Complete Title

Transcatheter arterial embolization with a mixture of absolute ethanol and iodized oil for poorly visualized endophytic renal masses prior to CT-guided percutaneous cryoablation.

Shortened Title

Lipiodol marking prior to Cryo

Manuscript type

Clinical Investigation

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All authors declare that they have no conflicts of interest.

Title

Transcatheter arterial embolization with a mixture of absolute ethanol and iodized oil for poorly visualized endophytic renal masses prior to CT-guided percutaneous cryoablation.

Abstract

Purpose: To retrospectively evaluate the feasibility of transcatheter arterial embolization (TAE) using a mixture of absolute ethanol and iodized oil to improve localization of endophytic renal masses on unenhanced computed tomography (CT) prior to CT-guided percutaneous cryoablation (PCA).

Materials and Methods: Our institutional review board approved this retrospective study. From September 2011 to June 2015, 17 patients (mean age, 66.8 years) with stage T1a endophytic renal masses (mean diameter, 26.5 mm) underwent TAE using a mixture of absolute ethanol and iodized oil to improve visualization of small and endophytic renal masses on unenhanced CT prior to CT-guided PCA. TAE was considered successful that accumulated iodized oil depicted whole of the tumor edge on CT. PCA was considered successful when the iceball covered the entire tumor with over a 5-mm margin. Oncological and renal functional outcomes and complications were also evaluated.

Results: TAE was successfully performed in 16 of 17 endophytic tumors. The 16 tumors underwent following CT-guided PCA with their distinct visualization of localization and safe ablated margin. During the mean follow-up period of 15.4 ± 5.1 months, one patient developed

local recurrence. Estimated glomerular filtration rate declined by 8% with statistical significance (P = 0.01). There was no procedure-related significant complication.

Conclusion: TAE using a mixture of absolute ethanol and iodized oil to improve visualization of endophytic renal masses facilitated tumor localization on unenhanced CT, permitting depiction of the tumor edge as well as a safe margin for ablation during CT-guided PCA, with an acceptable decline in renal function.

Key Words

Transcatheter arterial embolization, Iodized oil, Percutaneous cryoablation, CT guidance

Main Text

Introduction

The recent widespread use of high quality abdominal imaging has led to the increased incidental detection of early-stage renal cell carcinomas (RCC) [1]. Although partial or radical nephrectomy is the clinical standard to treat RCCs, percutaneous cryoablation (PCA) is increasingly recognized as a minimally invasive nephron-sparing treatment with comparable efficacy to that of nephrectomy, especially for patients who are poor candidates for surgery or those with multiple renal tumors or a single kidney [2].

Computed tomographic (CT) fluoroscopy is frequently used to guide the placement of cryoneedles. However, on unenhanced CT, some RCCs are poorly visualized because of their

intraparenchymal location and low contrast ratio relative to the renal parenchyma surrounding the tumor. Even tumors that are partly endophytic may demonstrate an unclear boundary between their intraparenchymal edge and the renal parenchyma around the tumor on unenhanced CT. To overcome this limitation, placement of a radiopaque marking coil at CT-guided biopsy for poorly visualized renal tumors was shown to facilitate tumor localization at CT-guided radiofrequency ablation (RFA) [3].

Transcatheter arterial embolization (TAE) is a well accepted treatment option for many renal conditions, including unresectable RCC, angiomyolipoma, and arteriovenous malformation [4, 5]. However, few reports have described its utility prior to PCA. Absolute ethanol has long been employed as a permanent embolic material for renal arterial embolization because of its convenience and devascularization effect [6], and iodized oil is occasionally emulsified with absolute ethanol as a radiopaque agent to improve visualization of embolic material under fluoroscopy [5, 6]. The selective injection of a mixture using iodized oil can facilitate localization of some neoplasm under CT imaging.

We retrospectively evaluated visualization of partially or completely endophytic renal masses during CT-guided PCA following their embolization using a mixture of absolute ethanol and iodized oil. Oncological and renal functional outcomes and complications of this procedure were also investigated.

Materials and Methods

The institutional review board of our hospital approved this retrospective study and waived the requirement for patient informed consent to use data for research. Written informed consent to undergo the procedure was obtained from all patients.

