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Original Article

Clinical applications of CT-guided percutaneous nanoknife ablation in retroperitoneal tumor

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Abstract: Objective: This present study was aimed to assess the effectiveness and reliability of CT-guided nanoknife ablation in retroperitoneal tumor treatment. Methods: 2 retroperitoneal tumor patients were selected, including one pancreatic cancer patient and one colorectal cancer retroperitoneal metastatic tumor patient. The surgery was performed under general anesthesia with large aperture multi-slice CT, electrocardio synchroscope and anesthesia monitoring device. Nanoknife ablation electrode was implanted through percutaneous conformal puncture in accordance with preoperative plan and ablation degrees were estimated by current waveform. It was significant to perform CT examination immediately to eliminate complications and monitor patients' vital signs continuously and comprehensively after surgery. Imaging test was implemented to observe curative effects and complications 3-5 days after surgery and each laboratory examination of blood needed to be reviewed. Results: 2 cases of surgery were completed successfully and the vital signs of patients were stable. Pancreatic cancer patient underwent mild abdominal pain without any severe complications after surgery. Imaging test displayed complete ablation, clear border, no intensification in ablation area, mild inflammatory change around and no damages on nearby blood vessels, biliopancreatic ducts and intestinal canals. The pancreatic cancer patient showed transient rises of lipase and diastase and mild rise of tumor marker via laboratory examination. There was no abnormality in laboratory index of retroperitoneal metastasis patient. Conclusion: Nanoknife ablation could protect blood vessels, biliopancreatic ducts and intestinal canals while inactivating tumors in the process of retroperitoneal tumor ablation. This technique was safe and effective, which might be further popularized and applied clinically.

Keywords: Irreversible electroporation, retroperitoneal tumor, ablation

Introduction

Retroperitoneal tumor was divided into primary retroperitoneal tumor (occurring in retroperitoneal potential lacuna, including pancreatic tumor, renal tumor and adrenal tumor) and secondary retroperitoneal tumor (spread from other parts). Retroperitoneal tumor patients usually have no obvious symptoms and signs because of its deep location. So it often has impinged some important structures, like nerves, blood vessels and intestinal canals et al when found and the patients lose the opportunities of surgery. Consequently, the preferred method is chemotherapy or radiotherapy clinically to prolong the survival time and ease symptoms. However, the prognosis is poor. For example, the mean survival time of pancreatic cancer patients is only maintained in six months to one year [1, 2].

Image-guided tumor ablation technique is developing quickly in recent years. It has been the forth therapeutic tool after surgery, radiotherapy and chemotherapy with assured curative effects [3]. Due to complicated structures around retroperitoneal tumor, regular physical ablations (radio frequency, microwave, refrigeration) usually induce severe complications (infection, hemorrhage and biliary tract injure) and restrict ablation medical system seriously. Image-guided tumor ablations can ablate tumor tissues selectively and protect adjacent significant structures [4-6]. CT-guided percutaneous nanoknife ablation was firstly used to cure retroperitoneal tumor in mainland China in current study, which was aimed to explore its indication

