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Original Article

Evaluation of Treatment Response in Prostate Cancer and Renal Cell Carcinoma Patients Using ^{11}C-choline PET/CT Findings

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We investigated the effectiveness of ^{11}C-choline-positron emission tomography/computed tomography (PET/CT) for evaluating treatment response in patients with prostate cancer or renal cell carcinoma. We performed 34 ^{11}C-choline PET/CT scans before/after a combined total of 17 courses of treatment in 6 patients with prostate cancer and 2 with renal cell carcinoma. The 17 treatments including hormonal therapy, radiotherapy, chemotherapy, radium-223, molecular target therapy, radiofrequency ablation, transcatheter arterial embolization, and cancer immunotherapy yielded 1 (5.9%) complete metabolic response (CMR), 3 (17.6%) partial metabolic responses (PMRs), 2 (11.8%) stable metabolic diseases (SMDs), and 11 (64.7%) progressive metabolic diseases (PMDs). Target lesions were observed in bone (n = 14), lymph nodes (n = 5), lung (n = 2), prostate (n = 2), and pleura (n = 1), with CMR in 4, PMR in 10, SMD in 8 and PMD in 2 lesions. SUVmax values of the target lesions before and after treatment were 7.87 ± 2.67 and 5.29 ± 3.98, respectively, for a mean reduction of −35.4 ± 43.6%. The response for the 8 prostate cancer-treatment courses was PMD, which correlated well with changes in serum prostatic specific antigen (PSA) (7 of 8 cases showed increased PSA). ^{11}C-choline-PET/CT may be an effective tool for detecting viable residual tumors and evaluating treatment response in prostate cancer and renal cell carcinoma patients.

Key words: treatment response, ^{11}C-choline PET/CT, prostate cancer, renal cell carcinoma

Monitoring the treatment response in cancer patients is crucial to making decisions regarding further treatment. Currently, the accepted standard for assessing responses to therapy involves the use of objective response criteria, including computed tomography (CT) findings (Response Evaluation Criteria in Solid Tumors [RECIST]) [1]. However, the RECIST 1.1 criteria have certain limitations, especially with respect to assessment of the therapy response in bone [1, 2].

Functional imaging modalities such as positron emission tomography (PET) represent an innovative approach for assessment of the therapy response. For example, PET/CT with fluorodeoxyglucose has been shown to detect therapeutic effects in cases with a number of different tumor entities earlier and more precisely

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than conventional imaging methods [3,4]. Also, PET/CT with ^{11}C-choline or ^{18}F-fluorocholine has emerged as a useful tool for investigating patients with prostate cancer because of its ability to show the site of tumor recurrence earlier than other imaging methods in a single examination [5-7], and a recent paper showed the results of choline PET/CT for staging and restaging renal cell carcinoma [8]. However, few studies have evaluated the use of choline PET/CT for the assessment of treatment response in patients with prostate cancer [9-12] or renal cell carcinoma [13]. Therefore, the usefulness of choline PET/CT for evaluating treatment responses in such cases has yet to be clarified.

In the present study, we investigated the role of ^{11}C-choline PET/CT in the evaluation of the response to various treatments in patients with prostate cancer and renal cell carcinoma.

Materials and Methods

Patients. This prospective study was approved by the ethics committee of our institution (approval no. 2213). Informed consent was obtained from each patient after a full explanation of the procedure details. From January 2016 to May 2018, a total of 8 patients (age range 44-79 years, median 62.4 years) — 6 males with prostate cancer and 2 females with renal cell clear cell carcinoma — underwent a total of 34 ^{11}C-choline PET/CT scans before and after 17 courses of treatment, including molecular target therapy (n = 3), hormonal therapy (n = 3), molecular target and radiation therapy (n = 2), hormonal and radiation therapy (n = 2), radium-223 therapy (n = 2), chemotherapy (n = 1), radiation therapy (n = 1), cancer immunotherapy (n = 1), radiofrequency ablation and molecular target therapy (n = 1), and transcatheter arterial embolization and molecular target therapy (n = 1) (Tables 1, 2).

