Androgen receptor axis-targeted agents are not superior to conventional hormonal therapy for treatment of metastatic prostate cancer

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Received April 22, 2022; Accepted July 7, 2022

DOI: 10.3892/ol.2022.13453

Abstract. The present study aimed to use real-world Japanese data to compare the treatment outcome of conventional hormonal therapy to that of using androgen receptor axis-targeted (ARAT) agents for patients with metastatic castration-resistant prostate cancer. The overall survival between the conventional hormonal therapy group and the ARAT agent therapy group was compared using a group of 75 Japanese patients who were treated for metastatic castration-resistant prostate cancer. A subgroup analysis was carried out and the risk factors that affected overall survival (OS) were determined. The median OS from the time of prostate-specific antigen recurrence was 73.1 months in the ARAT group and 45.2 months in the conventional treatment group (P=0.414). Although OS tended to be slightly longer in the ARAT group, the difference between the groups was not significant. Subgroup analysis suggested that the therapeutic outcome of using ARAT agents tended to be less beneficial in patients who were older, and in those with a higher tumor volume or low Gleason grade. In conclusion, use of ARAT agents did not impart a significant survival benefit to patients with metastatic castration-resistant prostate cancer when compared with survival rates in response to conventional therapy. However, there was some clinical benefit when ARAT agents were used after patients developed castration-resistant prostate cancer. These findings suggest that up-front therapy using ARAT agents at the time of the initial hormone therapy can impart clinical benefit in Japanese patients with metastatic prostate cancer.

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Abbreviations: ARAT, androgen receptor-axis targeted; mCRPC, metastatic castration-resistant prostate cancer; ADT, androgen-deprivation therapy; mCSPC, metastatic castration-sensitive prostate cancer; CAB, combined androgen blockade; EMP, estramustine phosphate; OS, overall survival; PSA, prostate-specific antigen; PFS2, progression free survival 2

Key words: prostatic neoplasm, castration-resistant, androgen receptor antagonists, estramustine, prednisolone, OS

Introduction

Androgen receptor axis-targeted (ARAT) agents are available for metastatic prostate cancer patients, and several randomized trials established that the use of ARAT agents improves the prognosis for patients with metastatic, castration-resistant prostate cancer (mCRPC) (1-4). The use of ARAT agents is clearly more efficacious in terms of survival improvement when compared to using androgen-deprivation therapy (ADT) alone; this holds true not only in patients with mCRPC but also those with metastatic castration-sensitive prostate cancer (mCSPC) (5-7). This finding has dramatically changed the treatment and clinical outlook of metastatic prostate cancer patients, especially those with mCSPC, heralding the arrival of the 'ARAT era' in prostate cancer therapy.

In Japan, the combination therapy of bicalutamide and ADT, which is referred to as 'combined androgen blockade (CAB)', has been widely used to treat metastatic prostate cancer patients due to the observation of long-term efficacy (8). The 2012 Prostate Cancer Guidelines of the Japanese Urological Association recommend alternative antiandrogen therapy with flutamide as second-line treatment for prostate cancer patients who have failed CAB; this regimen has often been used to treat CRPC patients (9). In addition, other oral agents (e.g., estramustine phosphate (EMP), ethinylestradiol, low-dose glucocorticoid therapy) are also effective in patients with CRPC (10-12), and conventional hormone therapy using these therapeutic agents was more common in Japan than in other countries owing to the characteristics of patients on the Japanese PREVAIL trial (13).

ARAT agents have been available for patients with mCRPC since 2014 and for those with mCSPC since 2019. Several studies have reported the clinical benefit of using ARAT agents in patients with mCSPC compared to CAB (14-18). However, few studies have compared the therapeutic outcome of conventional hormonal therapy, which is commonly performed in

Japan, and the therapeutic outcome of using ARAT agents in Japanese patients with mCRPC (19). In order to prove the effectiveness of ARAT agents for Japanese patients, we considered it very important to compare the outcome of treatment using ARAT agents with the outcome of conventional hormonal therapy.

We therefore designed this study to comparing the clinical outcomes after conventional hormone therapy with those after ARAT for the Japanese patients with mCRPC.