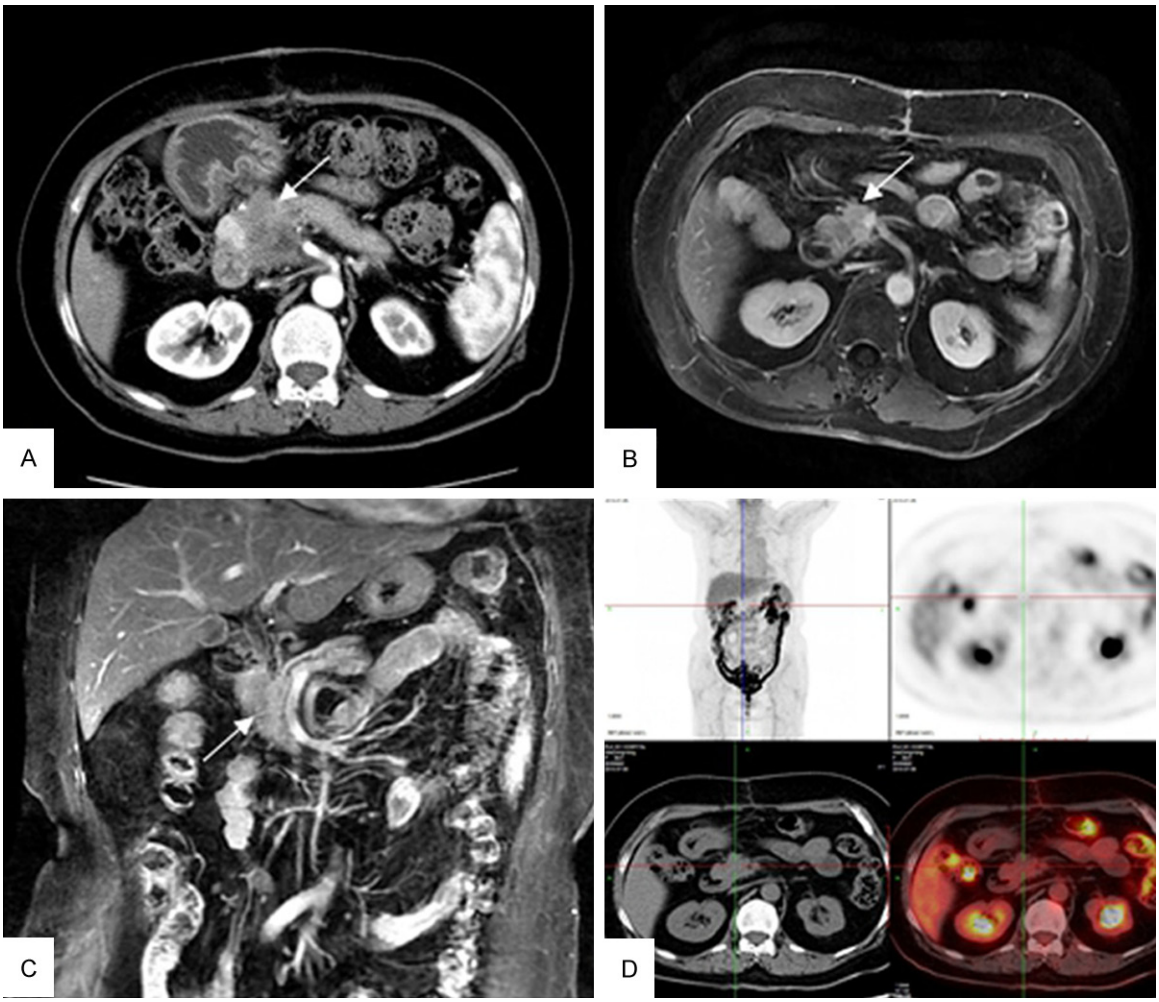

Figure 1. A. The lesion size on pancreatic neck was approximately 4.2 × 3.1 cm, which adjoined celiac trunk and descending duodenum around arteries and veins on mesentery (arrow); B. MRI examination demonstrated remarkable reduce of lesions in pancreatic neck after 4 cycles of chemotherapy. The delay image showed enhanced lesions in pancreatic neck 2.6 × 1.2 × 2.0 cm (front-back × side-side × up-down) around superior mesenteric veins with clear lesion border (arrow); C. MRI coronal image revealed break and slight dilation between pancreatic duct and lesions, and the lesions were next to blood vessels and intestinal canal (arrow); D. PET-CT examination didn't display clear uptake of lesions.

choice, technical advantages and application points.

Materials and methods

Objects of study

2 retroperitoneal tumor patients were obtained from oncology department of Chinese PLA General Hospital. One patient (female, 64 years old) was diagnosed adenocarcinoma of pancreatic neck more than 4 months. The imaging examination demonstrated remarkable reduce of lesions in pancreatic neck after 4 cycles of chemotherapy and PET-CT examination didn't display clear uptake of lesions. But MRI delay image showed enhanced lesions in pancreatic neck 2.6 × 1.2 × 2.0 cm (front-back × side-side × up-down), enveloping arteries and veins of mesentery and adjacent structures of celiac trunk, pancreatic duct and duodenum. The form was similar compared with previous imaging examination (**Figure 1**). The other one was also a female with the age of 46. After middle-low differentiated adenocarcinoma surgery, PET-CT examination revealed hypermetabolic nodule of retroperitoneal anterior renal space, being next to descending colon. It showed partial increase and slight enlargement of nodule