^{11}C-choline PET/CT. ^{11}C-choline was synthesized using a commercial module, as described by Hara [14], using a CYPRIS-325R cyclotron (Sumitomo Heavy Industries [SHI], Tokyo). Acquisition of emission scans from the mid-thigh to head was started approximately 6 minutes after the intravenous injection of ^{11}C-choline at 3.0 MBq/kg body weight. All PET/CT examinations were performed using a PET/CT scanner equipped with a 64-multi-detector CT device (Gemini TF64; Philips Medical Systems, Eindhoven, the Netherlands). Whole-body PET acquisition in 3D mode was performed from the mid-thigh to the top of the head (1.5 min per bed position, 6-8 bed positions) and reconstructed using the ordered-subset expectation maximization reconstruction algorithm (33 subsets, 3 iterations, 4 mm per slice), with attenuation correction based on low-dose CT (120 kVp, 100 mA, slice thickness 2 mm, transverse field of view 600 mm), which was also used for anatomical correlation.

Image analysis. Two experienced readers, each with 3 years of experience with ^{11}C-choline PET/CT and no knowledge of other imaging or clinicopathological results, interpreted all of the obtained ^{11}C-choline PET/CT images, with decisions based on consensus. Semiquantitative analysis of abnormal radiotracer uptake for each lesion was also performed using SUVmax, which was defined as the highest SUV value for pixels with the highest count within the volume of interest (VOI). Here, SUV was defined as VOI radioactivity concentration (Bq/mL)/[injected dose (Bq)/patient weight (g)]. Values were determined for focal areas of uptake and recorded.

Tumor response assessment. Post-treatment ^{11}C-choline PET/CT findings were compared with baseline PET findings to assess the imaging response to treatment according to the European Organization for Research Treatment of Cancer (EORTC) criteria [3], as noted in previous reports [9-12]. The appearance of a new PET-positive lesion in the second PET examination was considered to represent progressive metabolic disease (PMD). An SUVmax increase of < 25% or a decrease of < 25% for previously noted lesions without additional lesion development was considered to be stable metabolic disease (SMD), while an SUVmax decrease of ≥ 25% for previously noted lesions in the second PET in relation to the first PET examination without additional lesion development was considered to be a partial metabolic response (PMR). Second PET scan findings that were negative with no pathological choline uptake were considered to represent a complete metabolic response (CMR). When diffuse metastatic disease spread (> 10 lesions) was seen, SUVmax was determined for the 10 lesions with the highest level of uptake.

Statistical analysis. The final diagnosis was obtained based on radiological imaging findings or clinical follow-up results, including serum prostatic specific antigen (PSA) level, MRI, CT, bone scintigraphy, and ^{11}C-choline PET/CT findings. For comparisons of two

