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Carbon 11-choline positron emission tomography/computed tomography and palliative local therapy for castration-resistant prostate cancer

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Abstract

Purpose Carbon 11-choline positron emission tomography/computed tomography (11C-choline PET/CT) and subsequent local therapy for oligometastatic prostate cancer have been reported to be effective, but their effectiveness in castration-resistant prostate cancer (CRPC) remains unclear. Here, we evaluated the findings of 11C-choline PET/CT in CRPC patients and the efficacy of local treatments in correspondence of the pathologic choline uptake.

Methods We collected 12 cases of CRPC patients who underwent 11C-choline PET/CT between 2014 and 2016. The outcomes assessed included age, the prostate-specific antigen (PSA) value, the findings of 11C-choline PET/CT, the subsequent treatments, the PSA response following the treatments, and the progression-free survival (PFS).

Results Seven of 12 cases (median PSA, 3.29 ng/mL) had local prostate cancer and/or one or two metastatic lesions detected by the choline PET/CT. These localized lesions were treated with radiotherapy or lymphadenectomy. PSA decreased in all the seven cases and median PSA response was 86% (range, 23–100%). Median PFS was 8.5 months (range, 2.8–25.3 months). The other five cases (median PSA, 7.41 ng/mL) had multiple metastases and systemic therapies were continued in those cases.

Conclusions 11C-choline PET/CT and the correspondent local treatments may play an important role in the treatment sequence of CRPC in selected patients.

Keywords 11-Choline positron emission tomography/computed tomography · Castration-resistant prostate cancer · Local therapy · Radiotherapy · Lymphadenectomy · Oligometastasis

Introduction

In 2019, it is estimated that there were 174,650 new cases of prostate cancer and 31,620 prostate cancer-related deaths, in the United States [1]. Castration-resistant prostate cancer (CRPC) is defined by the presence of disease

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progression despite initial androgen deprivation therapy and represents an unfavorable prognosis. The outcome has significantly improved in recent years, through the addition of abiraterone, enzalutamide and cabazitaxel to the docetaxel, but remains reserved. In the same period, several prospective or retrospective studies of local treatments to primary tumor [2] or metastatic lesions [3] for oligometastatic prostate cancer with surgery or radiotherapy were published, demonstrating positive outcomes, delaying the progression of the disease. However, CRPC patients were usually excluded from these studies with few exceptions [4, 5]. One retrospective cohort study assessed the role of radiotherapy for node-negative, localized CRPC diagnosed by imaging modalities other than choline positron emission tomography/computed tomography (PET/CT). Radiotherapy was found to achieve excellent local control; however, it seemed to have a limited role in prolonging overall survival because most patients experienced progression with distant metastasis [4]. Another case series showed that radiotherapy improved local control and was associated with a significant prostate-specific antigen (PSA) response [5].

Radiolabeled choline PET/CT has been reported to be a useful modality for evaluating prostate cancer patients. Numerous retrospective studies and one meta-analysis have clarified the high accuracy of choline PET/CT in the detection of lymph node metastases and/or distant lesions in patients with PSA relapse after radical therapy for prostate cancer [6]. Several studies found that choline PET/CT was more sensitive and specific than magnetic resonance imaging in the identification of nodal involvement, and more sensitive and specific than bone scan and contrast-enhanced CT in initial staging phase [7].

Choline PET/CT and subsequent salvage lymph node dissection or external-beam radiotherapy in correspondence of the pathologic choline uptake for recurrent prostate cancer has been reported to be effective and well tolerated [8, 9]. Several studies have assessed the response to systemic therapies of CRPC detected by choline PET/CT [10–12]. However, there is only a case report describing the treatment of CRPC by choline PET/CT-guided palliative local treatment [13]. Thus, the role of choline PET/CT in CRPC and choline PET/CT-guided local treatments remains unclear.

We, therefore, hypothesize that palliative local treatment of CRPC corresponding to the findings in radiolabeled carbon-11 (11C) choline PET/CT is more effective than treatments based on the diagnoses by conventional imaging modalities [4, 5], and that will eventually lead to improved progression-free survival. To assess the role of 11C-choline PET/CT and the efficacy of 11C-choline PET/CT-guided local treatment in CRPC, we investigated the effects of 11C-choline PET/CT-guided local treatment in patients with CRPC.

Methods

This longitudinal case series study was performed at a single center and included 12 cases of CRPC patients who underwent 11C-choline PET/CT between April 2014 and December 2016. This study was approved by the ethical committee of National Center for Global Health and Medicine (authorization number: 1552). All of the participants gave their written informed consent.

