The Potential Clinical Value of FDG-PET for Recurrent Renal Cell Carcinoma

Koya Nakatani [1)], Yuji Nakamoto [1)], Tsuneo Saga [2)], Tatsuya Higashi [3)], Kaori Togashi [1)]

[1)] Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine.

[2)] Department of Diagnostic Imaging Molecular Imaging Center, National Institute of Radiological Sciences.

[3)] Research Institute, Shiga Medical Center for Adults.

Koya Nakatani [1)]: Corresponding author

Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Hospital,

54 Shogoin-kawahara-cho, Sakyo-Ku, Kyoto, 606-8507 Japan

Phone: +81-75-751-3419 Fax: +81-75-771-9709 e-mail: koyakn@kuhp.kyoto-u.ac.jp

Yuji Nakamoto [1)]:

54 Shogoin-kawahara-cho, Sakyo-Ku, Kyoto, 606-8507 Japan

Phone: +81-75-751-3762 Fax: +81-75-771-9709 e-mail: ynakamo1@kuhp.kyoto-u.ac.jp

Tsuneo Saga [2)] :

4-9-1 Anagawa, Inage-Ku, Chiba 263-8555, Japan

Phone: +81-43-206-3429 e-mail: saga@nirs.go.jp

Tatsuya Higashi [3)] :

5-4-30 Moriyama**,** Moriyama City, Shiga 524-8524, Japan

Phone: +81-77-582-6034 Fax: +81-77-582-6041 e-mail: higashi@shigamed.jp

Kaori Togashi [1)] :

54 Shogoin-kawahara-cho, Sakyo-Ku, Kyoto, 606-8507 Japan

Phone: +81-75-751-3760 Fax: +81-75-771-9709 e-mail: ktogashi@kuhp.kyoto-u.ac.jp

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Abstract.

Purpose:

The clinical value of positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) for follow-up or suspected recurrence of renal cell carcinoma (RCC) has not been fully evaluated. The purpose of this study was to assess the diagnostic performance of FDG-PET for post-operative assessment in patients with RCC.

Methods:

We reviewed 28 scans in 23 patients who had undergone FDG-PET scans after surgery for RCC. Diagnostic accuracy of visually interpreted PET was evaluated based on final diagnoses obtained histologically or by clinical follow-up at least 6 months. Also, additional information over CT, influence on treatment decisions, and the accuracy of FDG uptake as a predictor of survival were assessed.

Results:

Recurrence of renal carcinoma was histologically (n = 15) or clinically (n=6) confirmed in 21 of 28 cases. Overall, the sensitivity, specificity, and diagnostic accuracy using FDG-PET were 81%, 71%, and 79%, respectively. In papillary RCC, the sensitivity was 100%; however, that was 75% in clear cell RCC in patient-basis. PET correctly detected local recurrence and metastases in all cases in the peritoneum, bone, muscle and adrenal gland. Additional information was obtained from scans in 6 cases (21%), which influenced

therapeutic management in 3 cases (11%). Cumulative survival rates over 5 years in the PET-positive vs. the PET-negative group were 46% vs. 83%, respectively ($p = 0.17$).

Conclusions:

FDG-PET would be useful for postoperative surveillance in patients with RCC, although its impact on treatment decisions may be limited. Further investigations are necessary to conclude whether PET has a prognostic value.

Keywords

^{18}F-FDG-PET, renal cell carcinoma, recurrence, prognostic value

Introduction

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has been widely used in clinical oncology as an established modality for imaging cancer. FDG-PET is applicable especially for staging or re-staging, and monitoring therapeutic response in several cancers. As for renal cell carcinoma (RCC), Wahl et al. reported the feasibility of metabolic imaging using FDG, as well as morphological imaging for primary and metastatic tumors in their pilot study in 1991 [1], followed by reports describing high accuracy of FDG-PET for the diagnosis of RCC [2-4]. Conversely, other reports have indicated higher false negative rates [5, 6]. Kang et al. examined 90 PET scans in 66 patients, and concluded that the role of FDG-PET in the detection of RCC was limited due to its low sensitivity and that, with superior specificity; PET might have a complementary role as a problem-solving tool in cases that were equivocal using conventional imaging [7]. Thus, the clinical role of FDG-PET for RCC remains controversial, but has not been considered helpful for the evaluation of primary RCC.

Meanwhile, the role of FDG-PET for follow-up or suspected recurrence of RCC has been reported to be favorable [8-10]. Clinical courses in patients with recurrent RCC following nephrectomy vary, with a survival benefit associated with sufficient metastasectomy [11-15]. More accurate diagnosis of recurrent RCC is important, but morphological imaging modalities, such as computed tomography (CT), have certain

limitations for exact evaluation of recurrent RCC. Hence, metabolic imaging, including FDG-PET, is expected demonstrate increased accuracy, but not much has been reported yet on the efficacy of PET in the diagnosis of recurrent RCC.

In the present study, to elucidate the clinical value of FDG-PET for recurrence and distant metastases of RCC, we assessed diagnostic performance of FDG-PET for post-operative survey in patients with RCC. Furthermore, we assessed whether FDG uptake could be a predictor of survival in patients with recurrent RCC.

Patients and methods

Patients

Between August 2000 and January 2008, 39 patients underwent 45 FDG-PET scans at our institute in order to investigate RCC. Among them, 8 patients (undergoing 8 scans) did not histologically prove to have RCC because they didn't undergo surgery or biopsy, one patient (undergoing one scan) had bilateral renal tumors, one of which was not histologically proven, and 6 patients (undergoing 7 scans) had synchronous double cancer. These patients were excluded in our study. In this retrospective study, we reviewed records of 24 patients (18 men, 6 women; age range: 45 – 78 years, mean age: 63 years) who had histopathologically proven RCC and did not have synchronous malignant tumors. They underwent 29 PET scans. Periods from prior nephrectomy to PET scan ranged from one month to 27 years (average: 7.6 years, median: 3.5 years). All cases underwent both PET

and CT scans and had prior CT scans. Each scan was performed within 6 months (18 scans within a month). All these studies involved daily clinical diagnostic checkups and written informed consent, requested by our institutional review board, was obtained from each patient.

PET scanning

Fluorine-18 FDG was synthesized by nucleophilic substitution method using an FDG synthesizing instrument (F-100, Sumitomo Heavy Industries, Tokyo, Japan) and a cyclotron (CYPRIS-325R, Sumitomo Heavy Industries, Tokyo, Japan). For 22 patients (27 scans) in this study, PET was performed using an Advance scanner (GE Healthcare, Milwaukee, WI, USA). For the remaining two patients (2 scans), PET was performed using a C-PET plus scanner (ADAC, Philadelphia, PA, USA). After fasting for at least 4 hours, patients received intravenous administration of approximately 370 MBq (for the Advance scanner) or 130 MBq (for the C-PET plus scanner) of FDG, and whole-body PET images were acquired approximately 60 minutes later. Using the Advance scanner, each emission scan was obtained for 3 minutes per single bed position and each post-emission transmission scan was obtained for 1 minute per single bed position. In order to cover from the skull base to the upper thigh, 5 to 6 bed positions were scanned according to the height of each patient. Images were acquired in 2-dimensional mode. The ordered subset expectation maximization algorithm using 16 subsets, 3 iterations, and a 128 × 128 matrix

size reconstructed attenuation-corrected transaxial images. Data acquisition by the C-PET plus scanner was performed in 3-dimensional imaging mode with septae in place. Following a 56-second transmission scan, a whole body static image was then acquired for 6 minutes per bed position. The data were reconstructed using row action maximum likelihood algorithm.

CT scanning

CT scans were performed prior to PET scans using single or multidetector-row CT scanners (Aquillion 8, 16, or 64, Toshiba, Tokyo, Japan; W3000, Hitachi Medico, Tokyo, Japan; HiSpeed Advantage, GE Healthcare, Milwaukee, WI, USA). Thoracic and abdominal images were obtained separately or continuously with (19 scans) or without (10 scans) intravenous contrast material.

Image interpretation and analysis

Interpretations of PET images were performed by consensus of at least two nuclear medicine physicians, with all available clinical information, including anatomical information provided by prior CT and/or other conventional imaging modalities. In this study, interpretation criteria were as follows; lesions were regarded as being an abnormal finding or representative of tumor if metabolic activity of FDG was moderately or markedly increased, relative to comparable normal structures or surrounding soft tissues.