Table 1 Renal cell carcinoma patient and tumor characteristics

	Age	Initial stage	Previous treatment history	Lesion	Therapy	Size mm (pre)	Size mm (post)	% Size change	SUV max (pre)	SUV max (post)	% SUV max change	EORTC	New lesions
1	46	T2N1M0	Surgery, Molecular therapy and RT	Bone	RFA and Molecular therapy				8.41	0	−100	CMR	
	(Fig.1)			LN	Molecular target therapy	6	0	−100	3.7	0	−100	CMR	
				Total								CMR	Other LN
2	44	T2N1M0	Surgery	LNs	Molecular target therapy	10	6	−40	8.73	2.83	−67.6	PMR	
				Bone	RT				9.45	0	−100	CMR	
				Total								PMR	
3	54	T2N1M0	Surgery, Molecular therapy, and RT	Multiple Bone	TAE and Molecular therapy				7.17	3.8	−47	PMR	
				Multiple lung	Molecular target therapy	16	13	−18.8	5.8	2.72	−53.1	PMR	
				Total								PMR	
4	47	T2N1M0	Surgery, Molecular therapy, RT, RFA, and Cancer immunotherapy	LNs	Molecular target therapy	10	7	−30	9.39	3.23	−65.6	PMR	
				Multiple Bone	Molecular target therapy				6.77	4.25	−37.2	PMR	
				Multiple Pluera	Molecular target therapy	25	17	−32	9.12	2.78	−69.5	PMR	
				Total								PMR	
5	52	T2N1M0	Surgery	Multiple Bone	Molecular target therapy				10.48	8.69	−17.1	SMD	
6	53	T2N1M0	Surgery, Moleculart herapy, and RT	Multiple Bone	Molecular target therapy				8.99	7.17	−20.2	SMD	
				Multiple lung	Molecular target therapy	17	16	−5.9	7.39	5.8	−21.5	SMD	
				Total								SMD	
7	45	T2N1M0	Surgery, Molecular therapy and RT	LNs	Molecular therapy and RT	6	6	0	5.25	3.7	−29.5	PMD	Bone
8	52	T2N1M0	Surgery and Molecular therapy	Multiple Bone	RT				8.69	8.99	3.5	PMD	Lung
9	46	T2N1M0	Surgery, Moleculart herapy, RT, RFA	Multiple Bone	Cancer immunotherapy				7.08	7.65	8.1	PMD	Other bone, LNs, pluera

SUVmax, maximum standardized uptake value; EORTC, European Organization for Research Treatment of Cancer; CMR, complete metabolic response; PMR, partial metabolic response; SMD, stable metabolic disease; PMD, progressive metabolic disease; RCC, renal cell carcinoma; LN, lymph node; RT, radiation therapy; RFA, radiofrequency ablation; TAE, transcatheter arterial embolization.

Table 2 Prostate cancer patient and tumor characteristics

	Age	Initial stage	Previous treatment history	Lesion	Therapy	PSA (pre) ng/mL	PSA (post) ng/mL	% PSA change	SUV max (pre)	SUV max (post)	% SUV max change	EORTC	New lesions
1	79	T2N1M0	Hormonal therapy	Prostate	Hormonal therapy and RT				8.27	4.09	−50.5	PMR	
	(Fig. 2)			LNs	Hormonal therapy and RT				9.54	5.38	−43.6	PMR	
				Total		24.8	39.3	58.5				PMD	Other LNs
2	67	T2N1M1	Hormonal therapy	Multiple Bone	Hormonal therapy and RT	49.9	66.5	33.3	5.79	3.31	−42.8	PMD	LNs, Liver
3	69	T3N1M1	Hormonal therapy	Bone	Hormonal therapy	0.52	1.69	225	4.45	0	−100	PMD	Other Bone
4	79	T3N1M0	Hormonal therapy	Prostate	Hormonal therapy	2.09	5.33	155	6.26	8.26	31.9	PMD	
5	69	T3N2M1	Hormonal therapy	Multiple Bone	Ra-223	18.7	318.5	1,603	12.12	11.46	−5.4	PMD	Other Bone
6	80	T2N0M1	Hormonal therapy and RT	Bone	Hormonal therapy	4.2	19.9	373.8	2.82	8.17	65.5	PMD	Other Bone
7	67	T2N0M1	Hormonal therapy and RT	Multiple Bone	Chemotherapy	19.9	13.26	−33.4	8.17	8.45	3.4	PMD	Other Bone
8	57	T2N0M1	Hormonal therapy, RT chemotherapy	Multiple Bone	Ra-223	33.7	267	692.3	15.03	16.16	7.5	PMD	Other Bone

PSA, prostate specific antigen; SUVmax, maximum standardized uptake value; EORTC, European Organization for Research Treatment of Cancer; PMD, progressive metabolic disease; LN, lymph node; RT, radiation therapy.

groups, a non-parametric test was used. SAS, version 9.3 (SAS Institute, Cary, NC, USA), was used for the statistical analysis, with a value of $P < 0.05$ considered to be significant.