An in-house cyclotron and automated synthesis system (F200; Sumitomo Heavy Industry, Tokyo, Japan) was used in accordance with the authorized procedure to synthesize 11C-choline. PET/CT images were obtained using a PET/CT system (Biograph 16; Siemens, Erlangen, Germany) consisting of a PET scanner and multidetector row CT (16 detectors), measuring from vertex to the mid-thigh at 5 min after intravenous injection of 370 MBq of 11C-choline. Low-dose CT was performed first and used for attenuation correction and image fusion. Emission images were acquired in 3-dimensional mode for 2 min per bed position. PET data were reconstructed using a Gaussian filter with an ordered-subset expectation maximization algorithm (3 iterations, 8 subsets). Board-certificated nuclear medicine physicians interpreted PET, CT and fused PET–CT images.

The outcomes assessed included age and the PSA value at the time of 11C-choline PET/CT, the findings of 11C-choline PET/CT and other imaging modalities, initial radical treatment, time from the radical treatment to the 11C-choline PET/CT, the number of systemic treatments prior to 11C-choline PET/CT, the treatments before/after 11C-choline PET/CT, the PSA response following the subsequent treatments, the follow-up period, progression-free survival (PFS), and overall survival (OS). The PSA response rate was defined as a reduction in the PSA level from the baseline. Progression was defined as PSA progression, radiographic progression, or death from any cause. PSA and tumor progression were defined as a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir in PSA, and an increase in the size or number of lesions, respectively, based on the Response Evaluation Criteria in Solid Tumours version 1.1. The follow-up period, PFS, and OS were calculated based on the time from the local treatment to the onset of each event.

Results

The median age of 12 CRPC patients was 74 years (range, 66–83 years) and the median PSA was 5.74 ng/mL (range, 0.61–33.1 ng/mL) (Table 1). The patients had received

Table 1 The findings of 11C-choline PET/CT in CRPC patients and the subsequent treatments

Case	Age (years)	PSA (ng/mL)	11C-choline uptake (site)	SUV max	Findings of other imaging modalities	Intial radical treatment	Time from the radical treatment	No. of prior systemic treatments	Treatment before choline PET	Treatment after choline PET	PSA response rate (%)	Follow-up (months)	PFS (months)	Time to the introduction of further systemic therapy (months)	OS (months)
Cases with local therapy															
1	83	2.15	Prostate	3.9	Not performed	Not performed	–	2	Flutamide	RT (IMRT 76 Gy)	100	25.3	> 25.3	> 25.3	Alive
2	82	9.69	Prostate	6.6	CT: not detected Bone scinti: not detected	Not performed	–	4	Estramustine	RT (IMRT 78 Gy)	67	16.0	7.3	7.3	Alive
3	76	3.29	Unilateral internal iliac LN	14.8	CT: same as choline PET	IMRT	8 years 6 months	1	Bicalutamide	Salvage lymphadenectomy	86	10.6	2.8	2.8	Alive
4	66	33.13	Unilateral obturator LN	7.3	CT: same as choline PET	Brachytherapy	7 years 3 months	7	Abiraterone	RT (VMAT 50 Gy) + docetaxel	87	24.1	17.4	24.1	Alive
5	82	8.69	Unilateral pelvic LN + prostate	10.0	CT: not detected Bone scinti: not detected	Not performed	–	5	Dexamethasone	RT (IMRT 66 Gy) + dexamethasone	62	10.6	5.1	6.1	10.6
6	67	1.43	Pelvic bone (single site)	2.7	CT: not detected, Bone scinti: same as choline PET	Brachytherapy + EBRT	6 years 6 months	6	Docetaxel	RT (VMAT 37.5 Gy) + docetaxel	88	21.7	9.3	9.3	Alive
7	68	1.94	Pelvic bone (two sites)	4.5	Not performed	Brachytherapy + EBRT	7 years 4 months	8	Abiraterone	RT (VMAT 40 Gy) + abiraterone	23	11.7	8.5	11.7	Alive
Cases with systemic therapy only															
8	70	0.61	Multiple bone mets.	5.0	CT: multiple bone mets.	Not performed	–	4	Dexamethasone	Docetaxel	0	21.1	8.2	–	21.1

Table 1 (continued)