Findings provided by CT images, such as lesion size, shape, or enhancement patterns, were not taken into account for the purpose of the study. For example, a lesion with no or faint uptake of FDG was regarded as negative even if a recurrent tumor had been suspected by CT. Based on these criteria, the diagnostic accuracy of PET was estimated. Final diagnoses were made histopathologically or according to clinical follow-up using CT scans for at least 6 months.

When PET detected lesions that had not been observed by conventional imaging modalities, or when PET revealed characteristics of lesions other modalities interpreted inconclusively, the obtained finding was regarded as '*additional information*'. If patient treatments changed as a result of PET findings, these findings were considered to have offered '*clinical impact*'.

Patients were categorized into a PET-positive and a PET-negative group. Kaplan-Meier survival estimates were calculated from the first day of the PET scan to death.

Results

We evaluated a total of 28 PET scans in 23 patients and excluded one patient (using the Advance scanner) without definite final diagnosis. The patients' profile and their clinical outcome are shown in *Table 1*. Of 28 cases, 21 were finally confirmed to be in recurrence via surgery (n = 7), biopsy (n=8), and clinical follow-up (n = 6), i.e. the tumor had increased in size. The remaining seven cases were considered negative for recurrence.

Histopathology demonstrated that the type of recurrent cases were clear cell RCC in 16 patients, papillary RCC in 4 patients, and unknown in one case.

The PET results were true-positives in 17 cases (clear cell RCC in 12 cases, papillary RCC in 4 cases, and unknown histology in 1 case). *Fig. 1* demonstrates a true positive case which gave additional information and clinical impact. On the other hand, PET failed to show recurrent lesions in 4 cases, all of which were clear cell RCC. These missed observations included one case of brain and lung metastases, one case of multiple small liver metastases, and two cases of metastases to the pancreas. *Fig. 2* demonstrates one representative false-negative case. PET findings yielded false positive in two cases. One case revealed inflammatory changes in the lung and the other, mediastinal lymphadenitis. In the remaining 5 cases, the results of PET scans were true negative. As shown in *Table 2*, overall sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were 81%, 71%, 79%, 90%, and 56%, respectively. When objects were confined to the cases with clinically suspected recurrence by prior CT images or by clinical symptoms, such as general malaise or long-lasting fever, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET were 80%, 67%, 78%, 94%, and 33%, respectively.

All 4 false-negative cases had clear cell RCC, and the PET results in all 4 cases with papillary RCC were true-positive. However, there was no statistically significant difference about the diagnostic accuracy between the two histological subtypes according to Fisher’s

exact test (p=0.5376). No correlation was found between nuclear grades of primary tumors and FDG uptake of recurrent tumors, either.

PET correctly detected local recurrence, peritoneal dissemination, bone metastases, muscle metastases, and adrenal metastases in all cases. On the other hand, sensitivities of metastases to the brain, thyroid, liver, or contralateral kidney were low, although the number of metastatic lesions was limited *(Table 3)*. *Fig. 3* demonstrates a case with metastases to the peritoneum and kidney.

'Additional information' over CT was obtained in 6 cases (21%). In one patient (No. 1), who had been thought to be disease-free by prior unenhanced CT, PET revealed a hilar lymph node metastasis which was confirmed histologically. In another patient (No. 17), whose prior CT image investigating the cause of general malaise had not shown any remarkable findings, PET showed diffuse bone marrow metastases that were later biopsy-proven. In Patient No. 20, PET discovered an unknown chest wall metastasis on her back, for which excision and irradiation therapy was performed. For these 3 patients, the PET findings were considered to yield 'clinical impacts'. In the remaining 3 patients, PET additionally revealed an adrenal gland metastasis, a sternal bone metastasis, and vertebral metastases, but their clinical management did not change.

Among the 23 patients for whom final diagnoses were obtained, one female patient died of pneumonia irrelevant to cancer. The survival analysis was, therefore, performed after excluding this patient. During their follow-up periods, ranging from 6 to 2691 days with

the median of 711 days, nine patients died of primary disease. Of these patients, eight belonged to the PET-positive group (16 patients) and one patient, who died of liver failure due to multiple liver metastases, belonged to the PET-negative group (6 patients). Cumulative survival rates over 5 years in the PET-positive group and in the PET-negative group were 46% and 83%, respectively, as presented by Kaplan-Meier survival curves *(Fig. 4)*. The difference between the two groups did not reach statistical significance according to the log-rank test ($\chi^2 = 1.849$, $p = 0.1739$).

Discussion

The overall diagnostic performance of FDG-PET for recurrent RCC after nephrectomy was reasonably high, with a case-based sensitivity of 81%, specificity of 71%, and accuracy of 79%, which was considered comparable with those for other malignancies. These data indicate that FDG-PET would be a useful tool for postoperative surveillance even in patients with RCC.

The role of FDG-PET for re-staging of RCC was initially examined by Safaei et al, who examined 36 patients and demonstrated the sensitivity, specificity, and accuracy of 87%, 100%, and 89%, respectively [8]. According to published reports, overall sensitivity and specificity of FDG-PET for re-staging were 64-87% and 75-100% [8-10]. Our data were almost consistent with these observations. As for initial diagnosis and staging of primary RCC, overall sensitivity of FDG-PET varied, ranging from 32% to 100% [1-7]. The largest

study by Kang et al. showed a sensitivity of 60% [7], raising questions as to the clinical value of FDG-PET. FDG-PET may be helpful in the evaluation of recurrent RCC rather than in initial staging of RCC.

In general, there are many RCC that are not FDG-avid, with the reason behind this phenomenon remaining unclear. For example, Miyauchi et al. reported that renal cancers in their series of 11 patients with newly diagnosed RCC were well visualized with FDG-PET, had higher grade, higher glucose transporter-1 (GLUT-1) expression and tended to be larger than poorly imaged cancers (Miyauchi T et al., presented at the 1996 annual meeting of the Society of Nuclear Medicine).

In contrast, Miyakata et al. stated that there was no correlation between GLUT-1 expression and FDG-PET positivity [5]. Montravers et al. formulated the hypothesis that mild or absent FDG contrast observed in primary RCC was due to a lack of accessibility of radiotracers to tumor cells [3, 16].

As compared with primary tumors, it seems that recurrent or metastatic foci of RCC tended to be FDG-avid, resulting in higher sensitivity of FDG-PET, although a few recurrent tumors were not FDG-avid. In our study, uptake of FDG in recurrent tumors was not statistically correlated with histological type, nuclear grade, or presence of sarcomatoid components, as is demonstrated in *Table 1*. This might be because of the small number of cases. Further examination with increased number of cases with various histological types might be needed. One of the reasons explaining the difference in the diagnostic

performance could be attributed to the urinary system. FDG is excreted into urine yielding substantial tracer accumulation in a renal collecting system, and thus accumulation in primary RCC is sometimes obscured by or misrecognized as excretion itself [2, 8, 17]. FDG accumulation in metastatic tumors is not obscured by excretion, except in the contralateral kidney. Physiological uptake of FDG in background tissue can mask accumulation into tumors in liver, brain, and kidney. In fact, tumors metastasized to these organs tended to be missed in our population, although the number of the lesions was limited. Nevertheless, as shown in *Fig. 3*, there was a case in which a metastasis to kidney was identified because of FDG uptake in the tumor thrombus directly invading to a renal vein that could be easily distinguished from urinary tract.

Understanding how often additional information is obtained if FDG-PET is used in conjunction with morphological information, usually acquired by CT, is important in assessing the clinical utility of this technique. In our study, ‘Additional information’ over CT was obtained in 6 cases (21%), causing an alteration of therapeutic plans in 3 of these cases (11%). Among these cases, two patients (7%) who had been regarded as disease-free by prior CT turned out to have recurrence that was detected using PET. However, several reports noted that metastasectomy under the appropriate conditions can bring survival benefits in selected patients [11-15]. A tumor-free interval of more than 2 years between primary tumor and metastasis was reported to be accompanied by a longer disease-specific survival after successful metastasectomy [11]. Moreover, molecular-targeted therapies with

multi-kinase inhibitors such as sorafenib and sunitinib are now recommended as preferential therapy against metastatic RCC. Therefore, it is essential for starting these strategies to point out correct metastatic sites. In addition, there are no reliable specific tumor markers for RCC, although erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum immunosuppressive acidic protein (IAP) have been proposed to be a prognostic factor [18-20]. Therefore, the diagnostic imaging for evaluation of recurrence, including FDG-PET, may be helpful, even if clinical impacts cannot be obtained very frequently. Indeed, although postoperative surveillance is generally performed using CT, patients with renal insufficiency after nephrectomy are not permitted to perform CT with IV contrast material. CT without IV contrast provides limited information in pointing out unexpected metastases. Since renal carcinomas have a tendency to metastasize to a variety of organs, it would be difficult to detect metastases to pancreas or muscle only by unenhanced CT. Especially in these cases, we believe that FDG-PET (or PET/CT) can be effectively applicable.

