Original Research

The association of AR-V7 with resistance to Abiraterone in metastatic castration-resistant prostate cancer

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Abstract

Background: This paper sought to investigate the association between androgen receptor splice variant 7 (AR-V7) status in circulating tumor cells (CTCs) and resistance to abiraterone (Abi) and docetaxel (Doc) in men with metastatic castration-resistant prostate cancer (mCRPC). Methods: This was a prospective clinical study, newly confirmed mCRPC patients who were randomized going to receive Abi or Doc with age ≥18 years were enrolled to detect the AR-V7 mRNA in CTCs. The association of AR-V7 status with Gleason Score, prostate specific antigen response rate (PSA RR), hormone-sensitive duration time (HSDT), time-to event outcomes, including PSA progression-free survival (PFS), clinical PFS, radiographic PFS and cancer-specific survival (CSS) was examined. Results: 139 patients with mCPRC were enrolled; 67 received Abi and 72 received Doc. The proportion of AR-V7-positive patients was 35.8% in Abi-treated patients and 34.7% in Doc-treated patients. Our results were as follows: (1) among men receiving Abi, AR-V7-positive patients had a higher Gleason Score (8.34 ± 1.03 vs. 7.29 ± 0.76, p = 0.012) and lower PSA RR (20.8% vs. 65.1%, p = 0.001) compared with AR-V7-negative patients; in a multivariable COX model, AR-V7 positivity was an independent risk factor for shorter PSA PFS (p = 0.012), clinical PFS (p = 0.036) and radiographic PFS (p = 0.028); (2) among men receiving Doc, AR-V7-positive patients also had a higher Gleason Score compared with AR-V7-negative patients (8.86 ± 0.66 vs. 7.57 ± 0.94, p < 0.0001), but no differences in PSA RR, PSA PFS, clinical PFS, radiographic PFS or CSS were observed; (3) among AR-V7-positive patients, men receiving Abi had lower PSA RR compared with men receiving Doc (20.8% vs. 48%, p = 0.046); in a multivariable COX model, Abi was an independent risk factor for shorter PSA PFS (p = 0.040) and clinical PFS (p = 0.046); (4) among AR-V7-negative patients, there were no differences in PSA RR, PSA PFS, clinical PFS, radiographic PFS or CSS between Abi- and Doc-treated patients. Conclusion: AR-V7-positive patients commonly have a higher Gleason Score than AR-V7 negative patients, and AR-V7 positivity is strongly associated with Abi resistance in mCRPC but is not associated with the effectiveness of Doc.

Keywords: Castration-resistant prostate cancer; Androgen receptor splice variant 7; Abiraterone; Docetaxel

1. Introduction

Androgen deprivation therapy (ADT) is the most commonly used treatment for advanced prostate cancer (PCa); however, most patients still progress to castration-resistant prostate cancer (CRPC) [1]. Several agents have emerged for the treatment of CRPC, including docetaxel (Doc), abiraterone (Abi), Enzalutamide, Cabazitaxel, Radium-233 and Sipuleucel-T; these drugs not only significantly inhibit tumor progression but actually improve OS [2–4]. Among these agents, Doc and Abi are most commonly used in China due to their recent availability [5]. However, a proportion of patients are still not sensitive to Doc, Abi or Enzalutamide, and all eventually acquire secondary resistance; however, the mechanism of this remains unclear [6]. One plausible mechanism for agent resistance is the existence of androgen receptor variants (AR-Vs); androgen receptor splice variant 7 (AR-V7) is the most common sub-type of AR-Vs, its activation didn’t require the combination of androgen with androgen receptor leading to the therapy resistance [7], and it is much more common in CRPC than in localized PCa [8]. Our clinical study sought to investigate the association between AR-V7 status with resistance to Abi and Doc as well as time-to-event outcomes in men with metastatic castration-resistant prostate cancer (mCRPC), which is one of the first studies regarding that.