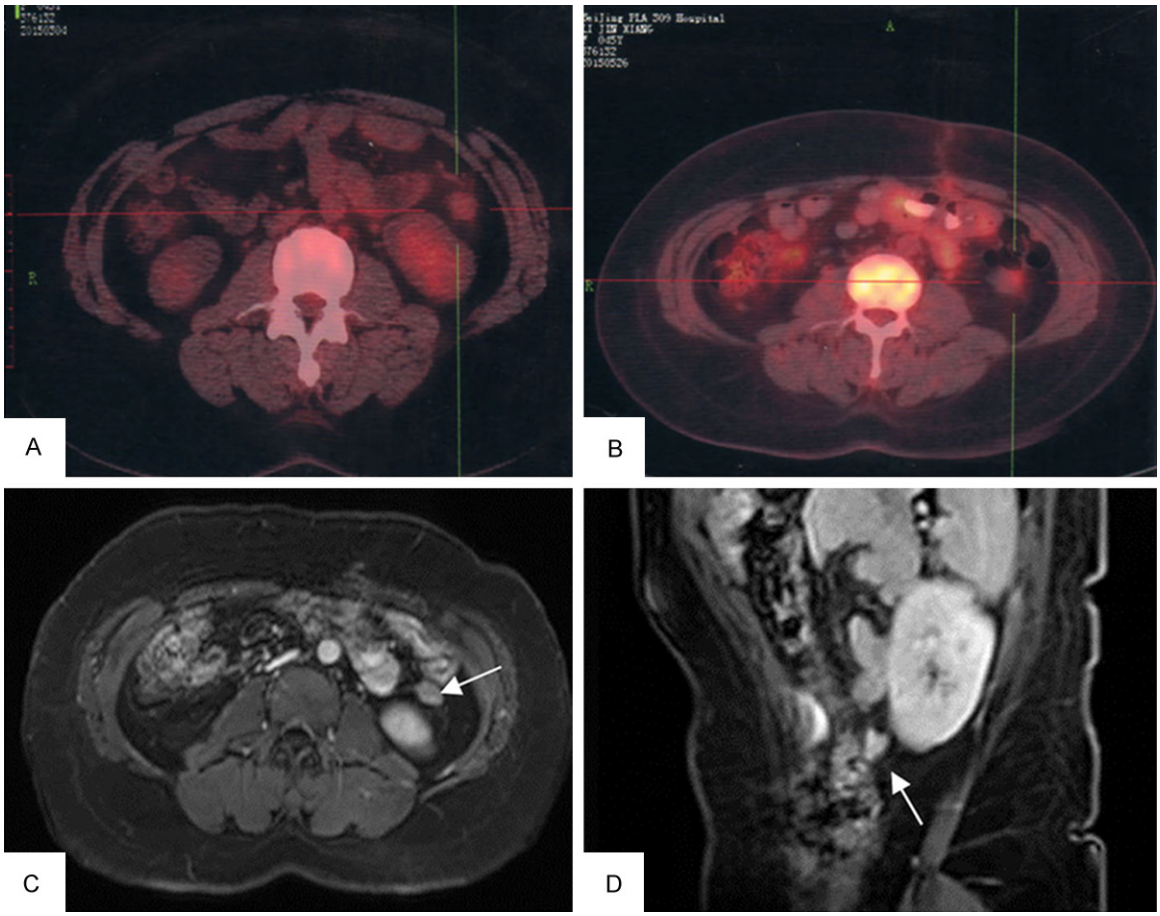

Figure 2. A. PET-CT showed hypermetabolic nodule of retroperitoneal anterior renal space in postoperative colorectal cancer patient; B. PET-CT reexamination displayed the increase of partial metabolism in lesions after 2 months. C. Preoperative MRI demonstrated moderate reinforcement of lesions with unclear delimitation with colon intestinal wall (arrow); D. MRI sagittal view revealed the close relation between lesions and colons (arrow).

metabolism after 2 cycles of chemotherapy (**Figure 2**). 2 patients were evaluated with good general conditions, excluded cardiopulmonary and hepatorenal dysfunctions. Tumors inactivation was advised to use percutaneous puncture nanoknife ablation after multidisciplinary consultations.

Facilities and appliances

CT located monitoring equipment adopted big bore 16-slice spiral CT (Philips Brilliance CT) with 85 cm aperture. Scanning parameters included 250 m. As electric current, 120 kV voltage, 5 mm slice thickness, 2 mm slice gap, multifaceted and arbitrary orientation realignment. Body surface location was completed by paliform metal logos. Nanoknife ablation system (Nanoknife generator, Angio-Dynamics), TOF-watch (TOF-watch SX), electrocardio synchroscope (Philips, Mp50), anesthetic machine (Datex-Chmeda Aespire) and disposable packets were applied in this study.