PCA is indicated in patients who are poor candidates for surgery because of medical comorbidities, who have a single kidney, or are likely to develop multifocal recurrent renal tumors because of such hereditary condition as von Hippel-Lindau syndrome, and those who refuse surgical intervention. TAE prior to PCA was performed for cases in which renal tumors were poorly visualized on non-contrast CT and 0.3-tesla magnetic resonance (MR) imaging (Artis, Hitachi Ltd., Tokyo, Japan) mainly because of the tumor's endophytic location or small size.

From September 2011 to June 2015, 89 consecutive stage T1a (<4cm in diameter) renal tumors in 84 patients underwent CT or MR imaging-guided PCA in our institution. Preoperative surveillance revealed no lymphatic or distant metastasis in any case. TAE was performed prior to CT-guided PCA for 25 tumors in 25 patients. Among these, we excluded 8 patients with tumors of relatively large diameters (mean, 35.4 ± 3.1 mm) and exophytic localization that extended more than 50% outside the renal capsule, as described by Kutikov and Uzzo [7], according to preoperative contrast-enhanced CT (CECT) using multiplanar reformatting. These tumors had undergone prior TAE primarily to prevent hemorrhagic complication related to the PCA. Our final study group consisted of 17 patients (13 men, 4 women; aged 51 to 81 years; mean age, 66.8 ± 9.9 years) with 17 endophytic renal tumors (maximum diameter, 12 to 36 mm; mean, 26.5 ± 7.5 mm).

All TAEs were performed using angiography guidance (Artis Zee BA Twin; Siemens Medical

Solutions, Erlangen, Germany). A 5-French (Fr) 25-cm sheath (Terumo Clinical Supply Company, Ltd., Gifu, Japan) was inserted into the abdominal aorta via the right femoral artery under local anesthesia, and a 5-Fr shepherd hook catheter (Terumo Clinical Supply) was placed into the renal artery. After acquisition of renal arteriography, a 1.9- to 2.5-Fr microcatheter (Progreat® Σ, Terumo Clinical Supply; Estream®, Toray Medical Company, Tokyo, Japan; Renegade®, Boston Scientific, Boston, Massachusetts, USA), chosen according to the operator's predilection, was advanced into the feeding arteries of the renal tumors, and a mixture of 5 parts of absolute ethanol (Fuso Pharmaceutical Industries, Ltd., Osaka, Japan) and 2 parts of iodized oil (Lipiodol, Andre Guerbet, Aulnay-sous-Bois, France) was injected as selectively as possible into the feeding arteries.

Guidance of all PCAs was performed using an 80-detector row CT scanner (Aquilion™ PRIME, Toshiba Medical Systems, Tochigi, Japan). Before starting the procedure, unenhanced CT image was obtained to evaluate accumulation of the iodized oil in the target lesion. A cryoablation system (CryoHit®, Galil Medical, Yokneam, Israel) and 17-gauge cryoneedles (IceRod®, Galil Medical) were used in all cases. Cryoneedles were punctured percutaneously under local anesthesia to target deposition of iodized oil using CT fluoroscopy. The ablation protocol consisted of a 15-minute freeze, 5-minute thaw, and 15-minute refreeze cycle. Iceball formation was monitored using CT every 5 minutes during ablation. When additional ablation was required, the positioning of cryoneedles was adjusted, and additional freezing was performed. Two interventional radiologists (K.M. with 4 years of experience and K.S. with 13 years of experience in interventional radiology) performed all TAE and PCA procedures.

Patients were followed as outpatients in our urology department. Treatment efficacy was surveyed by CECT and blood sampling one, 3, 6, and 12 months after the PCA during the first year and every 6 months thereafter. The period of follow-up was closed at the time of the patient's last visit to the outpatient basis.

We evaluated the technical feasibility of TAE and PCA and the visualization of embolized renal tumors on unenhanced CT during PCA. TAE was judged technically successful when the accumulation of iodized oil depicted whole of the tumor edge on unenhanced CT. PCA was considered technically successful when intraprocedural CT demonstrated iceball coverage of the tumor over a 5-mm margin. We also evaluated oncological and renal functional outcomes and complications of the procedure. Oncological outcome was judged based on follow-up CECT. Lack of enhancement of the ablated site on CECT and a continuous decrease in size of the tumor were diagnosed as complete ablation. Renal functional outcome was assessed by estimated glomerular filtration rate (eGFR) before and 3 months after the procedure. We analyzed statistics using a 2-tailed paired *t* test to compare renal function (Excel; Microsoft, Redmond, WA, USA). A *P* value less than .05 was considered to indicate statistically significant difference. Perioperative complications were categorized using the Clavien-Dindo classification system [8]. Significant complications were defined as those classified above grade 2, that is, complications that required medical intervention. The summary statistics of clinical data are expressed as means ± standard deviation.