Results

Of the 17 treatment courses analyzed, CMR, PMR, SMD, and PMD, as determined by the EORTEC criteria, were seen in 1 (5.9%), 3 (17.6%), 2 (11.8%), and 11 (64.7%) cases, respectively (Tables 1, 2). Target lesions were observed in a total of 24 regions, including bone (n = 14), lymph nodes (n = 5), lung (n = 2), prostate (n = 2), and pleura (n = 1), with CMR, PMR, SMD, and PMD shown in 4, 10, 8, and 2, respectively Figs. 1, 2. The mean SUVmax values of the target lesions before and after treatment were 7.87 ± 2.67 (2.82-15.03) and 5.29 ± 3.98 (0-16.16), respectively, for a mean reduction of −35.4 ± 43.6% (−100% to 65.5%).

Lymph nodal metastases in 5 cases, lung metastases in 2 cases, and pleura metastases in 1 case were measurable by the CT part of PET/CT. The mean reduction rate of size and SUVmax in 8 cases were −34.8 ± 31.4% (range −100 to 0%) and −56.3 ± 25.1% (−100 to −21.5%), respectively (Tables 1, 2). The reduction rate of SUVmax was higher than that of size without a significant difference ($p = 0.56$). CR/PR/SD was seen in 1/4/3 patients with RECIST, while CMR/PMR/SMD was seen in 1/6/2 patients with PERCIST, respectively.

The 6 patients with prostate cancer underwent a total of 16 ^{11}C-choline PET/CT scans before and after 8 different types of treatment courses. The response to all 8 treatment types was PMD and corresponded well with changes in the serum PSA level (7 of 8 cases showed an increasing PSA level).

Discussion

In this series with a small cohort, ^{11}C-choline PET/CT was shown to be useful for detecting viable residual tumors and evaluating the treatment response in patients with prostate cancer and renal cell carcinoma. In the prostate cancer patients, the treatment response by ^{11}C-choline PET was well correlated with serum PSA. In the measurable lesions (most renal cell carcinomas), ^{11}C-choline PET/CT tended to show a better treatment response than CT.

Several previous studies evaluated choline PET/CT findings for their usefulness in assessing treatment responses in patients with prostate cancer [9-12]. In one of these studies, Ceci *et al.* [9] investigated the role of ^{11}C-choline PET/CT in evaluating the response to docetaxel in 61 cases with metastatic castration-resistant prostate cancer and compared the radiologic response evaluated using ^{11}C-choline PET/CT to the PSA response. Disease progression was defined as the appearance of a new PET-positive lesion, while response after chemotherapy was defined as a decrease in the PSA level greater than or equal to 50%. Radiologic disease progression was observed in 44% of patients with a PSA response. Moreover, a higher tumor burden, expressed as > 10 PET-positive bone lesions prior to docetaxel treatment, was significantly associated with an increased probability of disease progression. More recently, a new generation of hormonal therapy drugs, such as abiraterone and enzalutamide, has become available for patients who develop castration-resistant prostate cancer, with good results shown in terms of biochemical response and pharmacologic effects. De Giorgi *et al.* [10, 11] assessed the usefulness of ^{18}F-choline PET/CT for evaluating metastatic castration-resistant prostate cancer patients with regard to their early response to treatment with abiraterone (n = 43) or enzalutamide (n = 36). The authors concluded that a radiologic response, assessed using ^{18}F-choline PET/ CT findings, was associated with more favorable overall survival than a PSA response greater than or equal to 50% alone. Maines *et al.* [12] evaluated the role of ^{18}F-choline PET/CT in monitoring the response to enzalutamide in 30 patients with metastatic castration-resistant prostate cancer. They noted that SUVmax determined by PET prior to enzalutamide treatment was significantly related to biochemical recurrence-free, radiologic progression-free, and overall survival rates. In comparison with these previous reports [9-12], our series had limitations: namely, the number of prostate patients was relatively small and the therapy for prostate cancer was not uniform.