Preoperative preparation

It was significant to choose appropriate position based on imaging information, establish vein channels and monitor systemic vital signs. Midazolam, sufentanil and remifentanil were used to induce and maintain anesthesia in patients. Rocuronium bromide was used to maintain flaccidity before intubation. Nanoknife therapeutic schedule was designed in accordance with CT scan image to get optimal puncture level, entry point and direction, angle, depth of needle insertion.

Surgical procedure

Draping was completed after routine disinfection. According to lesions situation, it was suit-

Figure 3. CT images displayed the parallel puncture distributions of ablation electrode needles around lesions during surgery.

able to use ablation electrode needles of 15 cm length (19 G/1.2 mm). 3 and 2 ablation electrode needles were respectively used in pancreas and colon metastatic lesions and the ablation electrode was exposed 1 cm. Based on surgery planning, percutaneous puncture conformal parallel needle placement was determined and checked by CT scan. Ablation range was assessed in time. Nanoknife ablation was performed after test ablation electrode with direct current and 3000 V/cm voltage. There were total 90 pulses in 10 groups and each pulse separation was 70 microsecond. Ablation degrees were estimated on the basis of current waveform and it was necessary to repeat ablation while failing to get expected effects. Above-mentioned ablation procedure was repeated after 1 cm withdrawal of needles (**Figures 3** and **4**).

Postoperative management

Anticoagulants (such as low molecular heparin) were used to avoid from thrombosis. Some drugs were used to protect gastric mucosa, like omeprazole and citric acid mosapride. If necessary, analgesics were properly applied to patients according to the VAS scores after surgery and antibiotics were applied routinely. Pancreatic cancer patient was inhibited from diet within 3 days after surgery. Octreotide acetate was used to suppress pancreatin secretion. Nasogastric tube and venous transfusion were performed for nutritional support.

Postoperative observation

Systemic vital signs and general conditions (including daily activities, pain and ingestion) of patients were monitored closely after surgical. Laboratory examinations of blood were completed, including blood routine examination, blood biochemistry and tumor marker. It was still important to pay attention to lipase and diastase in pancreatic tumor patient. Imaging examination was performed 3-5 days after surgery to observe adjacent organs (blood vessels and intestinal canals) and preliminarily evaluate the tumor ablation situation.

Results

Surgery situation

Surgeries were completed successfully. The time of pancreas tumor and colon metastatic tumor surgeries were respectively 120 min and 100 min. Preoperative intubation anesthesia was performed smoothly in 2 patients. Muscle relaxation and cardiopulmonary status monitored during surgery were stable and electrode needles placement were eligible, which conformed to preoperative plan. Multi-group pulse ablations were implemented successfully and current waveform displayed an increasing trend, which demonstrated desirable ablation effects on tumor tissues. Patients were revived from anesthesia and sent back to patients' rooms smoothly after surgery.

General conditions of postoperative patients

Patients were in good mental conditions. Postoperative mild abdominal pain occurred in pancreatic cancer patient that day and got worse when patient changed postures. Combined with relevant inspections, it conformed to mild pancreatitis symptoms and there were no vomit and fever symptoms. The pain disappeared generally after symptomatic