In survival time analysis, the PET-positive group tended to have poorer prognosis, but the difference of cumulative survival rates between the two groups did not reach statistical significance. One of the reasons might be the small number of cases. We need to perform a further investigation using an increased number of cases to conclude prognostic value of FDG-PET for recurrent RCC. In addition, the kind of adjuvant therapy the patients received, or whether metastatic tumors were successfully removed after being found, was

not taken into account in the present analysis. Survival curves for both the PET-positive and PET-negative group ultimately plateau. This observation may have been affected as a result of the removal of metastatic tumors, already being advocated as one independent prognostic factor [11-15].

The present study had several limitations. This study was not prospective, and the study population may have a bias. Clinical follow-up after nephrectomy was usually performed using a CT scan, whereas FDG-PET was performed only in limited cases. Indeed, in the present study, patients whose prior CT scan suggested presence of recurrent tumors were the vast majority, and so the overall prevalence of recurrence in the study was as high as 75%. If clinical follow-up after nephrectomy had been performed using FDG-PET first, the prevalence of recurrence would not have been so high and the diagnostic accuracy might have been different. The prior CT scans were not standardized either as enhanced CT or as unenhanced CT. FDG-PET/CT is often reported superior to FDG-PET alone. In spite of these limitations, we believe that our study could favor the use of FDG-PET for postoperative surveillance in patients with RCC, and throughout almost 10 years of our institution’s experience, we could undertake to determine whether FDG uptake could be a predictor of survival.

In conclusion, FDG-PET can be a complementary modality for postoperative surveillance in patients with RCC. Further investigations are needed to conclude whether PET can yield a prognostic value.

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Fig. 1—A case of true positive FDG-PET for metastatic renal cell carcinoma with additional information and clinical impact. An axial slice of unenhanced CT (a) and an axial slice (b) and maximum intensity projection (MIP) image (c) of FDG-PET are shown. A 61-year-old male (Pt. #1) respectively had a history of right nephrectomy and pulmonary metastasectomy 16 and 3 years earlier. He underwent unenhanced CT and no more lesions were found. PET showed significant uptake on the left hilar lymph node (arrows), indicating metastasis to the lymph node. Surgical resection was performed, and the lesion turned out to be a positive node.

Fig. 2—A case of false negative FDG-PET for metastatic renal cell carcinoma. An axial slice of arterial phase of enhanced CT (a) and an axial slice (b) and maximum intensity projection image (c) of FDG-PET are shown. A 56-year-old male (Pt. #16) underwent CT and was suspected of having metastasis. FDG-PET showed no significant uptake. The tumor was resected, and metastasis to the pancreas was histologically confirmed.

Fig. 3—A case with metastatic renal cell carcinoma to the peritoneum, right hilar nodes, and left kidney. A maximum intensity projection image of FDG-PET (a) and axial slices of enhanced CT (b-d) are demonstrated. Metastatic lesions to the contralateral kidney (a: black arrow, b: white arrow) and to the peritoneum (a, d: white arrows) were identified as

FDG-avid foci. Tumor thrombus in the left renal vein is also seen on PET and CT (a: arrowhead, c: white arrow).

Fig. 4—The overall survival of the PET-positive group including 16 patients (solid line) and the PET-negative group including 6 patients (dashed line). The PET-positive group tended to have a poorer prognosis, but was not statistically significantly different (p = 0.1739).

Table 1. Characteristics, results of images, and clinical outcomes of patients with RCC

Pt. #	Age/ Sex	Histology of prior specimen*			Result		Sites of metastases		Outcome
		Type	Grade	TNM	CT	PET	P/o by PET	Final Dx	
1	57/M	CCC	NA	NA	TP	TP	Lu	*Lu*	Rec.
	58/M				TN	FP	(Lu) ‡	None	Rec.
	60/M				TN	TN	None	None	Rec.
	61/M				FN	TP	LN	*LN*	No rec.
	62/M				TN	TN	None	None	No rec.
2	69/M	CCC	1	T3b	TN	TN	None	None	No rec.
3	54/M	CCC	2	T2a	FP	FP	(LN) ‡	None	No rec.
4	65/M	CCC	1	T2b	FP	TN	None	None	No rec.
5	76/M	CCC	2	T1a	TP	TP	Bo	*Bo*	Drop out (rec.)
	77/M				TP	TP	Bo	Bo, Lu	Drop out (rec.)
6	46/M	CCC	3	Tx	TP	TP	Ki, LN, Pe	Ki, LN, *Pe*	Death
7	52/M	CCC†	3	M1	TP	FN	None	Br, Lu	Rec.
8	77/M	CCC	2	T2	TP	TP	Bo, LN, Lu, Mu	Bo, Lu, LN, Mu, *Sk*	Death

9	62/M	CCC†	3	M1	TP	TP	Lu, Ad	Ad, Br, Lu	Death
10	58/M	PRC	2	T1a	TP	TP	Pe	*Pe*	Death
11	71/F	CCC†	3	T3b	TP	TP	Ad, Lo, Mu	Ad, Lo, *Mu*	Death
12	59/M	CCC	NA	NA	TP	TP	Pa	*Pa*	No rec.
13	58/M	CCC†	3	T1b	TP	FN	None	Ki, Pa, Thy	Rec.
14	73/F	CCC	NA	NA	TP	TP	Pa	*Pa*	No rec.
15	65/M	CCC	1	T2b	TP	TP	Pa	*Pa*	Drop out (rec.)
16	56/M	CCC	NA	T2	TP	FN	None	*Pa*	No rec.
17	66/M	PRC	3	M1	FN	TP	Bo	*Bo*	Death
18	54/F	PRC	3	M1	TP	TP	Ad, Bo, Lu	Ad, Bo, Lu	Death
19	78/M	NA	3	T1a	TP	TP	Lu	Lu	No rec.
20	45/F	PRC	2	T3b	TP	TP	Bo, LN, Lo, Mu	Bo, LN, Lo, *Mu*	Death
21	56/F	CCC	NA	NA	TP	FN	None	*Li*	Death
22	75/F	CCC	2	T1b	TN	TN	None	None	Death from pneumonia
23	64/M	CCC	3	M1	TP	TP	Bo, Li	Bo, *Li*	Drop out (rec.)

Abbreviations: Pt. #, Patient number; F, female; M, male; CCC, Clear cell carcinoma;

PRC, Papillary renal cell carcinoma; NA, not available; TP, True positive; TN, True negative; FP, False positive; FN, False negative; P/o, Pointed out; Dx, Diagnosis; Ad, Adrenal gland; Bo, Bone; Br, Brain; Ki, Contralateral kidney; Li, Liver; LN, Lymph node; Lo, Local recurrence; Lu, Lung; Mu, Muscle; Pa, Pancreas; Pe, Peritoneal dissemination; Sk, Skin; Thy, Thyroid; Rec., Recurrence.

* Histological findings are based on the 3rd edition of the General Rule for Clinical and Pathological Studies on Renal Cell Carcinoma (in Japanese).

† With sarcomatoid component.

‡ False-positive lesion.

Sites of metastases written in *oblique type* were biopsy-proven, and sites of metastases written in *oblique type and underlined* were surgically proven.