2. Materials and methods

2.1 Inclusion criteria

We prospectively enrolled patients with metastatic castration-resistance prostate cancer (mCRPC) who were beginning first-line treatment in our center between January 2016 and December 2017. Inclusion criteria: (1) age ≥18 years; (2) ≥1 systemic metastasis; (3) histologically confirmed prostate adenocarcinoma and progressive disease
Despite castration levels of serum testosterone (<50 ng/dL) with continued ADT; (4) ECOG score ≤ 2; Patients who had received Doc, Abi, Enzalutamide, apalutamide, cabazitaxel, radium-223, mitoxantrone and sipuleucel-T before enrollment were excluded. Abi was given at a dose of 75 mg/m² daily, with prednisone at a dose of 5 mg twice daily; Doc was given at a dose of 75 mg/m² every three weeks for 10 cycles, with prednisone at a dose of 5 mg twice daily. Radical prostatectomy allowed before enrollment and Doc or Abi were randomly selected after enrollment.

2.2 Detection of CTCs and AR-V7

Peripheral blood samples for analysis of CTCs were obtained from eligible patients before receiving Abi or Doc. CTCs collection protocol: 5 mL venous blood was collected by a vacuum blood collection vessel containing EDTA; the vessels were immediately sent to laboratory or stored in a 4 °C refrigerator for less than 48 hours. A human peripheral blood leukocyte removal kit was used to lyse red blood cells, and an immune micromagnetic particle method was used to remove white blood cells through negative screening of immunomagnetic beads. In this study, two kinds of magnetic beads, both of which are super-paramagnetic beads with a diameter of 4.5 meters, were used as a covalently coupled mouse-human anti-human CD45 antibody and as a monoclonal anti-human CD14 antibody. The remaining cell suspension was concentrated to collect CTCs and mixed with 100 µL separation buffer, which was stored at −20 °C [6,9]. A self-referenced CTC unit derived from a standard curve was used to indicate the abundance of CTCs in 5 mL venous blood.

AR-V7 mRNA detection in CTCs: Materials required: (1) QIAGEN-74034 RNeasy Plus Micro Kit: RNA extraction Kit (QIAGEN Biology, Cat. n.74034, Dusseldorf, Germany); (2) Vazyme HisScript ® II Q RT SuperMix for qPCR (+ gDNA wipers): Reverse transcription kit (Vazyme Botech Co, Cat. No. R233-01, Nanjing, Jiangsu province, China); (3) applied biosystems TaqMan ® Universal Master Mix II: PCR amplification reagents (Thermofisher, Cat. No. 4440040, Waltham, MA, USA). In this study, RNA was extracted from the collected samples for qPCR amplification after reverse transcription AR-V7 status was classified as positive or negative according to the literature [10,11]. Sequencing results: AR-V7 probe CCGGGTGGCAATGGCAA; GAPDH probe TC-CGGTTTCAGCCCTGGA.

2.3 Study design and assessment

In patients where CTCs were detected, a computer-based random distribution was used to randomized patients to receive either Abi or Doc, ADT therapy was continued in all the patients AR-V7 mRNA in CTCs was detected before patients received Abi or Doc. Total prostate specific antigen (tPSA), free PSA, f/t PSA ratio (the ratio of free PSA to total PSA) and serum testosterone was detected every 1–2 months. Emission-computed tomography (ECT) bone scan, magnetic resonance imaging (MRI) and computerized tomography (CT), including chest-, abdomen- and pelvis-or prostate-specific membrane antigen (PSMA) PET-CT were performed every 2 to 3 months to determine the number and diameter of bone and soft tissue lesions (10 cases with PSMA PET, 129 with ECT bone scan, MRI and CT).

Follow-up data was assessed after enrollment: (1) PSA RR—proportion of patients with PSA response, and patients with PSA response were defined as PSA that declined ≥50% from baseline and maintained for ≥4 weeks after receiving agents according to Prostate cancer working group 2 (PCWG2) criteria [12]; (2) PSA PFS—time free from PSA progression, and PSA progression was defined at a level of PSA ≥ 2 ng/mL that increased ≥25% above the nadir; (3) clinical PFS—time free from clinical progression, and clinical progression was defined as a worsening of cancer-related symptoms or new cancer-related complications according to Zubrod performance status (ZPS) criteria [6]; (4) radiographic PFS—time free from radiographic progression, which was defined as an increase in the diameter of soft tissue metastatic lesions by ≥20% or ≥2 new metastatic bone lesions observed through imaging according to response evaluation criteria in solid tumors (RECIST) guidelines [10]; (5) cancer-specific survival (CSS), time to death because of tumor progression by death certification; (6) PSA responding time (PSA RT), which was defined as PSA response (PSA decreased by 50% from the baseline) [12] at any time after being treated with Abi or Doc; (7) hormone-sensitive duration time (HSDT), which was defined as disease progression (any one of radiography, PSA or clinic progressed) any time after the initial application of ADT therapy.