Results

Seventeen endophytic renal masses (stage T1a) in the same number of patients underwent TAE prior to CT-guided PCA. Nine of the tumors (53%) were completely endophytic, and eight (47%) were partially endophytic, having more than 50% of their circumference inside the renal capsule [7]. Surgery was contraindicated in 9 patients with coexistent disease, including ischemic heart disease or cardiac arrhythmia; 6 patients with a single kidney who had undergone radical nephrectomy; and one patient with von Hippel-Lindau syndrome, who requested to undergo PCA rather than surgery.

TAE was successfully performed in 16 of 17 cases. Only one case, the first patient in our study group, demonstrated a completely endophytic tumor of 19-mm diameter, in which neither tumor stain nor feeding artery were detected, so embolization was not performed, and the patient was excluded from our analysis of PCA. The mean procedure duration was 76 ± 28 minutes (range, 27 to 120 minutes); the mean amount of the injected mixture of absolute ethanol and iodized oil was 1.3 ± 0.7 mL (range, 0.3 to 3.0 mL); and the median interval between TAE and PCA was one day (range, one to 5 days). The 16 embolized tumors were easily visualized on unenhanced CT during PCA. Most demonstrated a dense nodule-like accumulation of iodized oil with mild heterogeneity and whole of the tumor edge (Fig. 1). In a 73-year-old male patient, a left renal neoplasm of 35-mm diameter that showed predominantly peripheral enhancement in preoperative CECT revealed ring-like deposition and the entire tumor edge on non-enhanced CT (Fig. 2). Consequently, technical success of TAE was obtained in 16 of 17 cases (94%). Cryoneedles were placed without difficulty targeting the accumulation of iodized oil under CT fluoroscopy, and technical success of

PCA was obtained in all embolized 16 tumors (100%). The mean number of cryoneedles placed was 3.0 ± 0.7 (range, 2 to 4); the mean freezing time was 31 ± 4 minutes (range, 30 to 45); and the mean duration of the procedures was 72 ± 16 minutes (range, 45 to 110).

We analyzed oncological outcomes in 14 cases; the other 2 patients underwent follow-up at another hospital. Local control after initial session of PCA was obtained in 13 tumors (93%) during a mean follow-up period of 15.4 ± 5.1 months (range, 6 to 24). One case with an intraparenchymal tumor of 32-mm diameter that was ablated using 4 cryoneedles demonstrated a strongly enhancing nodule at the edge of the ablated site on CECT 12 months after the initial PCA, and recurrent renal cell carcinoma was histologically diagnosed by percutaneous biopsy. The patient was successfully performed second session of PCA for recurrent tumor 13 months after the initial session. Four patients with a history of radical or partial nephrectomy for RCC demonstrated distant metastasis on follow-up. Renal functional outcome was available in 13 of the 14 patients; we excluded one patient with chronic renal failure who had been maintained by hemodialysis. The mean eGFR was 58.1 ± 15.0 mL/min/1.73 m² (range, 30.5 to 82.1) before the procedure and 53.5 ± 15.7 mL/min/1.73 m² (range, 28.8 to 82.1) 3 months after the procedure. This 8% decline in renal function was statistically significant ($P = 0.01$). Subset analyses showed no significant difference between preoperative eGFR, which was below 60 mL/min/1.73 m² in 6 patients and above that in the other seven, and postoperative measurements (from 44.8 ± 9.4 to 38.8 ± 6.8 mL/min/1.73 m², $P = 0.07$, in the six; and from 69.6 ± 7.4 to 66.0 ± 8.7 mL/min/1.73 m², $P = 0.12$, in the other seven). No patient developed renal insufficiency or required dialysis. All patients underwent TAE and PCA without

significant procedure-related complication.

Discussion

Our treatment protocol using TAE with a mixture of absolute ethanol and iodized oil prior to CT-guided PCA could remarkably facilitate localization of poorly visualized endophytic renal masses. Some renal tumors, especially those of smaller size and with an intraparenchymal location, are poorly visualized on unenhanced CT, and the boundary between the intraparenchymal part of even large or partially exophytic tumors and the renal parenchyma around the tumor can be unclear. Local control requires ablation 5 to 6 mm beyond the edge of the tumor [9, 10], so poor definition of its boundary can result in treatment failure.