Table 2a. Cross-tabulation of the results of case-based analysis (n = 28)

		Final diagnosis	
		Recurrence (+)	Recurrence (-)
PET	Positive	17	2
	Negative	4	5
Sensitivity 81%, Specificity 71%, Accuracy 79%			

Table 2b. Cross-tabulation of the results of cases with suspected recurrence (n = 23)

		Final diagnosis	
		Recurrence (+)	Recurrence (-)
PET	Positive	16	1
	Negative	4	2
Sensitivity 80%, Specificity 67%, Accuracy 78%			

Table 3. Number of cases according to metastatic foci

Metastatic organ	No. of total cases	No. of PET true-positive cases	
Lung	7	5	(71.4%)
Mediastinal lymph node	3	2	(66.6%)
Abdominal lymph node	2	2	(100%)
Bone	7	7	(100%)
Contralateral kidney	2	1	(50%)
Brain	2	0	(0%)
Pancreas	5	3	(60%)
Adrenal gland	3	3	(100%)
Peritoneal dissemination	2	2	(100%)
Muscle	3	3	(100%)
Local recurrence	2	2	(100%)
Skin	1	0	(0%)
Liver	2	1	(50%)
Thyroid	1	0	(0%)

Fig.1(a)

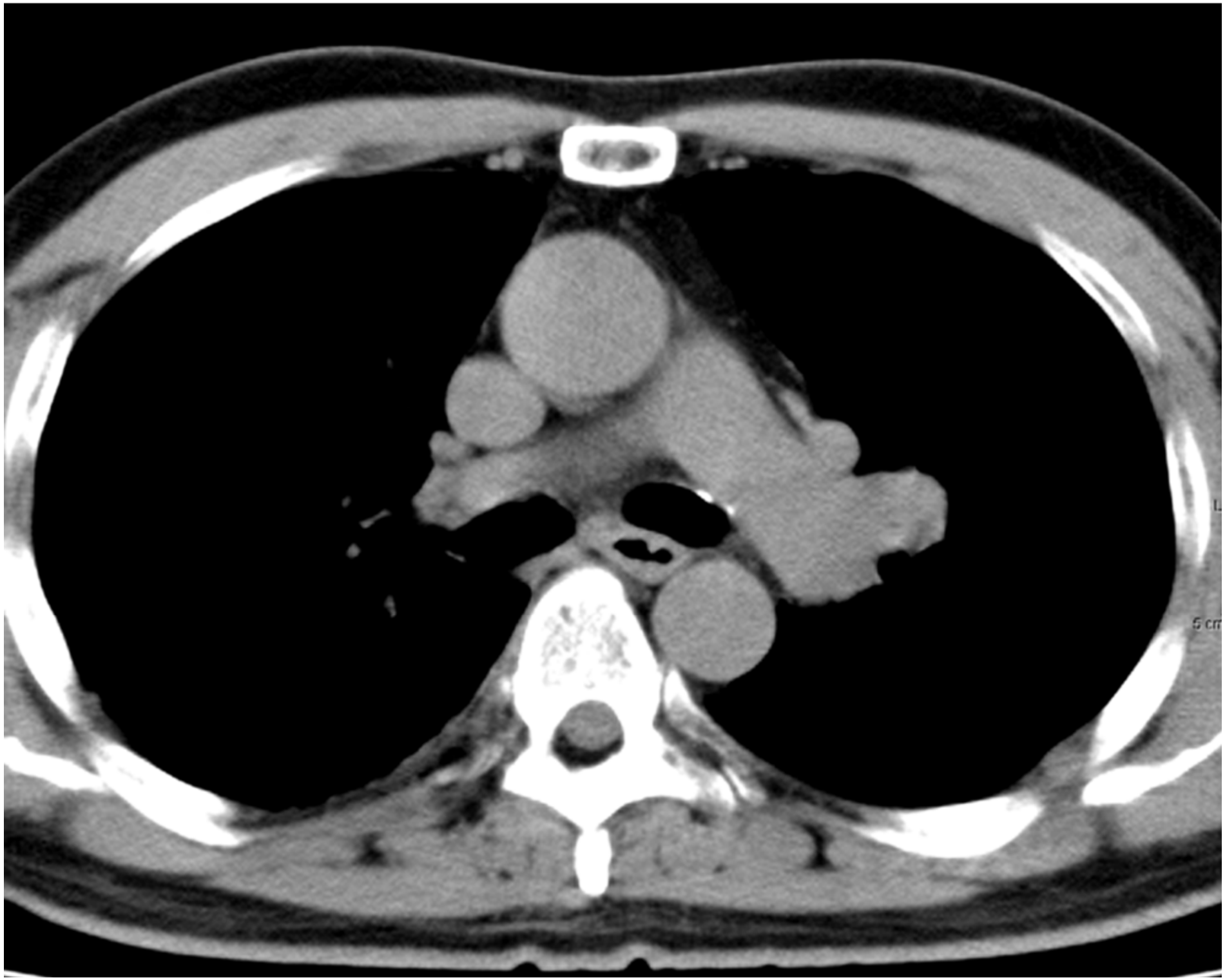


Fig.1(b)

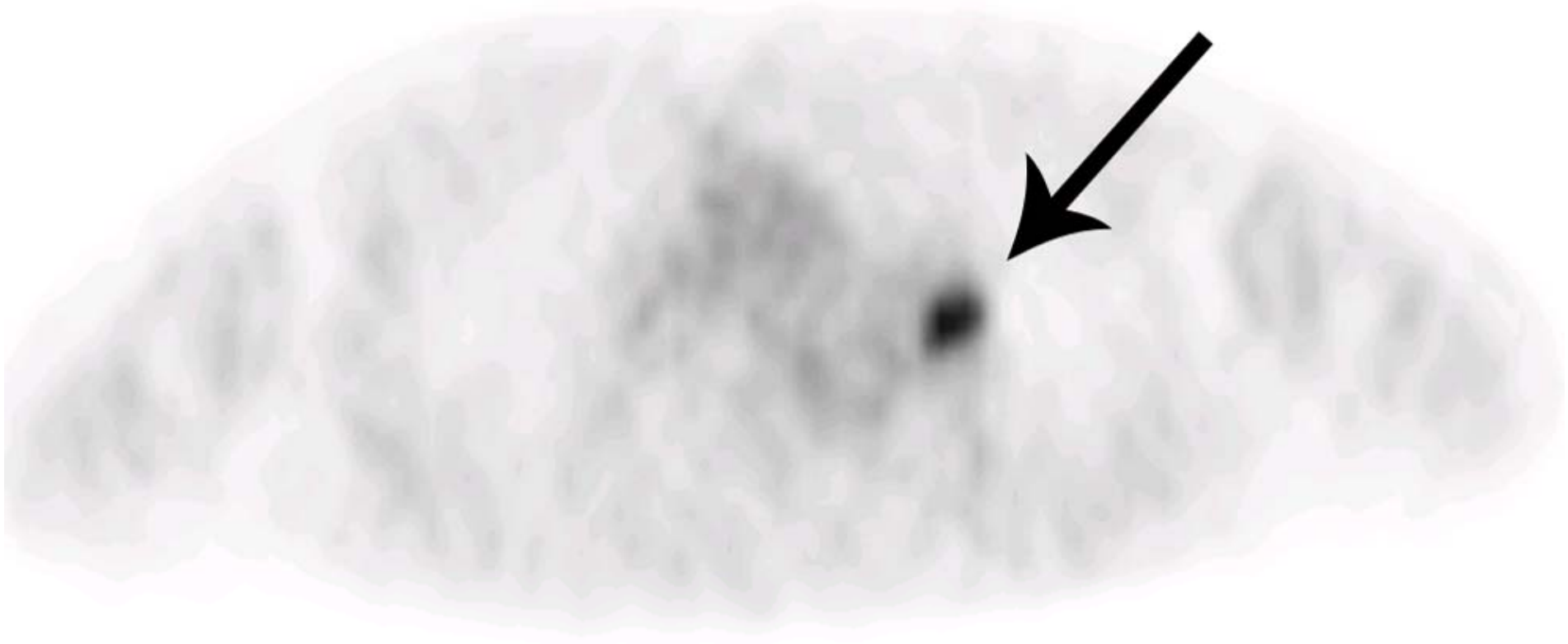


Fig.1(c)