2.4 Statistical method

Statistical analyses were performed in two parts: (1) clinical data were assessed and compared between AR-V7-positive and negative cases in patients receiving Abi and Doc, respectively; (2) clinical data were assessed and compared between Abi and Doc in AR-V7-positive and AR-V7-negative patients, respectively.

Measurement data conforming to normal distribution analyzed by Shapiro–Wilks test are represented as mean ± standard deviation (SD), and an independent sample t-test was used for comparison between groups. Data on categorical variables are presented as frequency with percentages and differences among groups are analyzed with Pearson’s chi-square test or Fisher’s exact test as appropriate. Kaplan–Meier and log-rank tests were used to evaluate the PFS and CSS in different subgroups and a survival curve was described. Multivariable COX mode was used to assess the relationship between detection of AR-V7 in CTCs and prognosis in patients receiving abiraterone, adjusting for age, baseline PSA level, Gleason score and visceral metastasis. The software used to run the analysis was IBM-SPSS.
Fig. 1. Kaplan–Meier analysis of prostate specific antigen (PSA) progression free survival (PFS), clinical PFS, radiographic PFS and cancer specific survival (CSS) according to androgen receptor splice variant 7 (AR-V7) status in abiraterone (Abi) treated patients. (A) PSA PFS of AR-V7-negative patients was longer than AR-V7-positive patients by log-rank test, \( p < 0.0001 \). (B) Clinical PFS of AR-V7-negative patients was longer than AR-V7-positive patients by log-rank test, \( p = 0.012 \). (C) Radiographic PFS of AR-V7-negative patients was longer than AR-V7-positive patients by log-rank test, \( p = 0.037 \). (D) No differences in CSS were observed according to AR-V7 status by log-rank test, \( p = 0.474 \).

3. Result

3.1 Patient characteristics

From January 2016 to December 2017, 155 patients were screened and 139 (89.7% yield) with detectable CTCs were enrolled, of whom, 67 received Abi and 72 received Doc. Among patients enrolled, 111 (79.86%) with only bone metastases, 14 (10.07%) with only visceral metastases and 14 (10.07%) with bone and visceral metastases (Table 1). Median age was 67.15 years (range, 56–83) and median follow-up time was 36.37 months (range, 28–52). There was no difference in median age or follow up time between the Abi and Doc groups. A total of 35.25% (49 of 139) patients were AR-V7-positive, and 35.8% (24 of 67) of the Abi-treated patients and 34.7% (25 of 72) of the Doc-treated patients were AR-V7-positive. The Gleason Score of the AR-V7-positive patients was significantly higher than for the AR-V7-negative patients (8.63 ± 1.08 vs. 7.42 ± 1.01, \( p = 0.009 \)), which was applicable for both Abi- and Doc-treated patients; HSDT of AR-V7-positive...
patients was significantly shorter compared with AR-V7-negative patients for both Abi- and Doc-treated patients (Table 2). Gleason Score, baseline PSA level and HSDT were compared between Abi and Doc in AR-V7-positive and -negative patients, respectively; differences were not statistically significant (Table 3). In patients with tumor progression, other anti-cancer therapies were needed.

3.2 Time-to-event outcome analysis

3.2.1 Comparison of time-to-event outcomes according to AR-V7 status in Abi-treated patients

In Abi-treated patients, the PSA RR of AR-V7-positive patients was significantly lower than that among AR-V7-negative patients ($p = 0.001$), while the PSA RT was significantly longer ($p < 0.001$) (Table 1). PSA PFS, clinical PFS and radiographic PFS among AR-V7-positive patients were significantly shorter than in AR-V7-negative patients; median CSS was 200 days shorter among AR-V7-positive patients than AR-V7-negative patients, but the difference was not statistically significant, $p = 0.144$ (Table 2).

A Kaplan–Meier analysis model was used to evaluate the association between AR-V7 status and time-to-event outcomes; AR-V7 positivity was associated with shorter PSA PFS, clinical PFS and radiographic PFS, but not of CSS (Fig. 1). In a multivariable COX model adjusted for baseline PSA level, Gleason Score, age and vesical metastasis, AR-V7 positivity remained an independent risk factor of shorter PSA PFS, clinical PFS and radiographic PFS (Table 4, Ref. [1]).