TAE is an established procedure for the treatment of various renal conditions, including RCC [7, 8]. Injected absolute ethanol induces vascular occlusion attributed to the combination of endothelial damage, vascular spasm, sludging of erythrocytes, and denaturation of serum proteins [11], and iodized oil is a well known radiopaque agent that allows visualization of embolic material under fluoroscopy. Use of a mixture of the two as an embolic agent has been reported to yield sufficient hemostasis and radiopacity [6]. In our study, the selective accumulation of iodized oil demonstrated each embolized renal tumor as a distinct focal area of high density surrounded by the soft-tissue density of the renal parenchyma. Consequently, cryoneedles were punctured without difficulty under CT fluoroscopy, targeting the focal accumulation of iodized oil. Moreover, the accumulation of iodized oil demonstrated a safe 5-mm margin during CT-guided PCA more distinctly because of

a high contrast ratio between iceball (area of low density) and iodized oil accumulation (area of high density) (Fig. 3).

As an alternative method to improve visualization of renal tumors, placement of marker coils at percutaneous biopsy under CT guidance prior to CT-guided RFA has been reported to facilitate tumor localization and reduce the duration of CT fluoroscopy during RFA [3]. Advantages of coil placement include simultaneous acquisition of histological diagnosis and marking of the renal neoplasm and lower cost than with our procedure. However, recognition of the tumor edge remains difficult on unenhanced CT, and there may be a potential risk of inaccurate placement or migration of the coil. A feasible alternative may be the prompt placement of cryoneedles during the intravenous contrast enhancement of renal tumors under CT guidance, which has been described for biopsies of hepatic masses [12]. However, this method risks the increased use of contrast material to compensate for the washout of renal tumor enhancement within a few minutes after infusion of the contrast medium. Although the reported identification of contrast material in the renal parenchyma up to 7 days following administration suggests that cryoneedles can be placed using an image of the tumor with negative contrast [13], this has some uncertainty relative to our procedure. Moreover, it may be difficult to evaluate the margin between the tumor and iceball using these methods. PCA under different imaging guidance is an attractive alternative. Ultrasonography guidance is reported safe [14], but precise manipulation is often impeded by strong acoustic shadowing from cryoneedles and the iceball [15]. The superior soft tissue contrast of MR imaging compared to that of CT may demonstrate renal tumors not visualized with CT without radiation exposure, but MR imaging

guidance tends to be more expensive and time-consuming [15].

The clinical efficacy rate of PCA for RCC ranges from 87 to 97% [16-18], and our oncological outcomes were comparable to those reported by others. Although the 8% decline in eGFR between that obtained before and 3 months after PCA demonstrated a significant decrease in renal function, the decrease did not impact clinical findings and was considered acceptable because it was comparable to a reported 5.8 to 12.3% decline in the eGFR following partial nephrectomy [19, 20]. Subset analyses grouped by preprocedural eGFR of below or above 60 mL/min/1.73 m^2 demonstrated no significant difference, probably because of our small sample size. The reported rate of major complications following PCA is 7.7%, with bleeding and hematouria most common [21], and the central location of neoplasm increases the rate of complications [22]. On the other hand, TAE using microspheres or coils prior to PCA reduced perioperative hemorrhagic complication [23, 24]. We believe the reduction in hemorrhagic complications is comparable between TAE using the mixture of absolute ethanol and iodized oil and previously reported embolic agents.

Our study is limited by its retrospective nature, small number of cases, and short clinical follow-up period. Further experience is necessary to establish the effectiveness of this procedure. Evaluation of follow-up CECT may be difficult because an enhancing nodule that suggests recurrence may hide in the deposition of iodized oil. However, in our study, one recurrent tumor that appeared at the edge of the site of ablation was diagnosed without difficulty.

In conclusion, TAE using absolute ethanol and iodized oil is feasible to improve visualization of

renal masses, such as endophytic tumors, on unenhanced CT prior to CT-guided PCA, demonstrating tumors as distinctly circumscribed areas of high density, improving visualization of a safe margin for iceball formation, and yielding an acceptable decline in renal function.

Conflict of Interest Disclosure Statement

All authors declare that they have no conflicts of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed Consent

Does not apply.