Middendorp *et al.* [13] reported that response evaluation based on ^{18}F-choline PET/CT results after tyrosine kinase inhibitor treatment was effective in 2 renal cell carcinoma patients. Our series included a larger number of renal cell carcinoma cases and various therapies. PMR/PMD was seen in 1/1 patients in the report of Middendorp *et al.* [13], while CMR/PMR/SMD/PMD were seen in 1/3/2/3 cases in our study, respec-

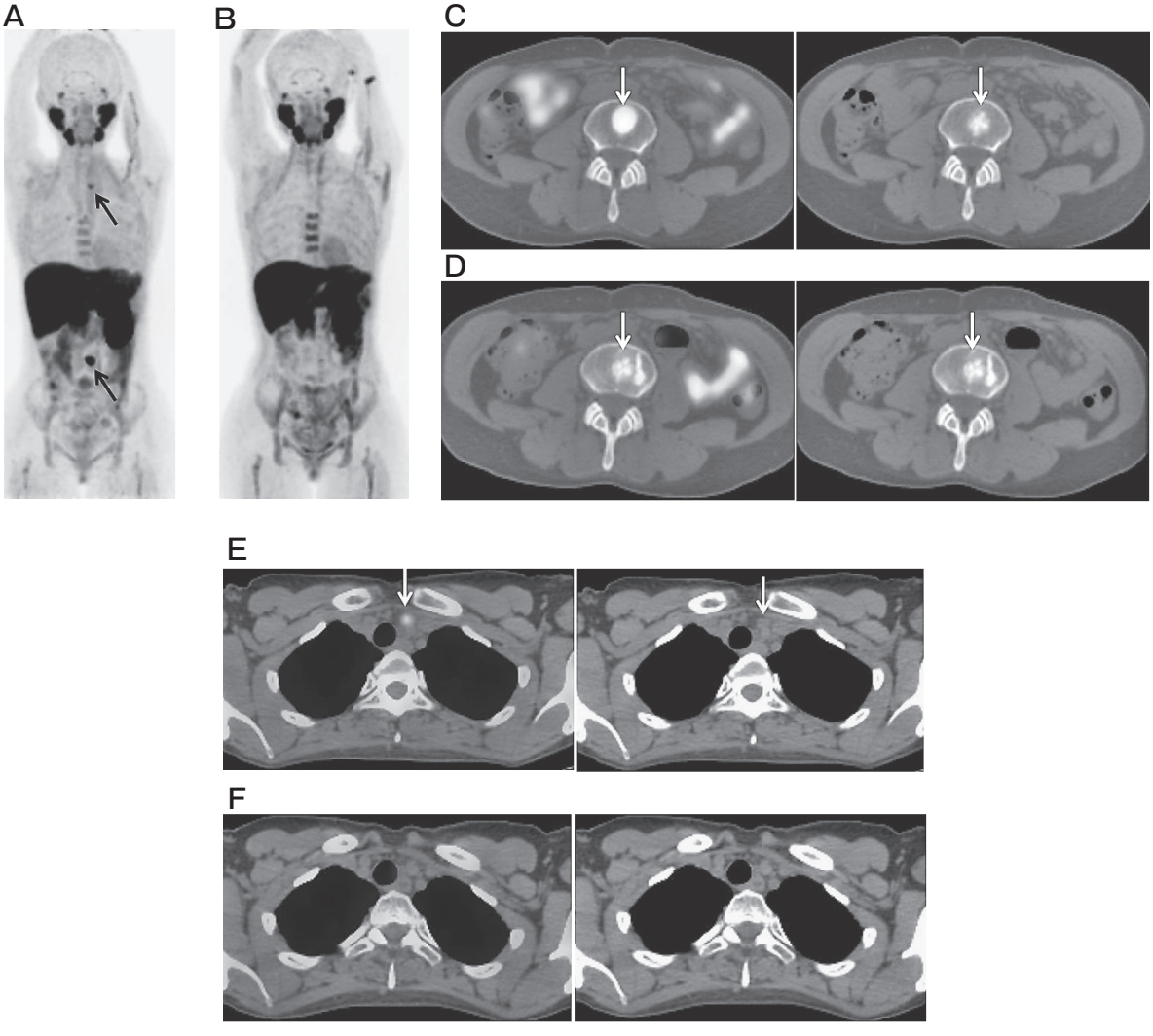

Fig. 1 Representative case of a 44-year-old woman with renal cell carcinoma after surgery for the primary tumor, molecular target therapy, and radiation therapy of mediastinal lymph node recurrence and lumbar L4 vertebra bone metastasis. **A**, Maximum intensity projection (MIP) from baseline ^{11}C-choline PET/CT shows two abnormal ^{11}C-choline uptakes in the mediastinum and lumbar spine (arrows); **B**, MIP from ^{11}C-choline PET/CT after radiofrequency ablation and molecular target therapy shows disappearance of two abnormal ^{11}C-choline uptakes, reflecting a complete metabolic response (CMR); **C**, Baseline ^{11}C-choline PET/CT and CT show strong ^{11}C-choline uptake (maximum standardized uptake value (SUVmax), 8.41) and sclerosing change of L4 vertebra (arrow), suggesting recurrence of bone metastasis; **D**, ^{11}C-choline PET/CT and CT after radiofrequency ablation and molecular target therapy show disappearance of the abnormal ^{11}C-choline uptake (arrow), suggesting viable tumor disappearance (CMR); **E**, Baseline ^{11}C-choline PET/CT and CT show mild ^{11}C-choline uptake (SUVmax, 3.7) and a small mediastinal lymph node measuring 6 × 9 mm (arrow), suggesting recurrence of lymph node metastasis; **F**, ^{11}C-choline PET/CT and CT after molecular target therapy show disappearance of the abnormal ^{11}C-choline uptake (arrow), suggesting viable tumor disappearance (CMR).

tively. Because there are no useful serum markers in renal cell carcinoma comparable to PSA in prostate cancer, choline PET/CT can be an important tool for assessing the response to treatment in renal cell carcinoma.

In conclusion, we consider that choline PET/CiT provides additional information regarding the extent of active disease, particularly in regard to the sites and number of active lesions in patients with prostate cancer or renal cell carcinoma. Thus, assessment of the ther-