3.2.2 Comparison of time-to-event outcomes according to AR-V7 status in Doc-treated patients

Among 72 Doc-treated patients, PSA RR, PSA RT, PSA PFS, clinical PFS, radiographic PFS and CSS were assessed and compared between AR-V7-positive and -negative patients; no statistically significant differences were found (Table 2).

3.2.3 Comparison of time-to-event outcomes between Abi and Doc in AR-V7-positive patients

Among 49 AR-V7-positive patients, PSA RR was significantly lower in Abi-treated patients than in Doc-treated patients, while PSA RT was significantly longer ($p < 0.001$) (Table 3). PSA PFS and radiographic PFS of Abi were significantly shorter than Doc; clinical PFS and CSS of Abi were shorter but the difference was not statistically significant (Table 3). A Kaplan–Meier analysis model was used to evaluate the association between agents and time-to-event outcomes in AR-V7-positive patients, and Abi was associated with shorter PSA PFS and radiographic PFS but not clinical PFS.

| Variables      | Bone only | Visceral only | Bone and visceral | $p$ value |
|----------------|-----------|---------------|-------------------|-----------|
| AR-V7(+)       | 37        | Abi 18        | 5                 | Abi 3     | 0.469 |
| n (%)          | (75.5)    | Doc 19        | (10.2)            | Doc 2     |       |
| AR-V7(–)       | 74        | Abi 36        | 9                 | Abi 5     |       |
| n (%)          | (82.8)    | Doc 38        | (10)              | Doc 4     |       |

There is no statistically difference of distribution of metastatic sites between AR-V7 positive and AR-V7 negative patients.

| Table 1. The distribution of metastatic sites. |
|-----------------------------------------------|
| Variables | Bone only | Visceral only | Bone and visceral | $p$ value |
|-----------|-----------|---------------|-------------------|-----------|
| AR-V7(+)  | 37        | Abi 18        | 5                 | Abi 3     | 0.469 |
| n (%)     | (75.5)    | Doc 19        | (10.2)            | Doc 2     |       |
| AR-V7(–)  | 74        | Abi 36        | 9                 | Abi 5     |       |
| n (%)     | (82.8)    | Doc 38        | (10)              | Doc 4     |       |

Table 2. Clinical characteristic and time-to-event outcomes according to AR-V7 status in Abi- and Doc-treated patients.

|                | Abi, n = 67 | Doc, n = 72 |
|----------------|-------------|-------------|
| Population, n (%) | 24 (35.80) | 43 (64.2)   |
| Age, years       | 66.91 ± 7.21| 67.43 ± 6.92|
| GS              | 8.43 ± 1.03 | 7.29 ± 0.76 |
| Baseline PSA Level, ng/mL | 4.68 ± 4.39 | 9.13 ± 12.8  |
| HSDT, days       | 440 ± 113.14| 524.9 ± 71.06|
| PSA RR, n (%)    | 5 (20.80)   | 28 (65.10)  |
| PSA RT, days     | 139.75 ± 30.97| 62 ± 24.98  |
| PSA PFS, days    | 139 ± 57.31 | 499.41 ± 242.74|
| Clinical PFS, days | 241.8 ± 124.23| 442.29 ± 167.12 |
| Radiographic PFS, days | 214.83 ± 112.96| 509.67 ± 213.14 |
| CSS, days        | 1000 ± 289.82| 1218.95 ± 314.62 |

Abi, abiraterone; Doc, docetaxel; HSDT, hormone-sensitive duration time; PSA RR, PSA responding rate; PSA RT, PSA responding time (time since patients began receiving Abi or Doc to PSA response); PFS, progression-free survival time; CSS, cancer-specific survival.
Table 3. Clinical characteristic and time-to-event outcomes of abiraterone- and docetaxel-treated patients with AR-V7-positive status or AR-V7-negative status.