Materials and methods

Patient selection. One hundred ten male patients who underwent hormonal therapy for the treatment of mCRPC in the Shiga University of Medical Science Hospital from July 2007 to December 2020 were evaluated. All cases were pathologically diagnosed as prostatic adenocarcinoma and already had distant metastases at diagnosis. Radiographic examinations, including CT scan and bone scintigraphy, were performed for all cases. Classification of tumor volume was determined according to the CHAARTED criteria, which was defined as the presence of visceral metastases or ≥4 bone lesions with one or more beyond the vertebral bodies and pelvis (20). Prostate-specific antigen (PSA) progression was determined using the criteria defined by the Prostate Cancer Working Group 2 (PCWG2) as an increase of 25% or greater and an absolute increase of 2 ng/ml or more from the PSA nadir that was confirmed by a second value obtained three or more weeks later (21).

Definition of each therapy group. All patients had received hormonal therapy with ADT alone or CAB using bicalutamide (80 mg/day) as first-line treatment. As a subsequent therapy, the patients treated with only conventional drugs [EMP (560 mg/day), ethinylestradiol (1.5 mg/day), prednisolone (10 mg/day), and flutamide (375 mg/day)] were defined as the 'conventional' group. The cases who were administered ARAT agents [enzalutamide (160 mg/day), abiraterone acetate (1000 mg/day), or both] with/without conventional drugs were defined as the 'ARAT era' group. Chemotherapy [docetaxel (70 mg/m^2 every 3 weeks) and cabazitaxel (20 mg/m^2 every 3 weeks)] was performed as appropriate at the discretion of the attending physician in both groups.

We compared OS in the ARAT era group to the conventional group. We also investigated risk factors that affect the OS of mCRPC patients. This retrospective observational study was approved by the internal ethical committee of Shiga University of Medical Science (approval number R2018-186).

Statistical analysis. The analysis of patient characteristics between the two groups was performed using the Mann-Whitney U-test and Fisher's exact test. Kaplan-Meier curves were prepared and analyzed using the log-rank test to evaluate the rate of OS. The factors affecting OS were examined using the Cox-proportional hazard model. Statistical analyses were performed using SPSS Statistics version 22 software (IBM, Armonk, NY, USA) and EZR software which is based on R and R commander (22). A $P<0.05$ denoted a statistically significant difference.

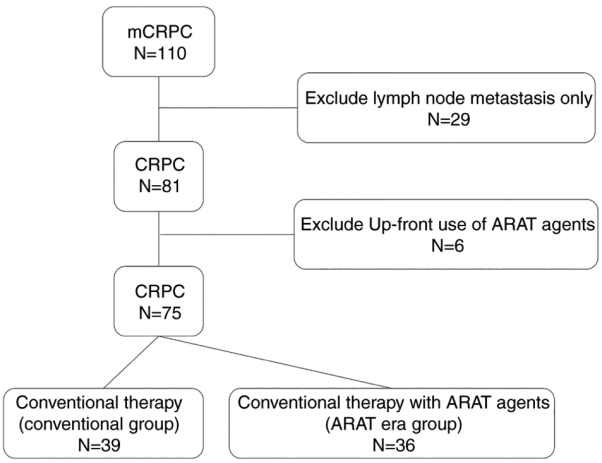

Figure 1. Trial profile of patients. ARAT, androgen receptor-axis targeted; mCRPC, metastatic castration-resistant prostate cancer.

Results

Patient characteristics. There were 110 cases of mCRPC patients who were treated with hormonal therapy. Thirty-five cases were ineligible for our study, as they had only local lymph node metastases (n=29) or were cases with up-front use of ARAT agents (n=6). Thirty-nine patients constituted the conventional group, and 36 patients constituted the ARAT era group (Fig. 1). In the ARAT era group, ARAT agents were used as a second-line therapy in fourteen patients, and as a third-line therapy in the remaining 22 patients.

Patient characteristics in the conventional and ARAT era groups are shown in Table I. The median follow-up period for all cases was 49.4 months (9.0-175.1 months). There were no significant differences between the two groups with regard to initial PSA value, Gleason grade at the time of biopsy, the state of organ metastasis, tumor volume, the PSA nadir value, and time to PSA nadir. In the ARAT era group, the age at diagnosis was significantly younger than in the conventional group. Time to CRPC was shorter in the conventional group than in the ARAT era group.