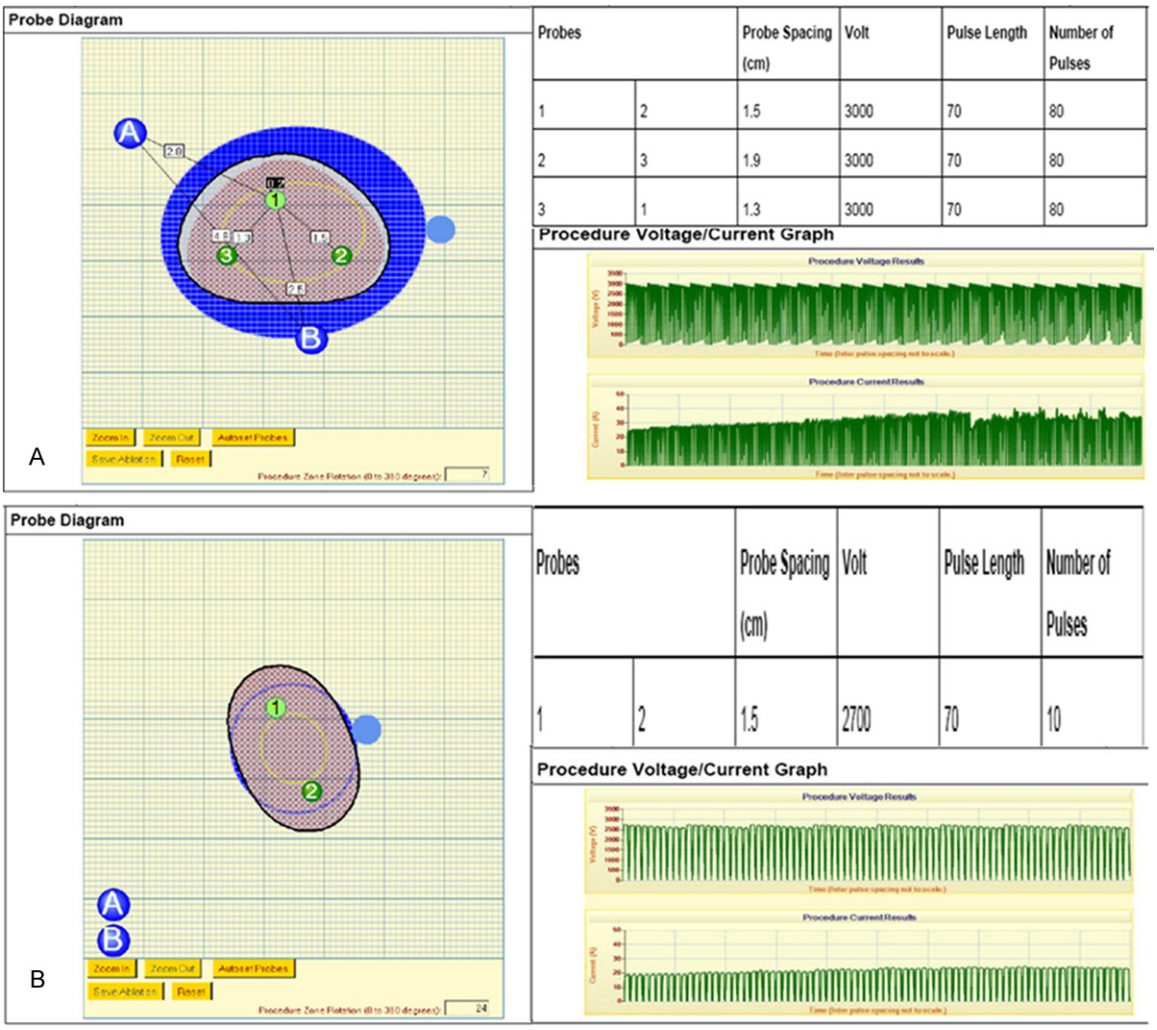

Figure 4. A. 3 ablation electrode needles were used in pancreatic lesion ablation. During surgery, ablation area coverage was assessed by needle position, and voltage and pulse frequency were set according to electrode spacing of three ablation needles with constant voltage (3000 V). Current waveform was in an increasing tendency, which meant entire ablation; B. 2 ablation electrode needles were used in colorectal cancer metastatic lesion ablation with the same procedure. Current waveform was observed with an increasing tendency.

treatment. Patient underwent exhaust in the fourth day after surgery and then took liquid diets after removal of nasogastric tube. There were no any unwell symptoms in colon metastasis patient, which might take food and participate in activities on the second day after surgery.

Imaging examination

Lesions in pancreatic cancer patient decreased remarkably indicated by MRI after 4 cycles preoperative chemotherapy. Pancreatic neck delay strengthened the lesions and PET-CT showed no metabolism in lesions. CT displayed slightly low density in ablation area and blurred fat spaces around pancreas with punctiform gas density shadows during surgery. Ultrasound contrast revealed integrated arteriovenous form in mesentery near lesions, normal blood flow signal without blood supply in ablation area 3 days after surgery. MRI demonstrated clear boundary in pancreatic neck ablation area, no enhancement within the lesions, normal arteriovenous form in mesentery, visible exudation surrounding pancreas and gastric wall edema in gastric antrum 5 days after surgery (**Figure 5**). Preoperative CT examination of colorectal cancer patient showed nodules enough of blood supply in retroperitoneal left anterior pararenal space and ambiguous