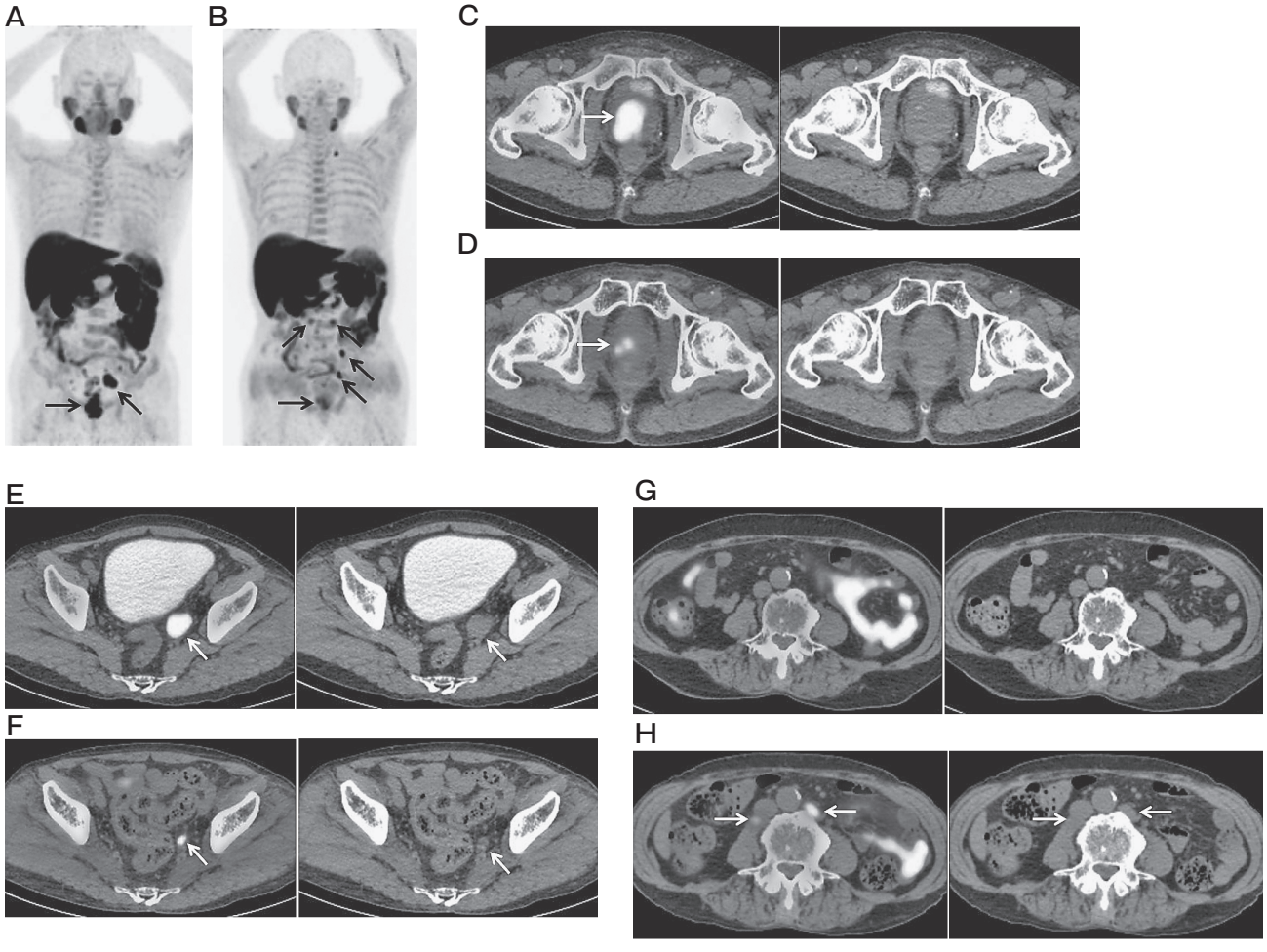

Fig. 2 Representative case of a 79-year-old woman with prostate cancer treated by hormonal therapy. **A**, MIP from baseline ^{11}C-choline PET/CT shows two abnormal ^{11}C-choline uptakes in the pelvis (arrows); **B**, MIP from ^{11}C-choline PET/CT after radiation therapy and hormonal therapy shows multiple abnormal ^{11}C-choline uptakes in the pelvis and abdomen (arrows), reflecting progressive metabolic disease (PMD); **C**, Baseline ^{11}C-choline PET/CT and CT show intense ^{11}C-choline uptake (SUVmax, 8.27) in the prostate (arrow), suggesting viable residual primary cancer; **D**, ^{11}C-choline PET/CT and CT after radiation therapy and hormonal therapy show decreases in the abnormal ^{11}C-choline uptakes (SUVmax, 4.09) in the prostate (arrow), suggesting decreased tumor viability (partial metabolic response (PMR)); **E**, Baseline ^{11}C-choline PET/CT and CT show intense ^{11}C-choline uptake (SUVmax, 9.54) and swollen left internal iliac lymph node measuring 25 × 35 mm (arrow), suggesting viable residual lymph node metastasis; **F**, ^{11}C-choline PET/CT and CT after radiation therapy and hormonal therapy show decreases in the abnormal ^{11}C-choline uptake (SUVmax, 5.38) and size (8 × 12 mm) (arrow), suggesting decreased tumor viability (PMR); **G**, Baseline ^{11}C-choline PET/CT and CT on this slice show no abnormal findings; **H**, ^{11}C-choline PET/CT and CT after radiation therapy and hormonal therapy on the same slice as in **G** show the appearance of two para-aortic lymph nodes with abnormal ^{11}C-choline uptakes (arrows), suggesting new lymph node recurrence (PMD).

apy response using choline PET/CT may enable more tailored treatment approaches, possibly leading to increased survival and improved quality of life. However, our cohort was small, and a larger prospective study is necessary to further explore and validate the potential of choline PET/CT for monitoring the treatment response in prostate cancer and renal cell carcinoma patients.

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