Comparison of OS between ARAT era group and conventional group. The median OS from the initial treatment was 86.2 months in the ARAT era group and 73.0 months in the conventional group. Although OS tended to be slightly longer in the ARAT era group, there was no significant difference among these groups (P=0.678, Fig. 2A). The median OS from the time of progression to CRPC was 73.1 months in the ARAT era group and 45.2 months in the conventional group. Again, although OS also tended to be slightly longer in the ARAT era group, the difference between groups was not significant (P=0.414, Fig. 2B).

Agents used in subsequent therapeutic regimens in each group. Several treatments were performed for PSA recurrence in each group, and proportion of patients receiving each treatment is shown in Table II. Flutamide was administered to 87.2 and 58.3% of patients, 48.7 and 19.4% of the patients were treated with EMP or ethinylestradiol, while 28.2 and 8.3% of patients were treated with prednisolone in the conventional group and the ARAT era group, respectively. Chemotherapy was

Table I. Characteristics of patients in the Conventional and ARAT era groups.

Variable	Conventional (N=39)	ARAT era (N=36)	P-value
Median age, years	73.0 (59.0-88.0)	68.0 (53.0-86.0)	0.037
Median initial PSA, ng/ml	355.0 (8.5-7225.3)	415.5 (6.6-3262.0)	0.907
Gleason grade, n (%)			0.161
1	1 (2.6)		
2	2 (5.1)		
3	6 (15.4)	4 (11.1)	
4	10 (25.6)	13 (36.1)	
5	12 (30.8)	17 (47.2)	
Unknown	8 (20.5)	2 (5.6)	
Metastases[a], n (%)			
Lung	5 (12.8)	9 (25.0)	0.242
Liver	3 (7.7)	1 (2.8)	0.615
Bone	34 (87.2)	33 (91.7)	>0.999
CHAARTED, n (%)			0.297
Low	12 (30.8)	8 (22.2)	
High	22 (56.4)	27 (75.0)	
Value of PSA nadir, ng/ml	0.6 (0.0-231.6)	1.3 (0.0-144.2)	0.206
Time to PSA nadir, months	8.2 (1.8-41.5)	6.3 (0.6-29.4)	0.259
Time to CRPC, months	16.4 (2.8-64.0)	9.7 (1.4-88.4)	0.027

[a]Since the prognosis differs depending on the metastatic site, the P-values have been calculated for each metastatic site. Statistical analyses of Gleason grade, metastases and CHAARTED were performed using the Fisher's exact test. For the continuous variables, the Mann-Whitney U-test was used. ARAT, androgen receptor-axis targeted; CHAARTED, chemohormonal therapy vs. androgen ablation randomized trial for extensive disease in prostate cancer; CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen.

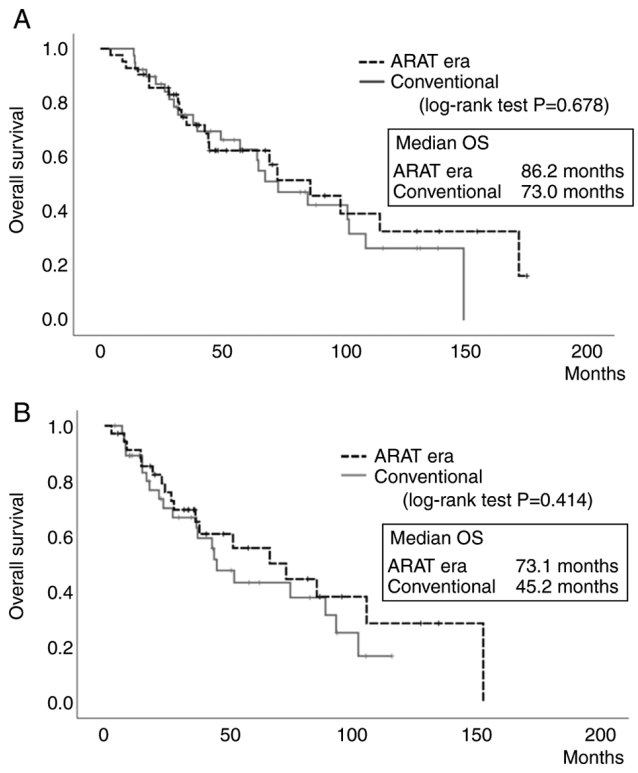

Figure 2. Kaplan-Meier curve for OS in the conventional group and the ARAT era group (A) from the time of performed initial treatment and (B) from the time of castration-resistant prostate cancer onset. ARAT, androgen receptor-axis targeted; OS, overall survival.