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Figure Legends

Fig. 1

A Renal mass is poorly visible on unenhanced CT. **B** Completely endophytic renal mass of 19-mm diameter is readily visualized on contrast-enhanced CT. **C** Renal mass is selectively embolized using mixture of absolute ethanol and iodized oil. **D** Renal mass is depicted as focal high density area on unenhanced CT after TAE.

Fig. 2

A Contrast-enhanced CT image revealed partially endophytic tumor with peripheral dominant enhancement. **B** Ring-like deposition of iodized oil depicted the tumor edge on unenhanced CT after TAE.

Fig. 3

High contrast ratio between iodized oil accumulation and iceball formation (arrowhead) demonstrated safe ablated margin distinctly on unenhanced CT (**A**, axial; **B**, coronal).

Fig1.A

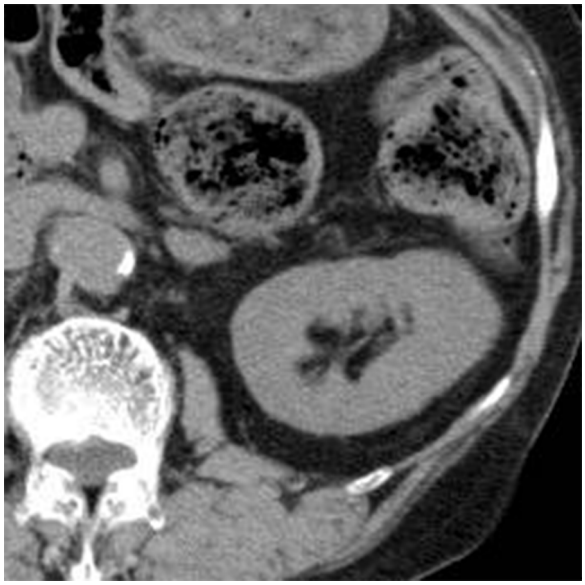
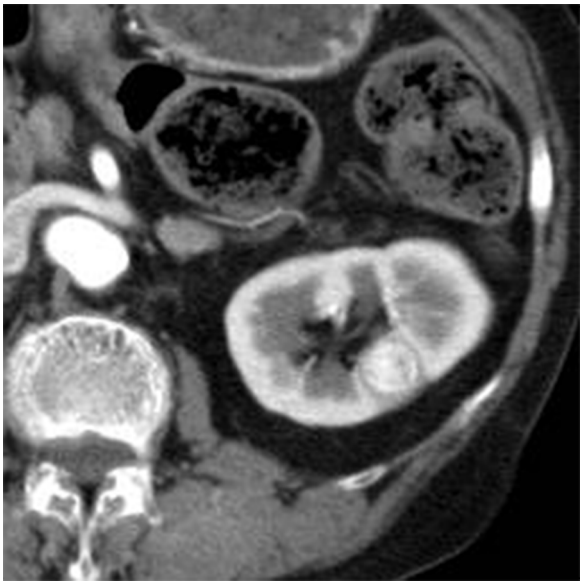


Fig1.B



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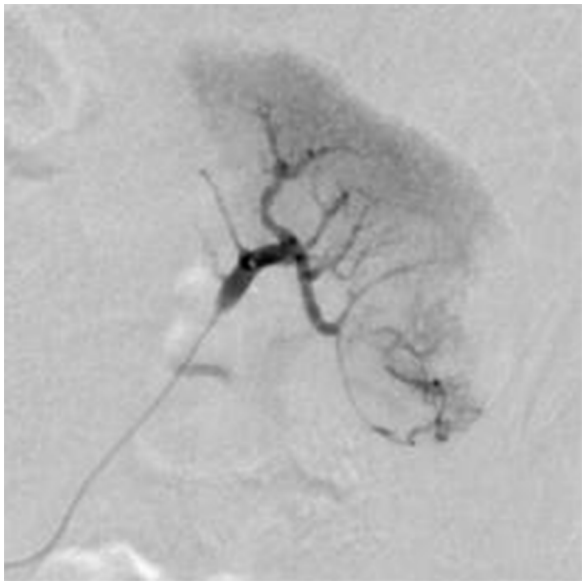