Case	Age (years)	PSA (ng/mL)	11C-choline uptake (site)	SUV max	Findings of other imaging modalities	Intial radical treatment	Time from the radical treatment	No. of prior systemic treatments	Treatment before choline PET	Treatment after choline PET	PSA response rate (%)	Follow-up (months)	PFS (months)	Time to the introduction of further systemic therapy (months)	OS (months)
9	72	4.06	Multiple bone mets.	9.2	Not performed	Not performed	–	1	Bicalutamide	Flutamide	83	13.8	10.4	–	Alive
10	78	7.41	Multiple bone mets.	8.5	CT: multiple bone mets.	Not performed	–	5	Docetaxel	Docetaxel	19	14.5	3.4	3.4	Unknown
11	79	12.97	Multiple LN mets. + prostate	9.4	Bone scinti: not detected MRI: same as choline PET	Not performed	–	4	Estramustine	Docetaxel	0	4.0	0.9	–	4.0
12	69	18.51	Multiple LN mets.	4.3	Not performed	IMRT	6 years 7 months	7	Estramustine	Abiraterone	98	20.7	20.7	–	Alive

PSA prostate-specific antigen, *SUV* standardized uptake value, *PET* positron emission tomography, *PFS* progression-free survival, *OS* overall survival, *RT* radiotherapy, *IMRT* intensity-modulated radiation therapy, *CT* computed tomography, *LN* lymph node, *VMAT* volumetric modulated arc therapy, *EBRT* external beam radiotherapy, *mets* metastases

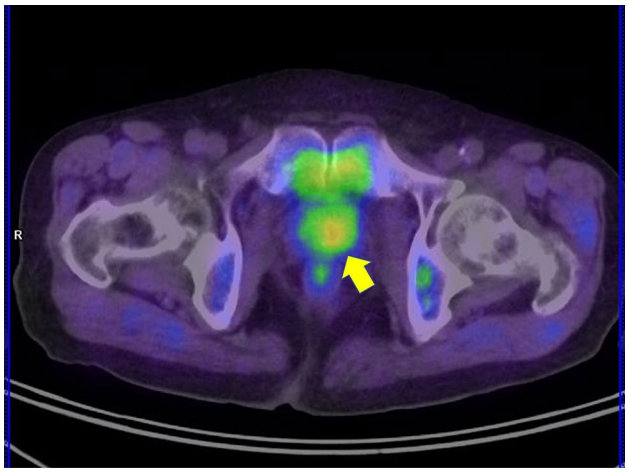

Fig. 1 In Case 1, an increased accumulation of 11C-choline in the left robe of prostate (arrow) was observed (SUV max 3.9)

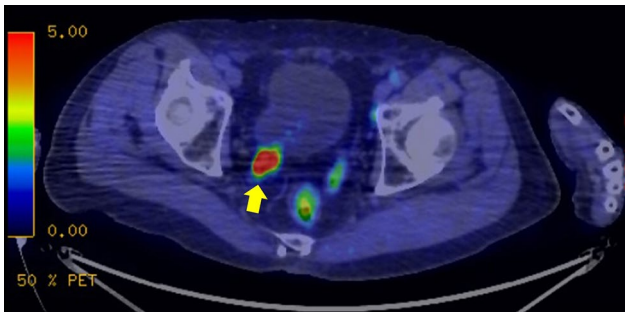

Fig. 2 In Case 3, an increased accumulation of 11C-choline in the unilateral internal iliac lymph node (arrow) was observed (SUV max 14.8)

a median of 4.5 systemic therapies (range, 1–8) prior to 11C-choline PET/CT; all of them were either surgically or medically castrated. Eight patients presented a biochemical relapse at the time of 11C-choline PET/CT. In all cases, metastatic or localized lesions were detected by 11C-choline PET/CT. A change in management occurred in five patients due to the findings in 11C-choline PET/CT.

Seven cases (PSA range, 1.43–33.1 ng/mL; median, 3.29 ng/mL) had local prostate cancer (Fig. 1) and/or one or two metastatic lesions of pelvic lymph node (Fig. 2) or bone detected by the 11C-choline PET/CT (Cases 1–7). Median SUV max was 6.6 (range, 2.7–14.8). These localized lesions were treated with external beam radiotherapy (range, 37.5–78 Gy; median, 58 Gy) or lymphadenectomy. Radiotherapy and lymphadenectomy were well tolerated, without any severe adverse events. The median PSA response was 86% (range, 23–100%). Median follow-up period was 16.0 months (range, 10.6–25.3 months) and median PFS was 8.5 months (range, 2.8–25.3 months). The median time to the introduction of further systemic therapy was 9.3 months (range, 2.8–25.3 months). Notably, Case 1 achieved complete remission, which continued for 25.3 months, without LHRH agonist, any anti-androgen drugs or chemotherapy.