also administered to about half of all patients; 48.7 and 52.8% of the patients were treated with docetaxel in the group of conventional therapy and ARAT era, respectively. Although no-one in the conventional group was treated with cabazitaxel, 36.1% of the patients in the ARAT era group received this drug.

Prognostic factors for OS. We performed univariate and multivariate analysis of prognostic factors for overall survival in patients with metastatic prostate cancer and it was shown in Table III. The factors affecting OS were examined using the Cox-proportional hazard model. In this analysis, treatment of using ARAT agents was not an independent factor associated with improved OS. The mortality risk was significantly lower in cases with a higher initial PSA value (>361 ng/ml), a lower value of PSA nadir (<1.0 ng/ml), a longer time to PSA nadir (<6.7 months), and a longer time to CRPC in univariate analysis. In the multivariate analysis, mortality was significantly higher in cases with a higher initial PSA value, a lower of PSA nadir value, and a longer time to CRPC.

Subgroup analysis revealed that the outlook was better for individuals in the conventional group who were older, had a lower Gleason grade or a higher tumor volume (Fig. 3).

Discussion

In this study, we did not observe a significant difference in OS for mCRPC patients in the ARAT era group vs. those in the conventional group. However, one study has reported the

Table II. Agents used in subsequent therapeutic regimens.

Agents	Conventional (N=39)	ARAT era (N=36)	Total (N=75)
Endocrine therapy, n (%)			
Flutamide	34 (87.2)	21 (58.3)	55 (73.3)
EMP or ethinylestradiol	19 (48.7)	7 (19.4)	26 (34.7)
Prednisolone	11 (28.2)	3 (8.3)	14 (18.7)
Antineoplastic agents, n (%)			
Docetaxel	19 (48.7)	19 (52.8)	38 (50.7)
Cabazitaxel	0 (0.0)	13 (36.1)	13 (17.3)

ARAT, androgen receptor-axis targeted; EMP, estramustine phosphate.

Table III. Univariate and multivariate analysis of prognostic factors for overall survival in patients with metastatic prostate cancer.

	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age at diagnosis (≥72 years vs. <72 years)	1.29 (0.68-2.45)	0.431		
Initial PSA (≥361 ng/ml vs. <361 ng/ml)	0.52 (0.28-0.99)	0.047	0.22 (0.10-0.49)	<0.001
Gleason grade (≥4 vs. <4)	0.67 (0.30-1.49)	0.333		
Existence of visceral metastasis (yes vs. no)	1.54 (0.76-3.12)	0.230	1.80 (0.83-3.80)	0.131
CHAARTED (high vs. low)	0.89 (0.44-1.79)	0.756		
PSA nadir (≥1.0 ng/ml vs. <1.0 ng/ml)	2.13 (1.12-4.02)	0.020	2.72 (1.27-5.83)	0.010
Time to PSA nadir (≥6.7 vs. <6.7 months)	0.24 (0.11-0.49)	<0.001	0.28 (0.10-0.77)	0.014
Time to CRPC (≥12 vs. <12 months)	0.28 (0.14-0.56)	<0.001	0.58 (0.20-1.67)	0.317
ARAT treatment (yes vs. no)	0.87 (0.46-1.63)	0.679		

ARAT, androgen receptor-axis targeted; CHAARTED, chemohormonal therapy vs. androgen ablation randomized trial for extensive disease in prostate cancer; 95% CI, 95% confidence interval; CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen.