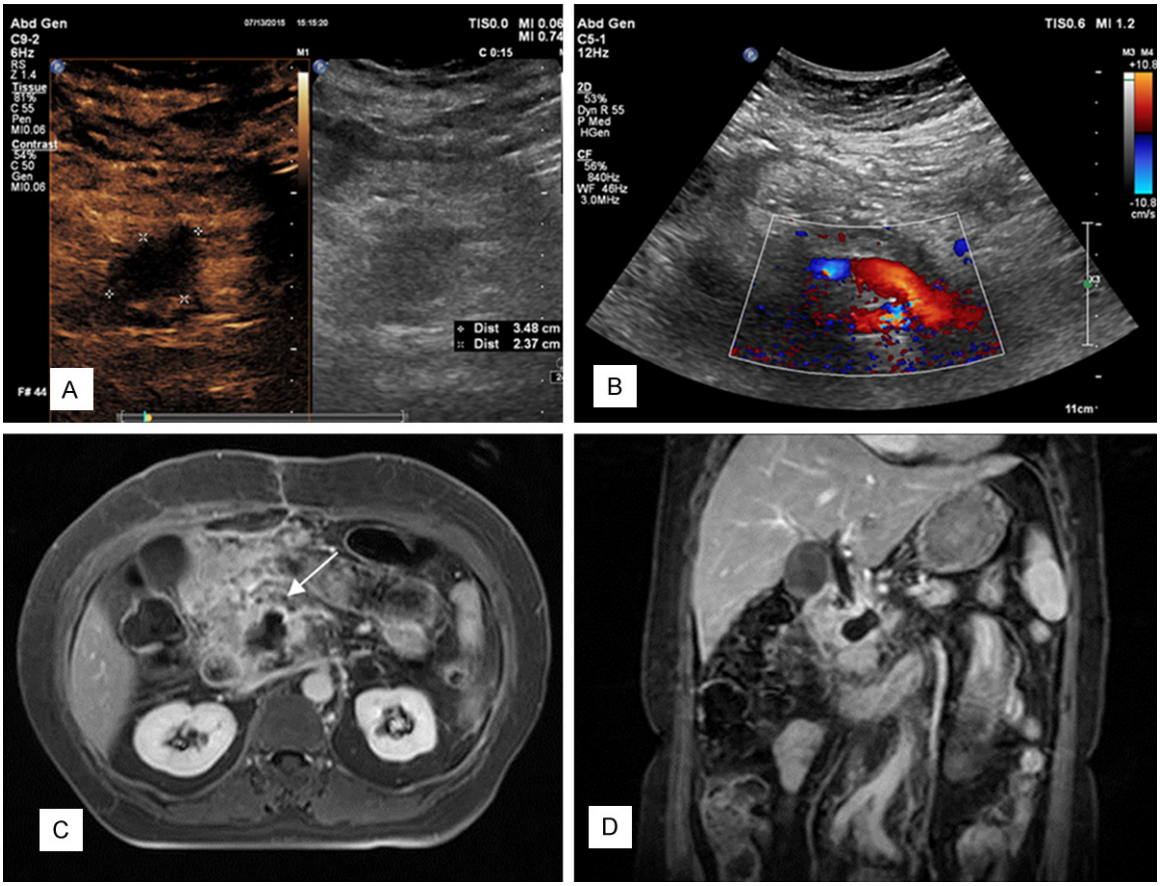

Figure 5. A. Ultrasound contrast revealed clear boundary of ablation area without obvious internal blood supply in pancreatic cancer patient 3 days after surgery. B. Blood flow signals were normal around ablation area; C. MRI enhanced images showed clear boundary of pancreatic neck ablation area with lacelike reinforcement, no internal reinforcement, exudation changes surrounding pancreas and gastric wall edema in gastric antrum 5 days after surgery (arrow); D. Coronal images demonstrated normal blood vessels and intestinal canal form around ablation area.