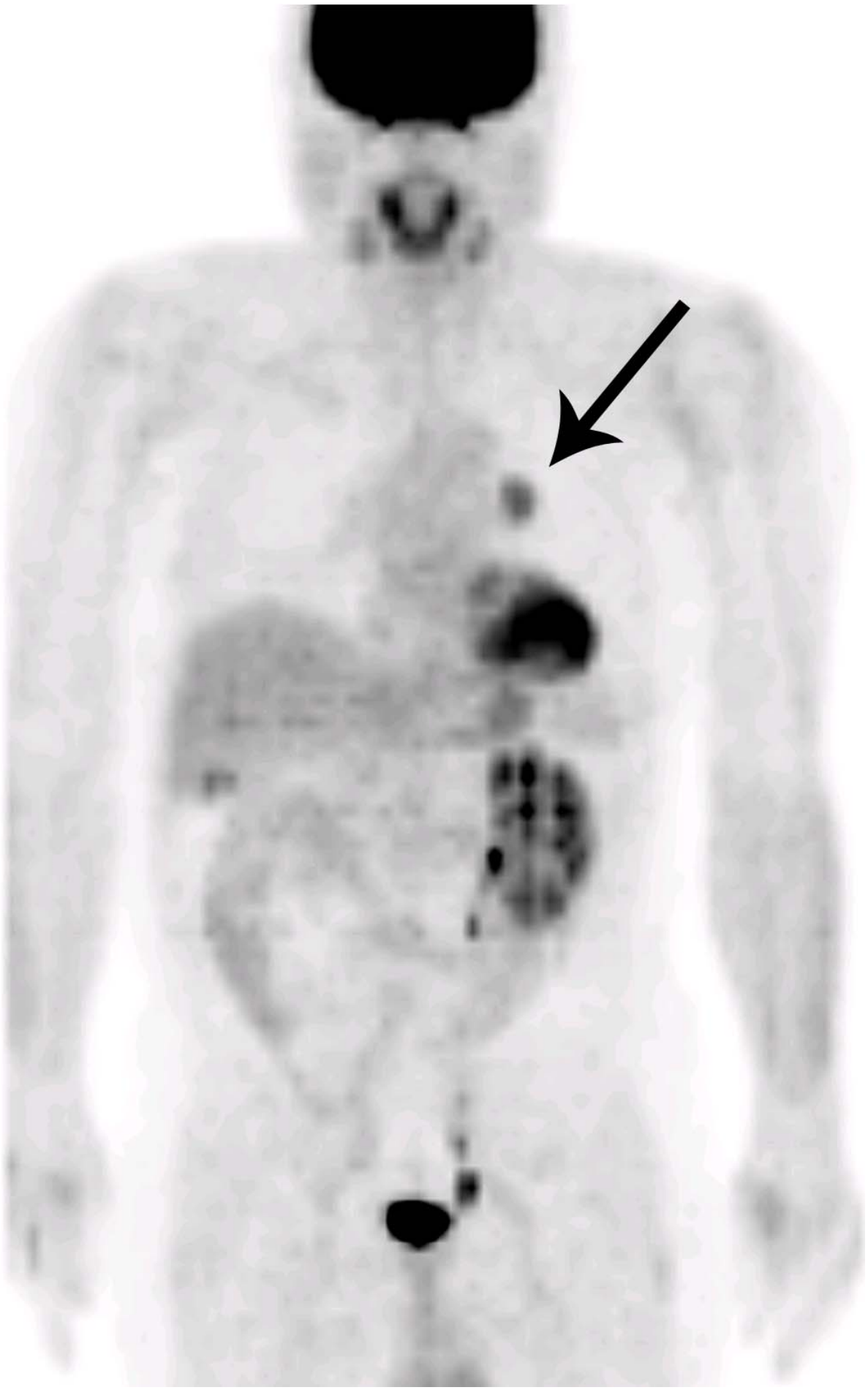


Fig.2(a)

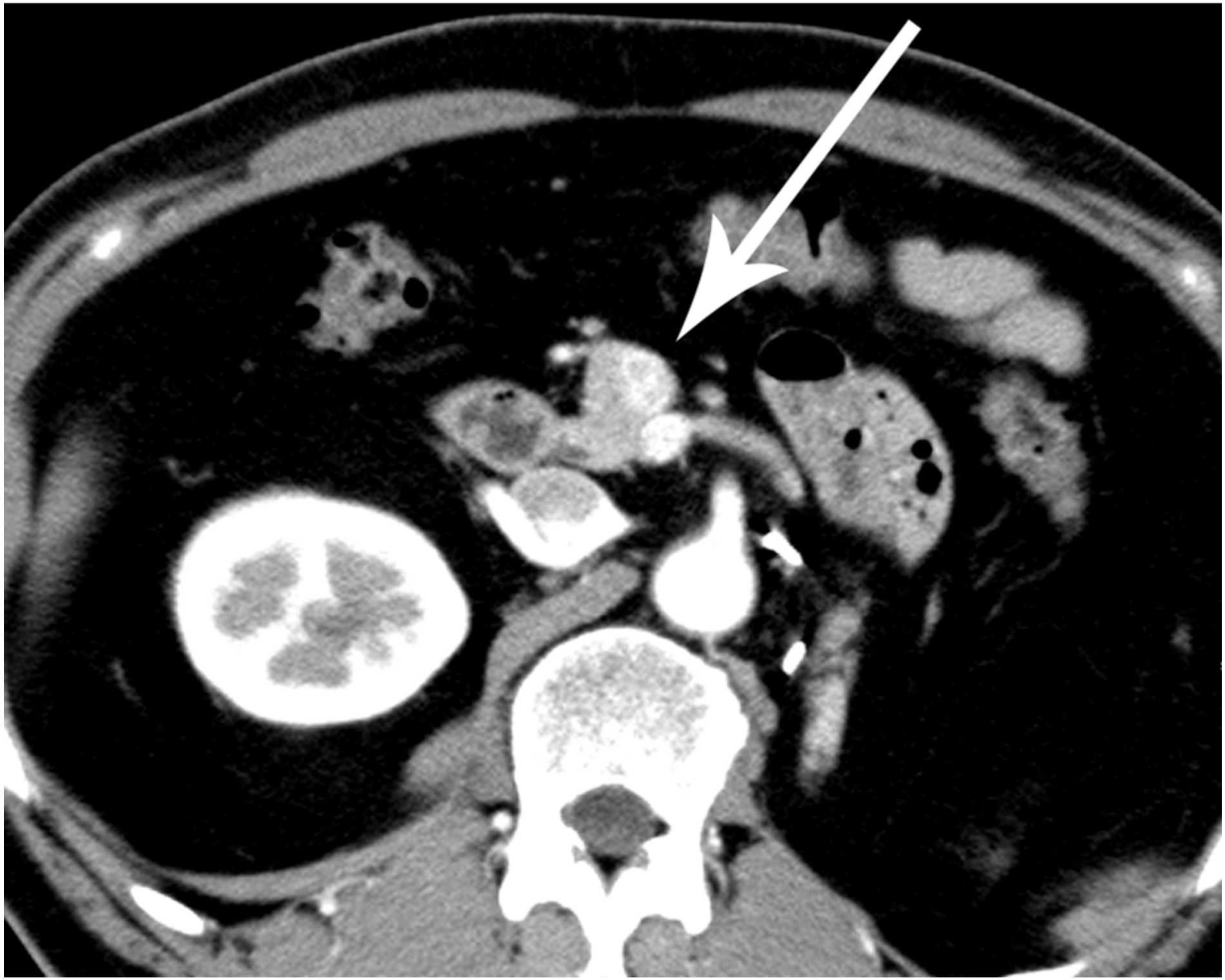


Fig.2(b)