effectiveness of using ARAT agents as second-line therapy for mCRPC patients. Uemura *et al* (19) compared the therapeutic outcomes after treatment with either enzalutamide or flutamide for Japanese patients with CRPC; they found that enzalutamide significantly extended the time to PSA failure for both first-line and second-line treatment. Recently, Chowdhury *et al* (23) have suggested that the time to PSA failure of second-line treatment, so-called progression free survival 2 (PFS2), can be used as a predictor of OS, and that PFS2 can be used to measure long-term clinical benefit when OS cannot be assessed. For this reason, we expected a significantly extended OS in the ARAT era cohort of our study; however, this was not the case. One explanation for this is that patients were started on ARAT agents too late after developing CRPC to benefit from their effects. Our study included many cases in which ARAT agents were used after treatment with flutamide, EMP, and steroids. Additionally, the ARAT agents were generally used later in our study than in the study performed by Uemura *et al* (19). Furthermore, the LATITUDE study reported that OS of high-risk mCSPC patients was improved when combinations of ARAT agents were used from the time of the initial hormonal therapy (24). Considering the result of those studies, we suggest that the therapeutic effect of ARAT agents is maximized if they are started at an earlier stage of the treatment. Conversely, ARAT treatment has a weak therapeutic effect if started after onset of CRPC.

In the present study, we showed that PSA nadir and initial PSA values are prognostic factors for metastatic prostate cancer. Hamano *et al* (25) examined the data of 321 Japanese patients who received hormonal therapy for metastatic prostate cancer, and reported that PSA nadir >0.64 ng/ml and time to PSA nadir <7 M are poor prognostic factors in Japanese patients. PSA nadir ≥1.0 ng/ml and time to PSA nadir <6.7 M were identified as poor prognostic factors in the current study. We conclude that the prognosis is good in cases where the PSA nadir value is low and when there is a prolonged time to PSA failure (i.e., in cases where initial hormonal therapy is effective). On the other hand, an initial PSA value ≥361 ng/ml was identified as a good prognostic factor for OS in our current study. Yamada *et al* (26) reported that Japanese patients who received hormonal therapy and had a high PSA developed CRPC more rapidly, but responded well to AWS and AA alternation therapy, and the OS rate did not change. From this