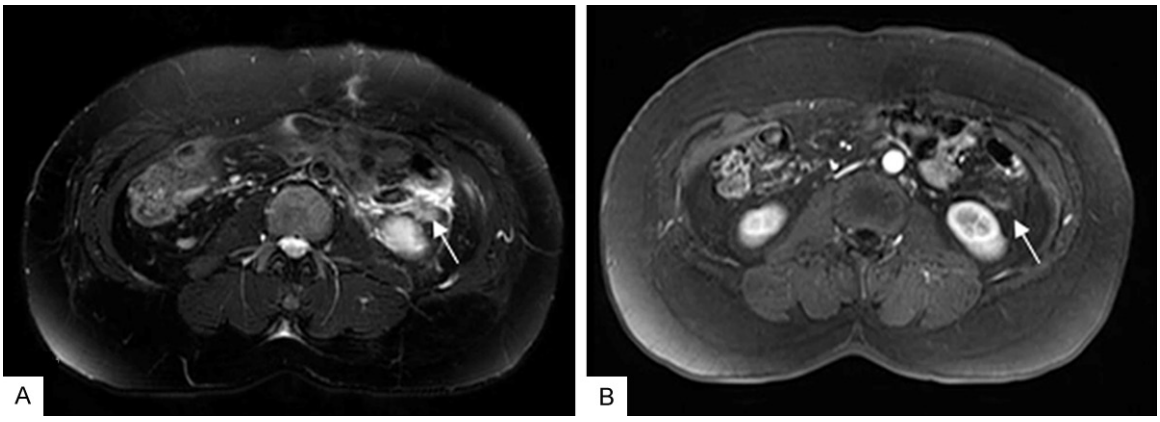

Figure 6. A. MRI showed lamellar T2 signal around ablation area, ambiguous fat spaces and exudation changes in colorectal metastatic tumor patient 3 days after surgery; B. Enhanced images displayed normal form of adjacent intestinal canal without intensive lesions.

boundary with intestinal wall of descending colon. And PET-CT displayed hypermetabolism of lesions. Intraoperative CT revealed slightly low density in ablation area, blurred fat spaces around this area and normal form of intestinal wall. MRI examination demonstrated no enhan-

Table 1. Each index of postoperative pancreatic cancer patient was in accordance with mild pancreatitis changes

	Lipase (U/L)	Diastase (U/L)	CA-199 (m/mL)
Preoperative 1 day	158.6	32.5	34.34
Postoperative day	2121.0	166.4	36.43
3 days after surgery	719.9	44.6	74.66
1 month after surgery	124.4	34.3	61.83

cement within the lesions, linear enhancement in border, no abnormal changes in kidney and colon 3 days after surgery (**Figure 6**).

Laboratory examination

Each index of postoperative pancreatic cancer patient was in accordance with mild pancreatitis changes, including transient increases of lipase and diastase, mild elevations of tumor marker and leucocyte, which decreased gradually via symptomatic treatment (**Table 1**). Each index of colon metastasis patient was normal.

Discussion

As a new type of minimally invasive technique, nanoknife ablation is different from physical ablations (like radio frequency, microwave and cryoablation), which depend on temperature variations to inactivate tumor cells. Nanoknife destroys the integrity of lipid bilayer to form nano-scale pores in cell membranes via high-frequency energy short burst, and changes membrane permeability, causing apoptosis. Nanoknife ablation may not induce temperature changes of local tissues in therapeutic process [7, 8]. This research team performed nanoknife ablation animal experiment on porta hepatis, kidney and pancreas before clinical application of nanoknife ablation, which has been verified its selective ablation effects and unique advantages [9-12].

This is the first time that CT-guided percutaneous puncture nanoknife ablation is applied to clinical treatment of non-removable retroperitoneal tumor. It is concluded that nanoknife ablation has 3 main advantages in retroperitoneal tumor treatment as follows. Firstly, it inactivates tumors selectively and protects blood vessels and adjacent structures (biliopancreatic ducts and intestinal canals). Nanoknife may only cause selective injures of membrane in ablation area and seldom damage skeleton structures (blood vessels, bile ducts and pancreatic ducts) which lack cell membranes and contain connective tissues or collagen. So it can protect these tissues furthest and contribute to functional rehabilitation of tissues [13]. Secondly, it estimates ablation degrees immediately according to current waveform. High voltage pulse breaks down tumor membranes and leads to permanent perforation, which induce apoptosis rapidly. And then the releases of intracellular ions decrease electric resistance and cause continuous increase on current waveform. If the elevation of current waveform is not obvious, repetitive ablations are performed till satisfactory. This technique is different from regular physical ablations, which estimates ablation degrees based on current waveform. Cryoablation assesses ablation area through low density ice hockey, but temperature on ice hockey edge usually can't reach tumor necrosis temperature, causing tumor residuals. And it's more difficult to identify ablation boundary on CT image through radio frequency and microwave ablations. Thirdly, it can inactivate tumors in a short time, decreasing greatly the risk of surgery. Nanoknife may induce irreversible injures and apoptosis of tumor cells in the time of microsecond and millisecond, which greatly shortens the time of therapy, improves the efficiency of surgery and reduce the risk of surgery compared with traditional physical ablations (like radio frequency and refrigeration et al) [14-16].

