Feasibility of EUS-guided Nd:YAG laser ablation of unresectable pancreatic adenocarcinoma

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Background and Aims: EUS has become an interventional technique in which a needle may be used as a vehicle to deliver therapeutic agents. Laser ablation (LA) has been used to treat many primary and secondary neoplasms. This study aimed to assess the feasibility of EUS-guided LA for unresectable (UR) pancreatic cancer.

Methods: Patients with stage IIb-III pancreatic cancer underwent EUS-guided LA. All patients were unresponsive to previous chemoradiotherapy. LA was performed by using a 300-μm flexible fiber preloaded onto a 22-gauge fine needle. A 1064-nm wavelength neodymium-yttrium aluminum garnet (Nd:YAG) laser light with different power settings of 2 W for 800 J, 1000 J, and 1200 J; 3 W for 800 J, 1000 J, and 1200 J; and 4 W for 800 J, 1000 J, and 1200 J was used. Each patient was treated with a single application of 1 of these settings. The application time of the power settings ranged from 200 to 600 seconds.

Results: Nine patients (median age, 74.7; range 55-85) underwent Nd:Yag LA. The mean size of the focal lesion was 35.4 mm (range, 21-45). The ablation area, demonstrated by 24-hour CT, ranged from .4 cm^3 (for the lower power setting of 2 W/800 J) to a maximum of 6.4 cm^3 (for 4 W/1000 J). The procedure was completed in all 9 patients without adverse events.

Conclusion: In our human experience, EUS-guided LA was feasible and well tolerated in patients with UR pancreatic cancer.

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of death in the Western world, with rates of incidence and mortality that are almost overlapping: 5-year overall survival is lower than 4%. Fewer than 20% to 30% of all pancreatic cancer patients are candidates for surgical exploration at the time of diagnosis.[1] Unresectable (UR) locally advanced PDAC is associated with a very poor prognosis, and the treatment of this group of patients remains highly controversial. The current standard therapy is limited to chemotherapy and/or radiotherapy.[2] The introduction of FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin) has become a viable option for advanced pancreatic cancer with or without metastasis. This treatment improves the overall survival and slows the clinical and functional deterioration compared with that of patients who receive gemcitabine.[3]

In recent years, several new, minimally invasive techniques for thermal ablation of malignancies were developed. Among these, LA with an Nd:YAG laser has been applied percutaneously in cases of hepatocellular carcinoma,[4] liver metastasis in colorectal cancer,[5] malignant thyroid nodules,[6] prostate cancer,[7] and brain tumors.[8] The rate of adverse events is lower than with other thermal techniques, such as radiofrequency and microwave treatments.[4,9] Among all thermal treatment modalities, LA is unique in enabling the use of a finer needle. These attributes make LA an attractive option for the treatment of focal lesions in high-risk locations,

Abbreviations: EUS-guided LA, EUS-guided Nd:YAG laser ablation; LA, laser ablation; Nd:YAG, neodymium-yttrium aluminum garnet; PDAC, pancreatic ductal adenocarcinoma; UR, unresectable.

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difficult-to-reach locations, or multiple nodules that differ in size.[4]

EUS has become more operative in the oncologic field based on the technical principle of EUS-guided puncture. The use of EUS in treating pancreatic cancer has progressively increased from the application of antitumoral therapy to ablative therapies, such as radiofrequency,[10] in combination with cryotechnology[11] and with the infusion of photosensitizer substances.[12] EUS control allows a highly accurate targeting of the pancreas, which is difficult to reach via a percutaneous approach. Previous preliminary studies performed in both animal models and humans[13,14] suggested that EUS-guided Nd:YAG LA (EUS-guided LA) is viable and encouraged a larger application. To our knowledge there are no studies on the application of EUS-guided LA on PDAC. The aim of this study was to assess the feasibility of EUS-guided LA for nonresponders with UR PDAC.

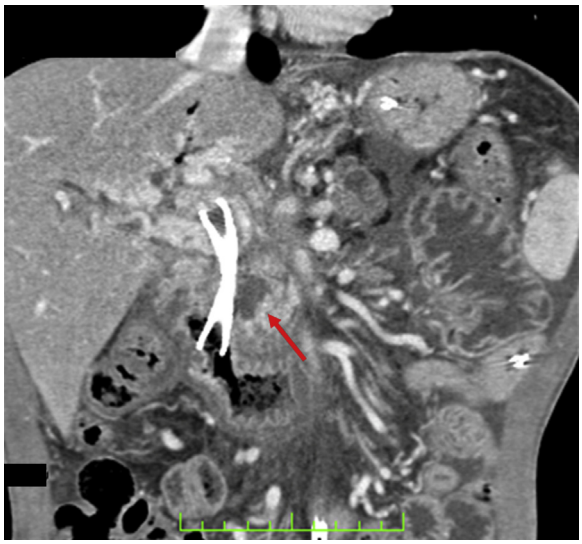

Figure 1. A delayed phase on CT showing the coagulation area (*red arrow*) adjacent the biliary metal stent, with a well-demarcated rim of postcontrast enhancement at 24 hours.