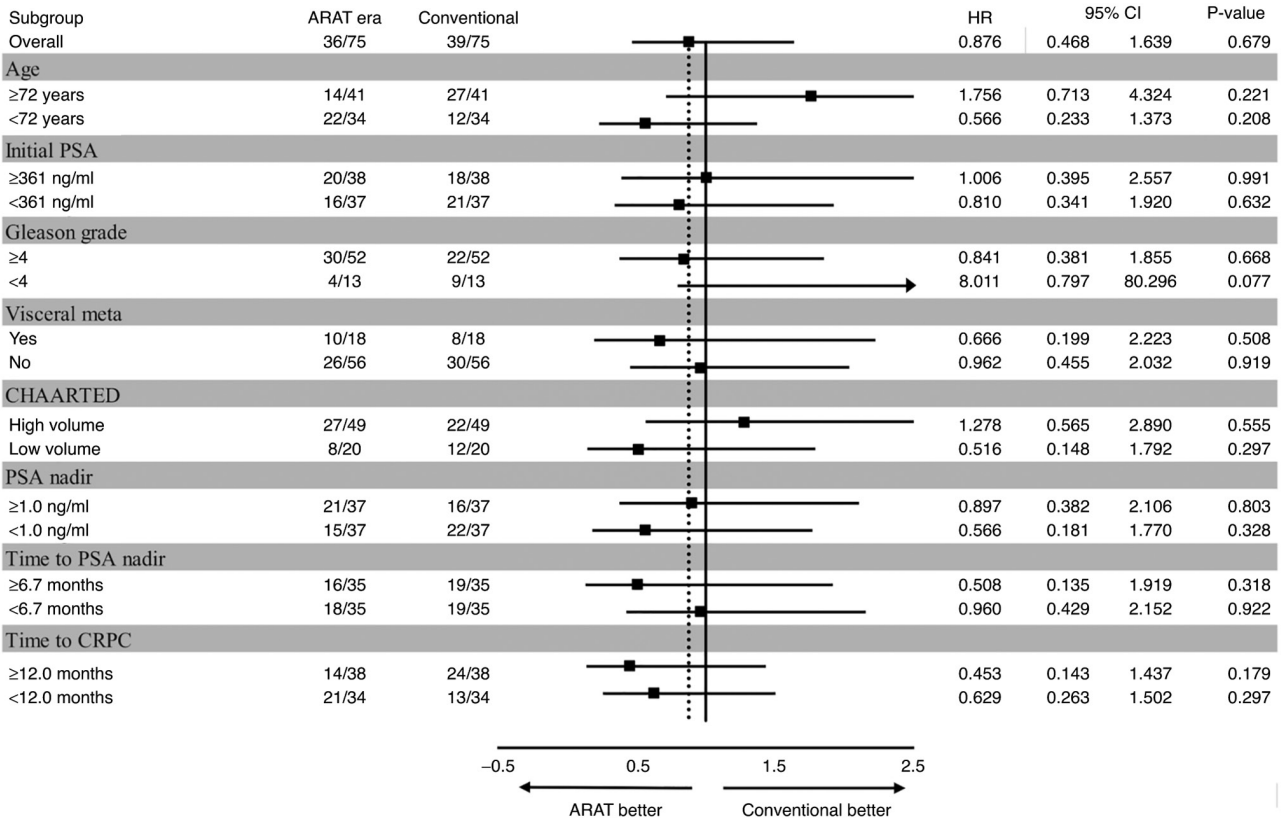

Figure 3. Subgroup analysis of overall survival. ARAT, androgen receptor-axis targeted; CHAARTED, chemohormonal therapy vs. androgen ablation randomized trial for extensive disease in prostate cancer; 95% CI, 95% confidence interval; CRPC, castration-resistant prostate cancer; HR, hazard ratio; PSA, prostate-specific antigen.

result, we infer those cases with high initial PSA value respond well to hormonal therapy, and high initial PSA value is a good prognostic factor.

In our subgroup analysis, the therapeutic effect of conventional hormonal therapy was better than that of ARAT agents in the older patients, and in those with high tumor volume, and high Gleason grades. In addition, we considered that the benefit of adding ARAT agents with conventional hormonal therapy may be small even in cases where the PSA nadir is high or the time to PSA nadir is short (i.e., patients who are likely to be refractory to hormonal therapy). However, this does not mean that the use of ARAT agents early in the initial treatment is futile. Regarding high-volume cases, Narita *et al* (27) reported that upfront use of abiraterone significantly improved OS when compared to ADT/CAB treatment. Considering these results, we recommend that ARAT reagents should be used from the time of initial hormonal therapy to obtain the maximum therapeutic effect. The problems associated with the use of ARAT agents are related to side effects specific to this class of therapeutics, as well as the increased costs. The results obtained in this study may provide useful to physicians who are considering whether to use ARAT agents at the beginning of treatment or instead add them to conventional hormonal therapy.

The present study has a few limitations. Due to its retrospective nature, there are several differences in patient characteristics, and the number of examined patients is relatively small. Although there are limitations as mentioned above, we consider that this result accurately reflects the actual clinical practice in Japan. Thus, when considering the therapy of metastatic prostate cancer in Japanese patients, we are convinced that this result from the present study is sufficiently informative and significant. We are planning further investigate this topic using an increased number of cases in future research.

In conclusion, although ARAT agents appeared to prolong the survival of patients with metastatic prostate cancer, this effect did not reach the level of statistical significance. We infer that ARAT agents have only a minimal impact on survival outcome when they are used in later lines of treatment for mCRPC. Therefore, we suggest that upfront therapy using ARAT agents at the time of the initial hormone therapy is essential, and that this can have a significantly positive effect on survival in mCSPC patients.

Acknowledgements

Not applicable.

Funding

No funding was received.

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

AW, MiN, MaN, TK, SKu, TY, KJ, AK and SKa substantially contributed to the study design and conceptualization. AW, TK and TY performed the acquisition of data for the work. SKu, KJ and MaN contributed to data analysis and interpretation. AW, SKa, MiN and AK substantially contributed to the manuscript drafting. TY, MiN and AK provided expertise and feedback. AW and SKa confirm the authenticity of all the raw data. All authors critically reviewed and revised the manuscript draft. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of Shiga University of Medical Science (Otsu, Japan; approval number R2018-186). The informed consent was obtained in the form of opt-out on the website of Shiga University of Medical Science Hospital (Otsu, Japan).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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