| AR-V7 positive, n = 49 | AR-V7 negative, n = 90 |
|------------------------|------------------------|
| Abi 24 25 p 0.236 Abi 43 47 p 0.851 |
| Doc 70.14 ± 3.37 0.178 Doc 7.57 ± 0.94 0.494 |
| Age, years 66.91 ± 7.21 0.410 Age, years 67.43 ± 6.92 0.580 |
| GS 8.43 ± 1.03 0.662 GS 7.29 ± 0.76 0.494 |
| PSA, ng/mL 4.68 ± 4.39 0.031 PSA, ng/mL 9.13 ± 12.80 0.372 |
| HSDT, days 440 ± 113.10 0.560 HSDT, days 524.9 ± 71.06 0.588 |
| PSA RR, n (%) 5(20.80) 0.046 PSA RR, n (%) 28(65.10) 0.120 |
| PSA RT, days 139.75 ± 30.97 0.029 PSA RT, days 62 ± 24.98 0.478 |
| PSA PFS, days 139 ± 57.31 0.031 PSA PFS, days 437.55 ± 238.42 0.372 |
| Clinical PFS, days 321.50 ± 224.63 0.031 Clinical PFS, days 476.93 ± 265.28 0.388 |
| Radiographic PFS, days 624 ± 24.98 0.478 Radiographic PFS, days 75.75 ± 33.64 0.478 |
| CSS, days 1000 ± 289.83 0.332 CSS, days 1139.43 ± 284.95 0.588 |

Abi, abiraterone; Doc, docetaxel; HSDT, hormone-sensitive duration time; PSA RR, PSA responding rate; PSA RT, PSA responding time (time since patients began receiving Abi or Doc to PSA response); PFS, progression-free survival; CSS, cancer-specific survival; PSA, prostate specific antigen.

Table 4. Multivariable Cox regression analysis of time-to-event outcomes in patients treated with Abi according to AR-V7 status.

| Variables | Multivariable Cox regression analysis |
|-----------|--------------------------------------|
| PSA PFS   | AR-V7 (–) [1] HR 0.15 95% CI 0.13–0.45 0.012 |
| AR-V7 (+) | AR-V7 (–) [1] HR 0.41 95% CI 0.24–0.83 0.036 |
| AR-V7 (+) | AR-V7 (–) [1] HR 0.32 95% CI 0.18–0.73 0.028 |
| Clinical PFS | AR-V7 (–) [1] HR 0.48 95% CI 0.35–0.78 0.040 |
| AR-V7 (+) | AR-V7 (–) [1] HR 0.65 95% CI 0.44–0.98 0.046 |
| AR-V7 (+) | AR-V7 (–) [1] HR 0.99 95% CI 0.75–1.15 0.772 |

Ref, reference; each multivariable model included 5 variables (AR-V7 status, baseline PSA level, Gleason Score, age and vesical metastasis). AR-V7 positive was the independent factor predicting the outcome of PSA PFS, clinical PFS and rPFS in patients treated with Abi.

Table 5. Multivariable Cox regression analysis of time-to-event outcomes in AR-V7 positive patients treated with Abi or Doc.

| Variables | Multivariable Cox regression analysis |
|-----------|--------------------------------------|
| PSA PFS   | Doc [1] HR 0.48 95% CI 0.35–0.78 0.040 |
| Ar-V7 (+) | Doc [1] HR 0.65 95% CI 0.44–0.98 0.046 |
| Ar-V7 (+) | Doc [1] HR 0.99 95% CI 0.75–1.15 0.772 |

Ref, reference; each multivariable model included 5 variables (AR-V7 status, baseline PSA level, Gleason Score, age and vesical metastasis). Abi was the independent factor associated with the outcome of PSA PFS and clinical PFS in AR-V7 positive patients.

4. Discussion

This study evaluated the association of AR-V7 status and Abi resistant in mCPRC patients. According to multivariable COX model we concluded that AR-V7 was the independent factor associated with Abi resistant and might be used as a biomarker guiding treatment strategy, the result was consistent with results of previous studies [6]; we also found that in AR-V7 positive patients, the HSDT time and PSA RR was much lower while PSA RT was much longer than that in AR-V7 negative patients, AR-V7 might be associated with the rapid tumor progression in mHSPC phase, and influence the therapy efficiency of Abi in mCRPC phase due the longer PSA RT and lower PSA RR, to our knowledge, there is little or no information in the
Fig. 2. Kaplan–Meier analysis and comparison of PSA PFS, clinical PFS, radiographic PFS and CSS between Doc and Abi. (A) PSA PFS of docetaxel (Doc)-treated patients was longer than Abi by log-rank test, $p = 0.002$. (B) No significant difference in clinical PFS between Doc and Abi by log-rank test, $p = 0.107$. (C) Radiographic PFS of Doc-treated patients was longer than Abi by log-rank test, $p = 0.004$. (D) No significant difference in CSS between Doc- and Abi-treated patients by log rank test, $p = 0.485$.