METHODS

This was a prospective cohort single-center study in a tertiary referral center. From December 2014 to February 2016 patients with locally advanced PDAC were evaluated. Inclusion criteria were histologically confirmed PDAC, UR PDAC, and unresponsiveness to chemotherapy or radiotherapy. Exclusion criteria were grades 4 and 5 according to Eastern Cooperative Oncology Group score[15] and advanced heart or pulmonary disease (American Society of Anesthesiologists grade IV).

We intended to evaluate the feasibility of EUS-guided LA in patients with locally advanced pancreatic cancer unresponsive to previous radiochemotherapy. Therefore, the primary outcome was the ability to create a coagulative necrosis of the tumor, as demonstrated by CT scan at 24 hours and confirmed by the involution of the same area on CT scan on 30 days.

Adverse events were defined as major if the events prevented completion of the scheduled procedure and/or resulted in prolongation of hospital stay, another procedure (needing sedation/anesthesia), or subsequent medical consultation.[16] Any potential adverse event according to previous experience[10,11] (such as pancreatitis, burns of the gastric or duodenal walls, bowel injury, or peritonitis) was recorded and graded according to the above-mentioned classification.

Adverse events observed during the treatment or in the first week after the ablation were defined as early adverse events. Late adverse events were defined as any adverse event that was potentially related to the procedure arising at the site of the primary tumor within 3 months of the Nd:YAG LA. Pancreatic enzymes, liver function tests, and blood tests for complete blood cell counts were monitored before the procedure and at 12 hours, 24 hours, and 1 week after the procedure. To collect all these data, a hospital stay of 7 days was scheduled. Contrast-enhanced CT scan was performed after LA, at 24 hours, and at 7 and 30 days.

The Ethics Committee of the Campus Bio-Medico University of Rome provided approval (Prot. no. 41/11) on May 03, 2014. Each patient provided informed consent for all procedures.

EUS-guided LA technique

EUS was performed using a EG-3830UTK echoendoscope (Pentax Medical, Hamburg, Germany), and all procedures were performed with the patient under deep sedation with propofol. Prophylactic antibiotics were administered immediately before the procedures and for 3 days thereafter (ceftriaxone 1 g twice daily intravenously). LA was performed using a 1064-nm wavelength laser (Echolaser; Elesta s.r.l., Florence, Italy) with the insertion of a 300-μm optical fiber (Elesta s.r.l.) through a 22-gauge needle (Expect Slimline; Boston Scientific, Marlborough, Mass).

All procedures were performed by an experienced endoscopist (F.M.D.M.). Contrast-enhanced US, using an intravenous 5-mL SonoVue injection (Bracco International B.V., Amsterdam, Netherlands) through an antecubital vein with a 20-gauge catheter followed by a 10-mL saline solution flush, was performed before and after each LA.

The ablation was started if the placement of the probe inside the tumor was successful without difficulties such as angulation of the distal part of the instrument, hardness of the tumor, stiffness of the GI wall, or vessel interposition. Once in the target lesion the needle was slightly pulled back, and the fiber was gently pushed outside the tip of the needle to a length of 5 mm (Supplementary Fig. 1A and B, available online at www.giejournal.org). The fiber was placed in the upper part

TABLE 1. Characteristics of patients

Patients	Age (y)/sex	Eastern Cooperative Oncology Group score at LA	Location	Previous treatment type before LA	Stent	Treatment (W/J)	Maximum tumor size (mm)	Tumor volume (cm^3)	Volume of ablation at 24 h (cm^3)	Volume of ablation at 30 days (cm^3)	Survival (days)
1	81/M	2	Head	RT	SEMS	2/800	39	1.5	.4	.1	260
2	72/F	2	Head	CT	SEMS	2/1000	21	3.5	2.5	.6	56
3	73/F	2	Tail	CT	—	2/1200	43	5.8	2	1.27	662
4	76/F	2	Head	CT	SEMS	3/800	27	2.5	1.03	.4	326
5	55/M	2	Head	CRT	SEMS	3/1000	45	8.0	.7	.2	237
6	79/F	2	Body	RT	SEMS	3/1200	33	2.7	1.03	.4	253
7	78/M	2	Head	CRT	SEMS	4/800	22	3.8	2.1	0	29
8	74/M	3	Head	CT	SEMS	4/1000	44	10.2	6.3	1.6	45
9	85/F	2	Body	CRT	—	4/1200	45	11	2	1.27	150

LA, Laser ablation; *RT*, radiotherapy only; *CRT*, chemoradiotherapy; *SEMS*, self-expandable metal stent; —, none.