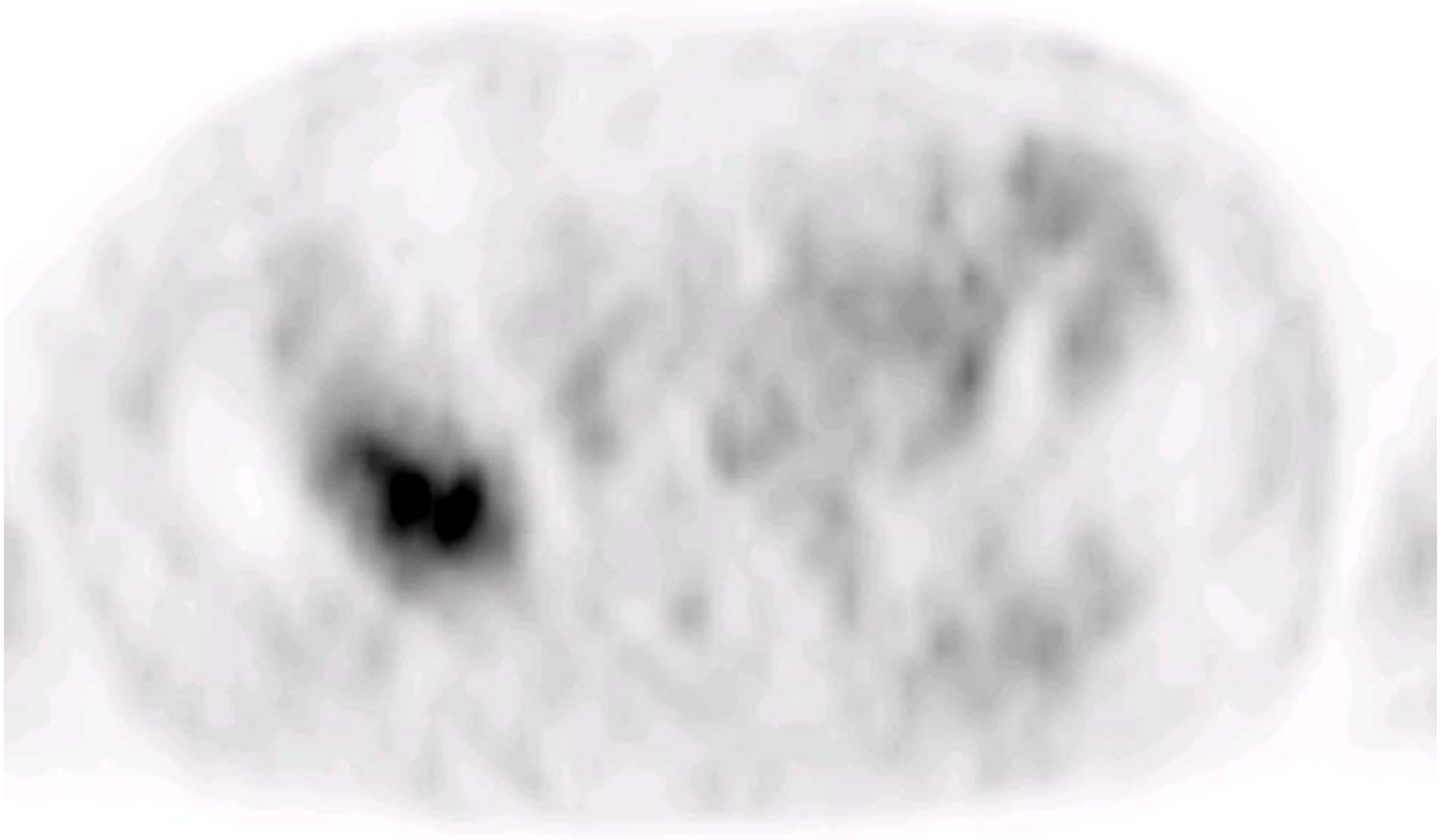


Fig.2(c)

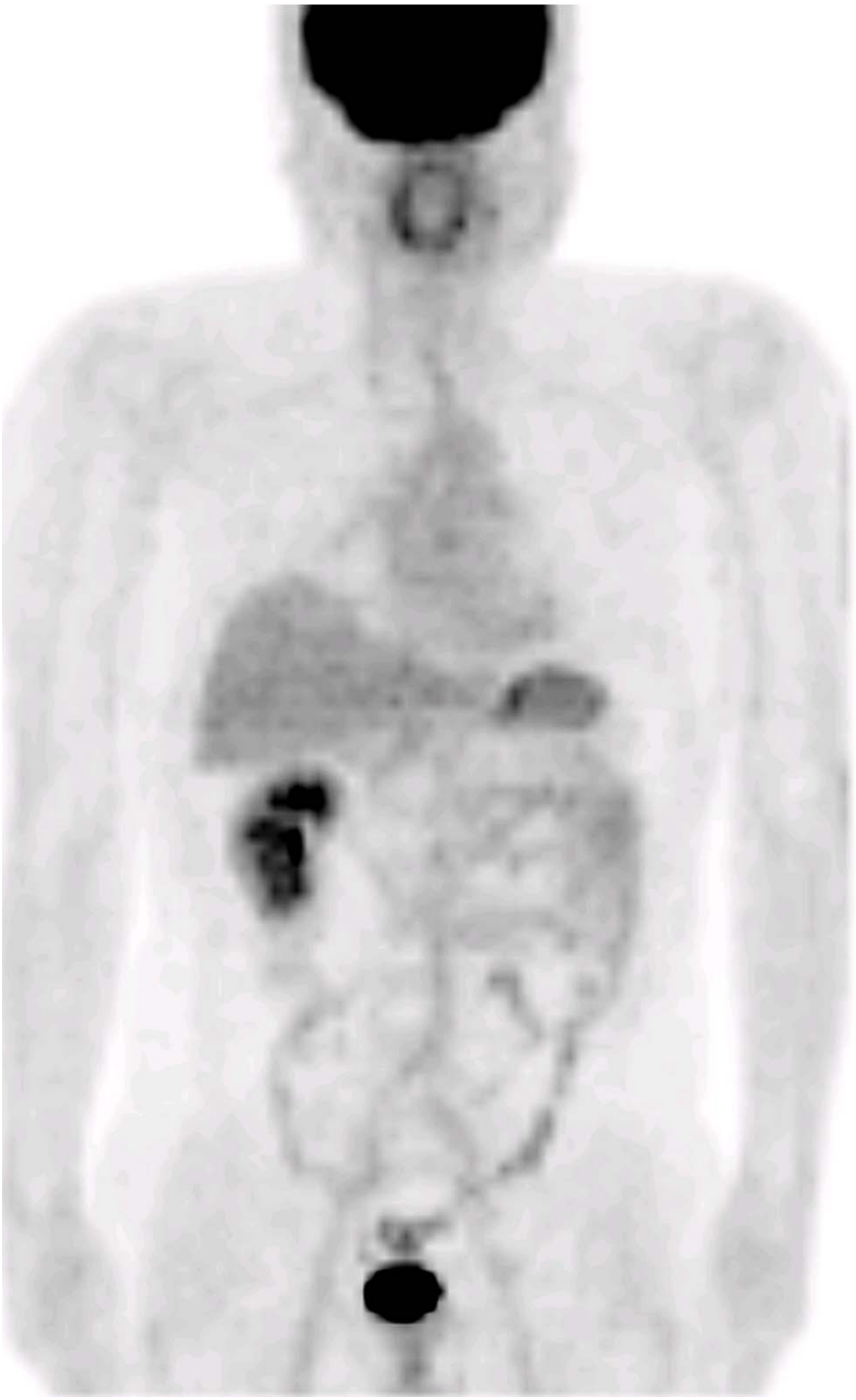


Fig.3(a)

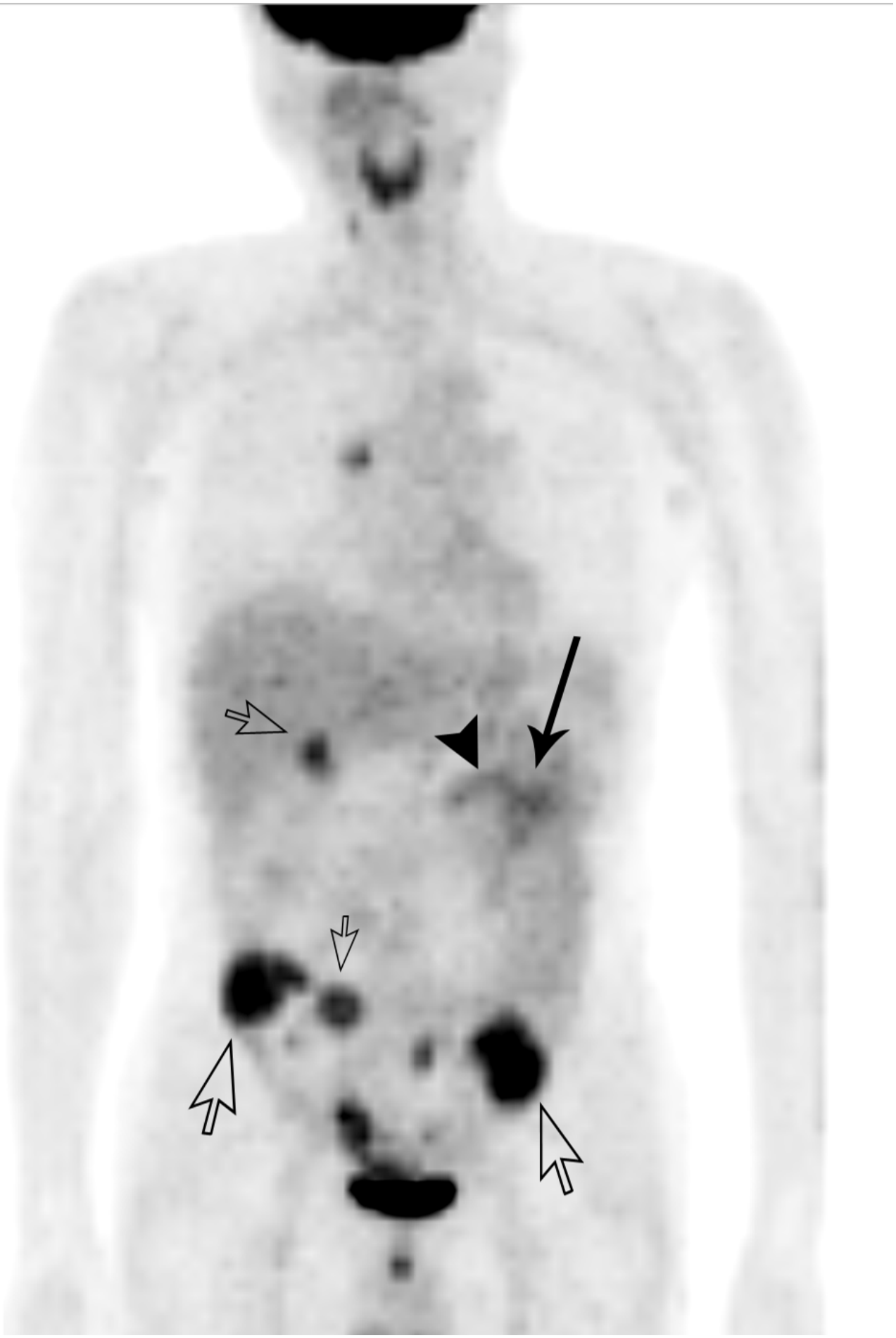


Fig.3(b)