literature regarding that. Since the mechanism of CRPC is complicated and not well understood, recently some studies suggested that AR-Vs might be associated with CRPC [13]. As a subtype of AR-Vs, studies found that AR-V7 is more common in CRPC than in mHSPC and local PCa, it might be associated with tumor progression [14,15]. Another study shows the same conclusion that the presence of AR-V7 is responsible for tumor progression [9]. Abi and Doc are the most commonly used agents for CRPC in China. However, the response rate for Doc is about 50%, yet half of men do not benefit from it. The mechanism of agent resistance has been detected by many studies [15–19] but the mechanism is still unknown. In recent years, several studies began to detect the association of AR-V7 status and therapeutic outcomes of Doc. Research in 2015 analyzing AR-V7 mRNA in CTCs in 37 CRPC patients who received Doc has shown that AR-V7 positive is not associated with PSA RR and PSA PFS [20]. Thadani Mulero, et al. [21] claimed that AR-V7 is associated with Doc resistance while AR-V567es is not. Another study suggested that AR-V7 could affect the efficiency of Doc only when above a certain level [22].

The association of AR-V7 with Doc resistant is still controversial. In our study, clinical data support the claim that AR-V7 status is not associated with the therapeutic efficiency of Doc. As for Abi, our study supports a growing body of literature suggesting that PCa patients with AR-V7 positive were resistant to Abi [7,23,24]. Hu R, et al.
claimed that AR-V7 is commonly expressed in CRPC and the response rate of Abi is low. Another clinical study claims that there is a strong association between the presence of AR-V7 in CTCs and resistance to Abi [6], and a subsequent study shows that, in AR-V7-positive patients, Doc is more beneficial than Abi or Enzalutamide; however, the scale of this study is small, with only 37 patients included [19]. A prospective study enrolled 118 CRPC patients treated with Abi or Enzalutamide, showing that AR-V7 positivity is associated with shorter PFS and OS [25]. Our study supports the claim that AR-V7 positivity is associated with Abi resistance in mCRPC patients as previous study reported, and clinical data suggest that AR-V7 positivity is strongly associated with a higher Gleason Score, lower PSA RR, and shorter HSĐT and PFS (PSA, clinical and radiographic) which all suggested a poor prognostic of AR-V7 positive patients. In fact, the frequency of AR-V7-positive patients was higher in our cohort than in previous work [6], raising the possibility of an association between AR-V7 positivity and ethnicity. From the results of our research, the role of AR-V7 in guiding treatment strategy was reliable. Thus, tremendous time and money could be saved as a recent study presumed that USD 1.5 billion could be saved if AR-V7 detection were to be used for agent selection in CRPC [26].

This study still has some limitations. First, the short follow-up time; second, not all CRPC patients have detectable CTCs, which may limit the role of AR-V7 in CTCs as predictive marker for agent resistance; third, inconsistent imaging methods may cause bias; fourth, not all the factors (i.e., comorbidities) related to the prognostic of PCa were included, this may cause bias. Further studies are required.

5. Conclusions
In conclusion, our study confirmed that AR-V7-positive was the independent factor associated with Abi resistance in mCRPC but is not associated with the effectiveness of Doc, the predictive value of AR-V7 in guiding treatment strategy is reliable; we also found that in AR-V7 positive patients, the HSĐT time was much shorter than that in AR-V7 negative patients, AR-V7 might be associated with the rapid tumor progression in mHSPC phase.

Author contributions
PD and SW designed the study. SW, YC and XT made the same contributions to this study as the first co-author. SW, YC, XT, JM, ZY, YY and XY performed the study and analyzed the data. PD and SW wrote the manuscript draft and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate
This study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Peking University Cancer Hospital and Institution in April 2018 (protocol code 2018KT27). All the patients signed informed consent before enrollment.

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Conflict of interest
The authors declare no conflict of interest.

Data availability
The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy of patients.

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