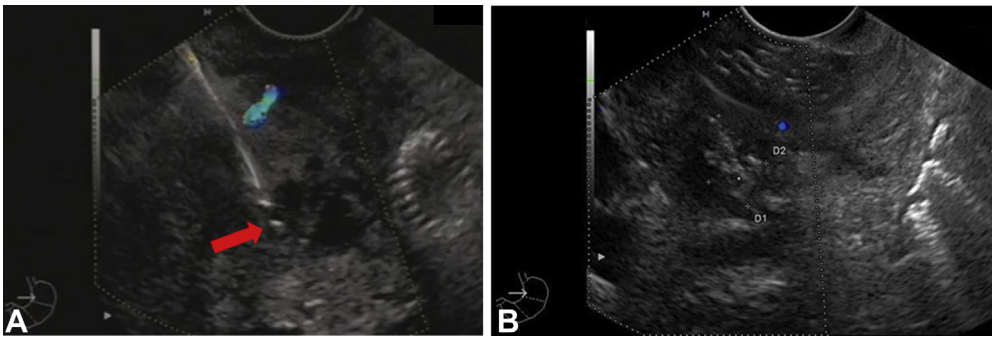

Figure 2. A, The hyperechoic spot visible at 5 mm from the tip of the needle inside the tumor (*red arrow*). **B,** At the end of the procedure, EUS showed a hyperechoic area along the path of the probe surrounded by nonhomogeneous tissue with hyperechoic spots.

of the lesion, and based on our previous results,[13,14] the laser was turned to the following power settings: 2 W for 800 J, 1000 J, or 1200 J; 3 W for 800 J, 1000 J, or 1200 J; or 4 W for 800 J, 1000 J, or 1200 J. The application time automatically ranged from 200 to 600 seconds based on the power settings. Because we did not aim to ablate the entire tumor, each of the 9 patients was treated with only a single application of 1 of the 9 settings.

If the patient received a previous placement of a biliary self-expandable metal stent, we attempted to apply the thermal energy away from the stent to avoid an abnormal distribution of the heat through the metal mesh (Fig. 1). A minimum distance of 1 cm was kept during the procedures, and the laser fiber was placed parallel to the stent. This positioning ensured that the temperature was always maintained below 40°C a few millimeters from the stent.[17]

RESULTS

In the study period, 44 patients with locally advanced PDAC were treated in our hospital. Among them, 9 patients (5 women; median age, 74.7 years [range, 55-85]) fulfilled the inclusion criteria and were enrolled in our study. All eligible patients gave informed consent and participated in the study.

Seven patients had previous chemotherapy. Five patients had previous sessions of radiotherapy (50.4-59.4 Gy); among them 2 patients received only radiotherapy.

All patients had histologically proven pancreatic adenocarcinomas, located in the head of the gland in 6 patients, in the body in 2 patients, and in the tail in 1 patient (Table 1). The median size of the lesions was 35.4 mm (range, 21-45). EUS-guided LA was completed as scheduled in all 9 patients.

Needle placement in the target lesion was always obtained without difficulties. The position of the echoendoscope was mainly in the second part of the duodenum (6 patients), in the bulb in long position (2 patients), or in the stomach (1 patient).

The fiber was clearly visible in the target lesion during the application of the laser energy (Fig. 2A). During the procedure a hyperechoic area progressively surrounded the tip of the fiber; however, this did not hamper the endosonographic visualization of the needle within the

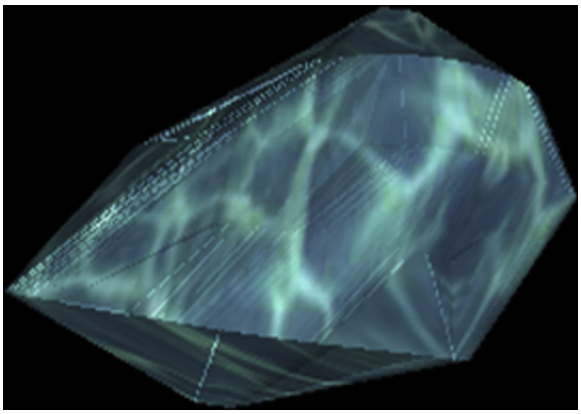

Figure 3. Three-dimensional reconstruction of the area by Syngo 3D software (Siemens Healthcare GmbH, Erlangen, Germany) showing the elliptic shape of the ablated area.

lesion. At the end of the ablations EUS revealed a hyperechoic area along the path of the probe surrounded by nonhomogenous tissue with hyperechoic spots (Fig. 2B).