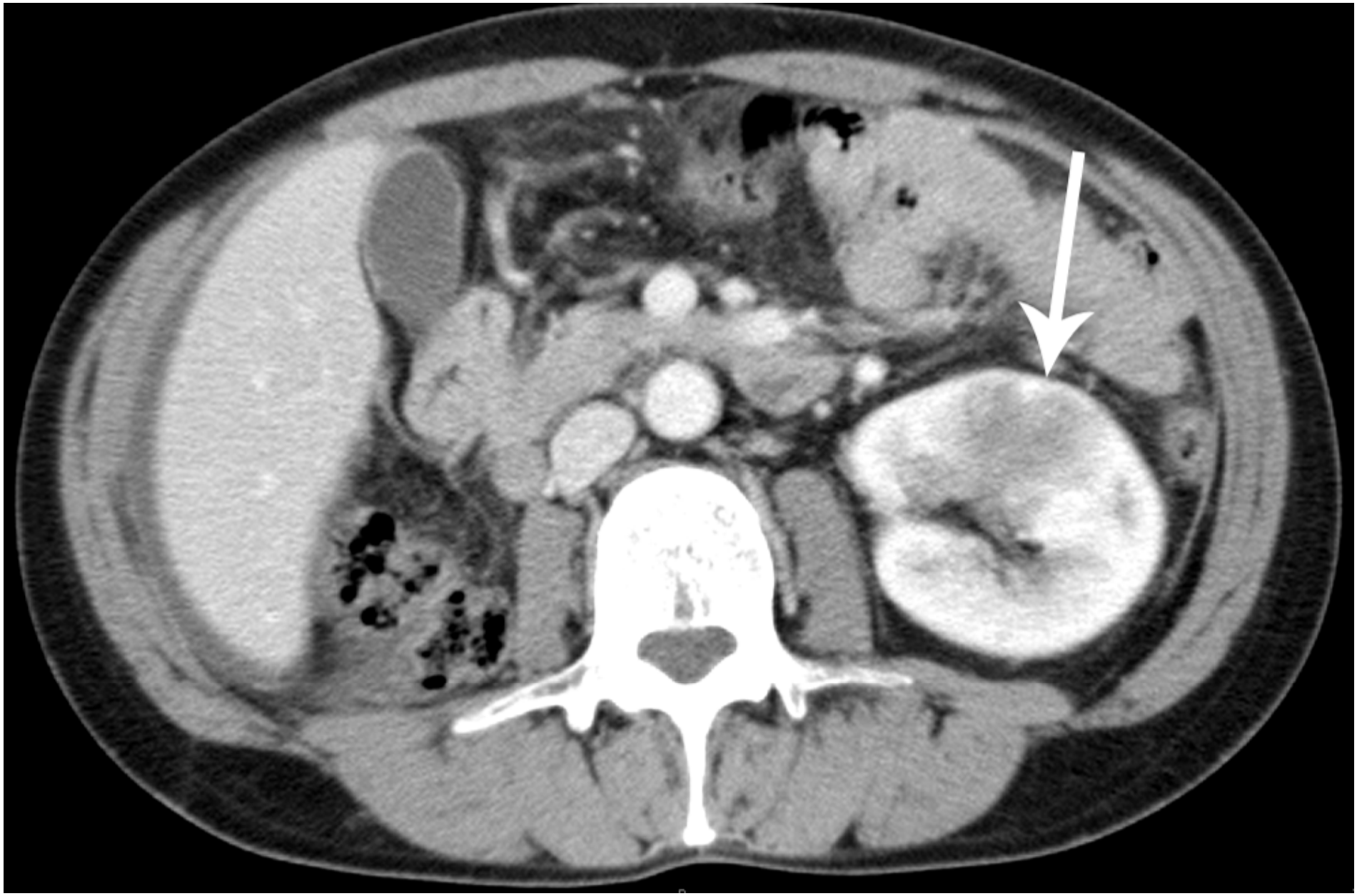


Fig.3(c)

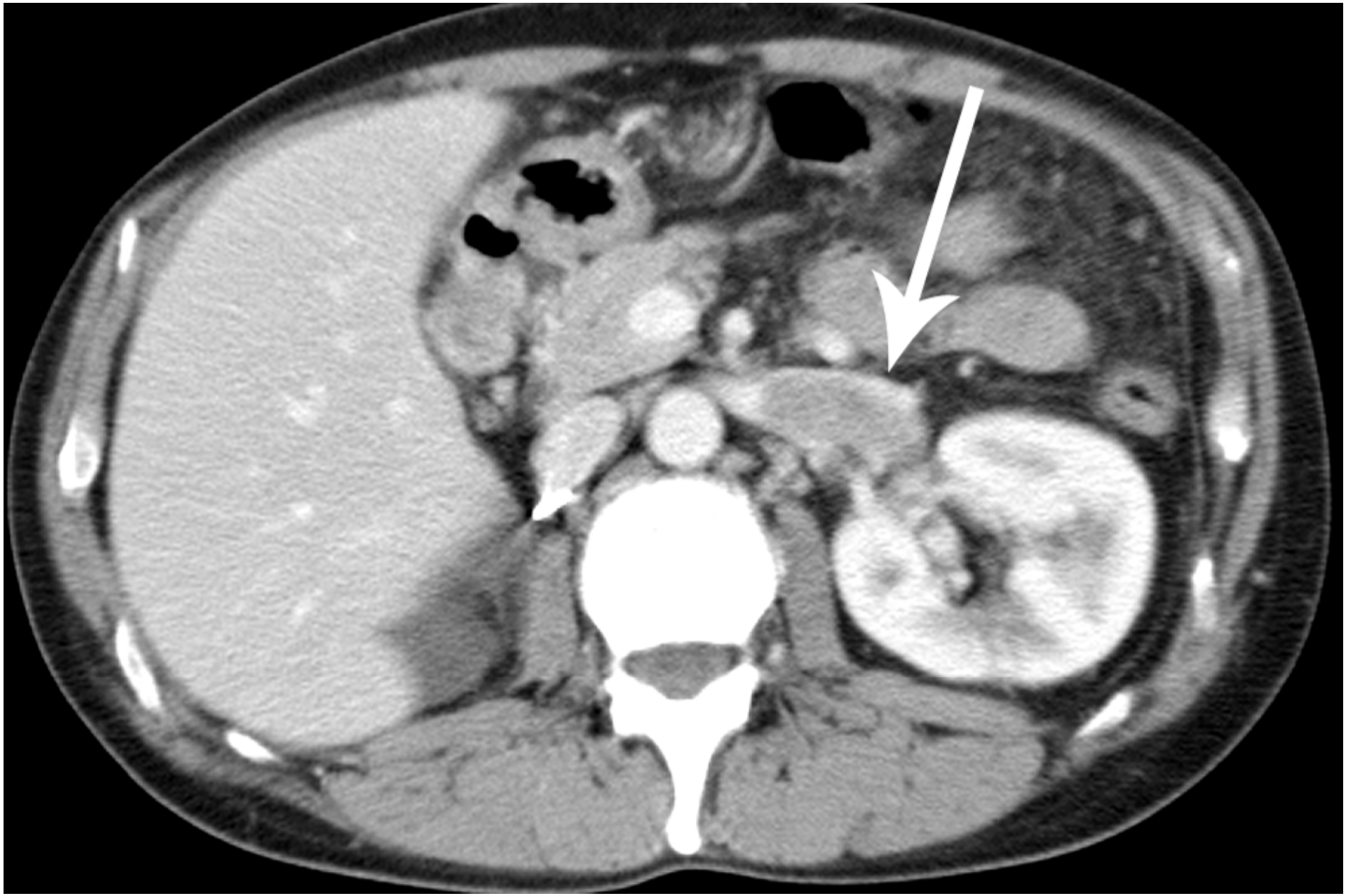


Fig.3(d)

