intermediate- and high-risk patients in the elder group. Even regarding adverse events, no significant difference in the incidence rates of both GI and GU could be found between elder and younger groups. The incidence rates of GU tended to increase after five years in both groups; this tendency was particularly strong in the elder group. Therefore, we think that long-term follow-up is necessary even for elderly patients treated with IMRT.

Our study had one major limitation. Since we retrospectively investigated the paper-based medical chart, we could not accurately evaluate any acute adverse events including skin toxicity. The presence or absence of complications was of course confirmed prior to treatment, but we could not accurately record this from the paper-based medical charts.

In conclusion, IMRT has an equivalent treatment effect for prostate cancer in patients aged 75 years or older as in patients younger than 75 years, and the incidence rates for adverse events are also comparable between the two groups. In elderly prostate cancer patients who have good general condition and long life expectancy, IMRT should be considered as a treatment option.

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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

HT, SI, SG, SO and MM conceived and designed the experiments. HT, YN, MI, TY, KE, SK, SI, MH and MM analyzed the data. HT, YN, MI, TY, KE, SK and SG wrote the first draft of the manuscript. HT, YN, MI, TY, KE, SK, SI, MH, SO, SG and MM contributed to the writing of the manuscript, and discussed the results and conclusions. HT, YN, MI, TY, KE, SK, SI, MH, SO, SG and MM jointly developed the structure and arguments for the paper, critically revised the manuscript for important intellectual content, and reviewed and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Kizawa Memorial Hospital. Written informed consents were obtained from the patients.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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