Nanoknife ablation has unique advantages in the treatment of retroperitoneal tumor, but it is involved into local treatment and cannot control forward metastasis or relapse. Therefore, it's significant to choose indications and seize ablation time strictly, which is essential to the curative effects of nanoknife ablation. Numerous literature indicated that nanoknife ablation couldn't remarkably lengthen the average lifetime of patients who suffered from overlarge tumor volumes or systemic multiple metastasis. And it hasn't been recognized for the effects of nanoknife ablation on cytoreduction or analgesia. Consequently, it's recognized internationally that nanoknife ablation has definite effects on patients who undergo tumors with less than 3 cm diameter and without distant metastasis [17-20]. In addition, tumor

lesions develop rapidly, which invade nearby organs and induce symptoms easily without control. Nanoknife ablation also can be used to control the development of lesions and improve the prognosis. So the patients were selected strictly. The tumor of pancreatic cancer patient reduced to 3 cm with obvious decrease in CA-199. Preoperative PET-CT examination didn't show clear hypermetabolism and distant metastasis of lesions. But MRI delay reinforcement displayed enhancement of lesions. It was considered that primary tumor occurred regression and fibrosis and lesions were in stagnate phase after multicycle chemotherapy. It was easy to recur without control. Except retroperitoneal lesion, other lesions were controlled effectively in colorectal cancer after multicycle chemotherapy. The 2 times PET-CT examinations indicated the elevation and enlargement of lesion metabolisms, which might invade descending colon and cause perforation without prompt control. It was hard to remove by surgery because pancreas lesions were around arteries and veins of mesentery and metastatic lesions of colorectal cancer closed to intestinal wall. So nanoknife ablation was performed in this case.

Nanoknife ablation treatment risks also existed due to deep location of retroperitoneal tumor and complexity of adjacent structures. The common complications included the following aspects. First, all invasive manipulations (nanoknife ablation included) caused mechanical injury of pancreatic duct easily. And nanoknife ablation also resulted in slight damage of pancreatic cells around ablation area and induced mild or moderate pancreatitis frequently. Second, the needles were often inserted on ventral side through gastric wall or intestinal wall in the treatment of pancreatic tumor via nanoknife percutaneous puncture approach to ensure parallel arrangement of ablation electrode. Although nanoknife electrode was thinner (19 G) than radio frequency and refrigeration electrodes, it was still possible to cause mechanical puncture damages of gastric wall or intestinal wall (like local edema and hemorrhage). Third, nanoknife could protect vascular structures extremely, but numerous studies demonstrated that it damaged vascular endothelium to varying degrees. So thrombosis might exist in venous system with slow flow rate. Forth, nanoknife ablation relied on partial high-voltage pulse to complete treatment, so it was likely to induce arrhythmia when lesions closed to heart. It was significant to take measures on these complications. Inhibition of enzyme drugs (like hydrochloric acid and octreotide) was used in perioperative period of pancreatic tumor therapy. Patients were prohibited eating and drinking seriously within 3 days after surgery and obtained nutritional support by nasogastric tube and venous transfusions. Analgesics and antibiotics were used in patients with pancreatitis symptoms, like abdominal pain and fever. Patients undergoing gastric and intestinal wall injures might use proton pump inhibitors (such as omeprazole), who usually got better faster by themselves. Anticoagulant drugs (like low molecular heparin) were used routinely after surgery. It was crucial to assess cardiac function before surgery and monitor electrocardiogram severely during surgery. Electrocardio-defibrillator was essential to deal with intraoperative emergency situations timely, especially to the ablation of lesions around heart.

As the latest ablation technique, nanoknife ablation has unique advantages in the therapy of retroperitoneal tumor. Indication and treatment timing are especially important for surgery. And perioperative managements also should be appropriate and timely. This study explored clinical application in retroperitoneal tumor, and the study objects and follow-up time were still insufficient. It's significant to further detect the applications of nanoknife ablation in various tumors and the combined applications with other therapies, so that it can be applied and popularized safely and effectively in clinical practice.

Disclosure of conflict of interest

None.

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