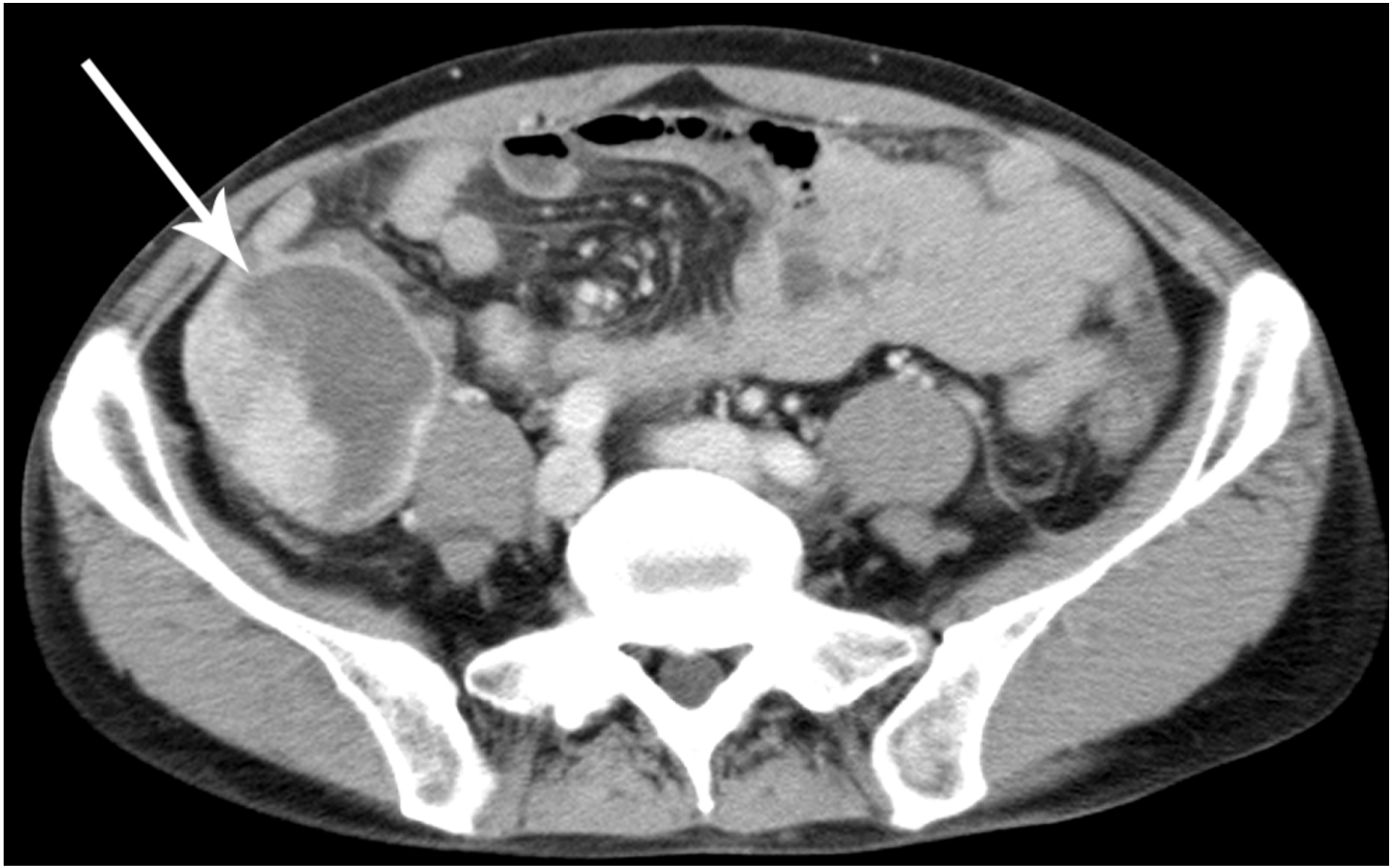
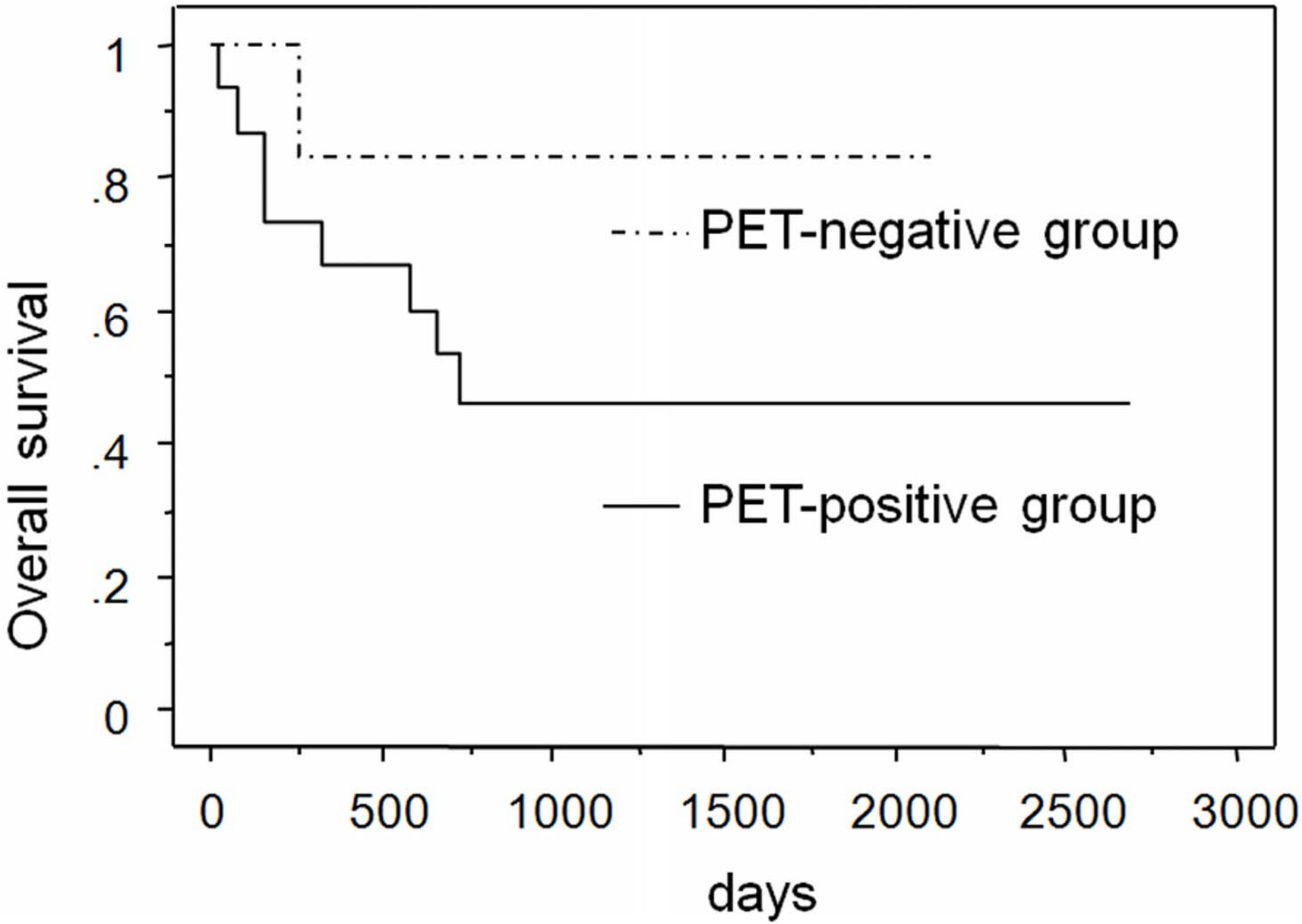


Fig.4


Overall survival
1
.8
.6
.4
.2
0
PET-negative group
PET-positive group
0
500
1000
1500
2000
2500
3000
days