In the other five cases (PSA range, 0.61–18.5 ng/mL; median, 7.41 ng/mL), multiple bone or lymph node metastases were detected, and systemic therapies were continued (Cases 8–12). After a median follow-up period of 14.5 months (range, 4.0–21.1 months), two of the five cases experienced progression and died of prostate cancer. Median PFS of the systemic therapies after the 11C-choline PET/CT was 8.2 months (range 0.9–20.7 months). Case 9 achieved a PSA response with flutamide, and subsequent 11C-choline PET/CT also revealed the decreased accumulation of 11C-choline.

Discussion

We reviewed 12 CRPC patients who underwent 11C-choline PET/CT. There were seven patients with one or two metastatic and/or primary lesions. They underwent local therapy and all of them experienced a PSA response. The other five patients with multiple metastases were not considered to be indicated for local therapy.

At the time of writing, there is only one case report describing the treatment of CRPC with stereotactic body radiotherapy (SBRT) against the active lesions revealed by choline PET/CT [13]; the patient with CRPC underwent five courses of 18F-choline PET/CT and subsequent SBRT to five metachronous lesions over a period of 4 years, which yielded good PSA control and postponed the start of the next systemic therapy for almost 5 years. To our knowledge, our report is the first case series to demonstrate the outcomes of palliative local treatment against the viable lesions revealed by choline PET/CT in CRPC patients.

In the present study, the median PFS of the palliative local treatment in CRPC patients was 8.5 months and could delay the initiation of the subsequent systemic therapy for the median period of 9.3 months. It is consistent with one prospective study, which demonstrated that 18F-choline PET/CT and corresponding stereotactic body radiotherapy delayed the start of systemic therapy in 29 hormone-naïve patients with oligometastatic prostate cancer [14]. Notably, Case 1 achieved complete remission by salvage radiotherapy to the prostate with radical doses. Case 1 and 2 did not present oligometastases but only local progression when they progressed to CRPC after a palliative hormonal therapy. Our results suggest that the prognosis in these cases is better, even if they have been already castration resistant.

Choline PET/CT can detect lesions that are undetectable by conventional modalities [7]. Thus, it is hypothesized that local therapy based on the findings in choline PET/CT would

be more effective than that led by conventional examinations. The viable primary lesions of Cases 2 and 5 were only detected by 11C choline PET/CT, and not by enhanced CT. In both cases, radiation to the prostate reduced the PSA level by more than 60%; the PFS of Cases 2 and 5 was 7.3 months and 5.1 months, respectively.

In the present study, all patients had 11C-choline PET/CT-positive lesions. One previous retrospective study demonstrated that detection rate was 73% for a PSA value ≥ 3 ng/mL, while 36% for a PSA value < 1 ng/mL; it showed a strong relationship with the serum PSA level [15]. Thus, for palliative purposes, choline PET/CT may have more advantages than other modalities because choline PET/CT can accurately detect the most viable lesions in CRPC patients, due to the relatively high PSA. In our study, the number of locally treated lesions was up to two. However, further investigation is required to define the optimal number of lesions [14, 16, 17].

As shown in previous studies, choline PET/CT is useful for the evaluation of systemic therapy [10–12]. There was only one case in the present study in which a patient received a second 11C-choline PET/CT examination to evaluate the response to systemic therapy (Case 9). The second 11C-choline PET/CT examination showed a decreased accumulation, which corresponded with the PSA response.

Our results suggested that intention of administering palliative local treatments in CRPC patients may be a new indication for 11C-choline PET/CT, that 11C-choline PET/CT and subsequent local treatment may play an important role in the treatment sequence of selected CRPC patients, and that it may postpone the initiation of the subsequent systemic therapy. 11C-choline PET/CT and palliative local treatment might be indicated for some patients with few remaining treatment options, or patients who have severe comorbidities and cannot tolerate systemic therapy.

Recently, several studies have reported that PET/CT using 68 gallium-prostate-specific membrane antigen (PSMA) shows a higher detection rate than 11C-choline PET/CT for metastases of prostate cancer [18, 19]. In the future, if PSMA PET/CT is more available for clinical use and stereotactic body radiotherapy with it can improve outcomes, our report will provide useful information on local treatment for CRPC patients.

The present study is associated with some limitations. In some cases, concurrent systemic therapy made it difficult to assess the efficacy of local therapy. Furthermore, the study population was relatively small, and the follow-up period was relatively short; thus, the survival benefit is not clear. It also has the limitation of availability because 11C-choline has a short half-life of 20 min. Further studies are required to assess this treatment strategy.

In conclusion, this is the first case series to describe a high PSA response rate to palliative local treatment in patients with either oligometastatic or localized CRPC detected by 11C-choline PET/CT.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval This study was approved by the ethical committee of National Center for Global Health and Medicine (authorization number: 1552). All of the participants gave their written informed consent.

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