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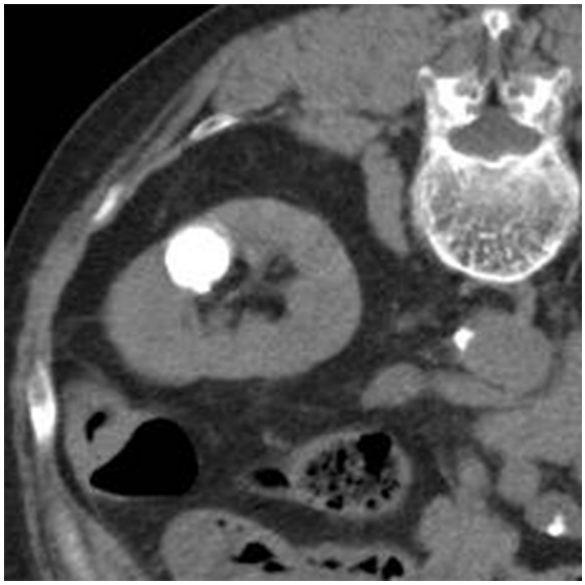
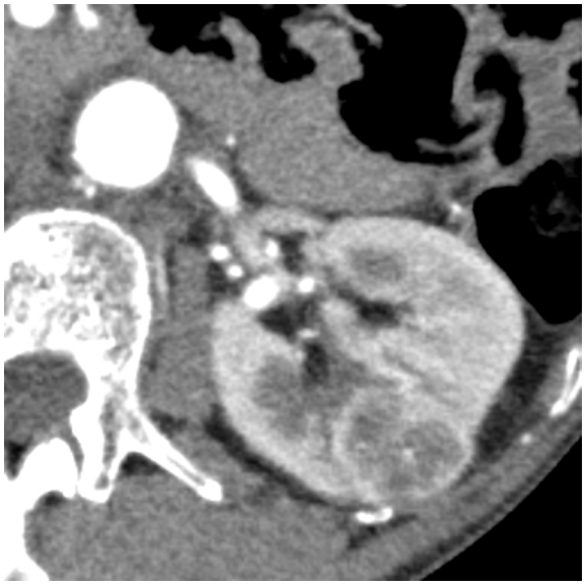


Fig2.A



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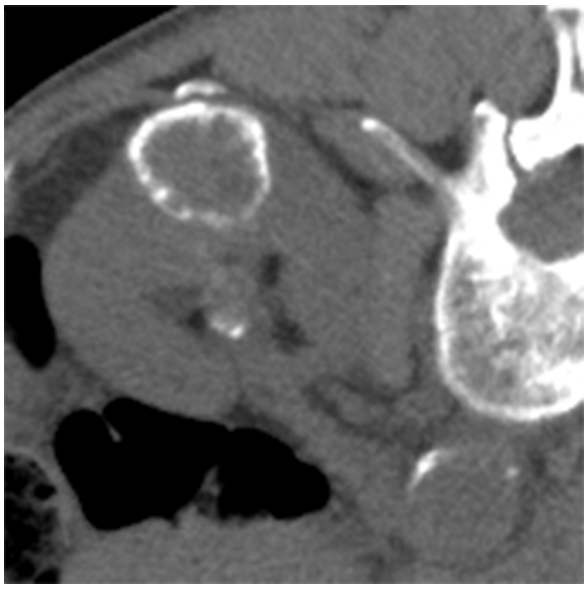

Fig3.A

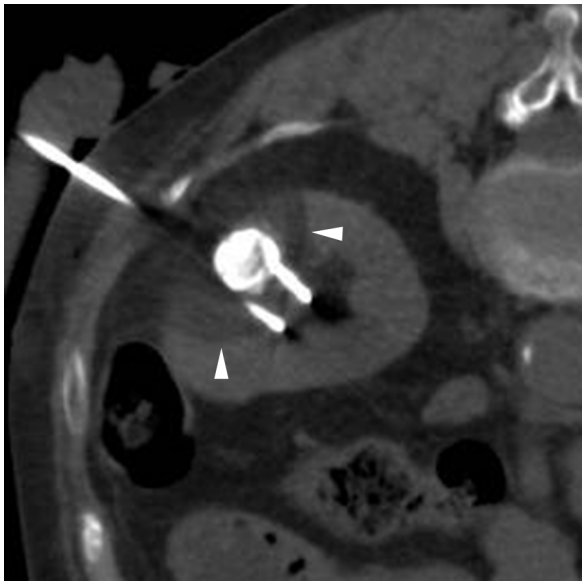

Fig3.B