Elliptical volumes of the ablated areas (Fig. 3) were analyzed by Syngo 3D software (Siemens Healthcare GmbH, Erlangen, Germany). At 24 hours and 7 and 30 days after the procedure, the CT control scans provided well-defined coagulative necrotic areas (Figs. 4 and 5). There were similar clear margins at 7 and 30 days after the procedure.

The involution of the ablation areas and the hypoenhancement in the ablation site were confirmed on follow-up by CT scan.[18] At 30 days from the treatment the ablated areas decreased in all cases: The mean ablation volumes obtained at 800 J collapsed in 85% (1.18 cm^3 at 24 hours vs .17 cm^3 at 30 days). The mean ablation volumes at 1000 J collapsed in 76% (3.16 cm^3 at 24 hours vs .80 cm^3 at 30 days). Finally, the mean ablation volumes at 1200 J collapsed at 44% after 30 days from treatment (1.77 cm^3 at 24 hours vs .98 cm^3 at 30 days) (Fig. 6).

No major adverse events were recorded. Three patients developed thin peripancreatic fluid collections that were demonstrated by the 7-day follow-up CT scan; the fluid collections spontaneously disappeared at 30 days. None of the patients experienced clinical symptoms after the procedure. Two patients showed a postablation increase of 3 times the serum amylase level. In these patients hospital stay was not prolonged.

One patient (4 W/800 J) died from myocardial infarction before the CT-scan follow-up at 30 days. Median post-LA survival of the patients was 7.4 months (range, 29-662 days). All patients died after disease progression.

DISCUSSION

This is the first in vivo study of EUS-guided LA in patients with locally advanced PDAC after ineffective chemoradiotherapy. We used thin fibers that were applied through a 22-gauge needle. This standard needle allowed us to accurately position the probe inside the pancreatic tumors in all 9 patients while overcoming the stiffness of the GI wall, the desmoplastic reaction of the tumor, and infiltration and fibrosis because of previous radiation treatment. As previously described for liver application, the flexibility of the needle and fiber could potentially allow the performance of additional consecutive applications to the tumor, in accordance with the tumor volume.[4]

The accuracy of EUS guidance with color Doppler analysis prevented injury to the vessels and surrounding structures. Unlike with radiofrequency ablation we did not have adverse effects.[19-21]

In patients who had a self-expandable metal stent, the minimum distance of 1 cm was kept between the stent and the fiber. In most cases the fiber and stent were kept parallel to each other. This positioning implies a safe and marked temperature drop a few millimeters away from the laser tip. Recently, the authors evaluated temperature distribution in low power (4 W) LA in an in vivo animal model. At a lateral distance of 5 mm from the tip, the temperature is 44°C, whereas at 8 mm it is 40°C. These data proved that placing the source of heat at least 1 cm away from the metallic stent is not dangerous.[17]

Based on previous data from in vivo and ex vivo animal models and theoretical simulations,[22,23] the lowest effective power settings were applied to avoid potential damage to the adjacent normal parenchyma. According to the results of this human application, the power setting 4 W/1000 J achieved the largest ablation volume without clinical adverse events. As expected, it was not possible to monitor the precise extension of the LA in real time by EUS. The contrast-enhanced EUS at the end of the procedure did not allow us to define the final volume of the ablation. On the contrary, the postprocedural imaging obtained by CT scan allowed us to clearly measure the ablation zone and to exclude early adverse events.[18]

In this preliminary experience our aim was not to ablate the entire tumor but to observe an evident cytoreductive effect on the primary tumor. Nevertheless, we could speculate that to obtain a complete tumor ablation, it may be possible for the small size of the needle and fiber to perform multiple applications to the target lesion and to customize the ablated area to the shape of the tumor.

The cytoreductive effect on the tumor has been described to trigger and modulate systemic immune response against the tumor.[24] Therefore, some authors have proposed the combination of ablative treatment and systemic chemotherapy to enhance the efficacy.[25] Further studies of LA in advanced pancreatic cancer are needed to confirm this role.

The limitations of this study include the dearth of information about human effects of LA on the neoplastic pancreatic tissue,[20] the small sample size, and

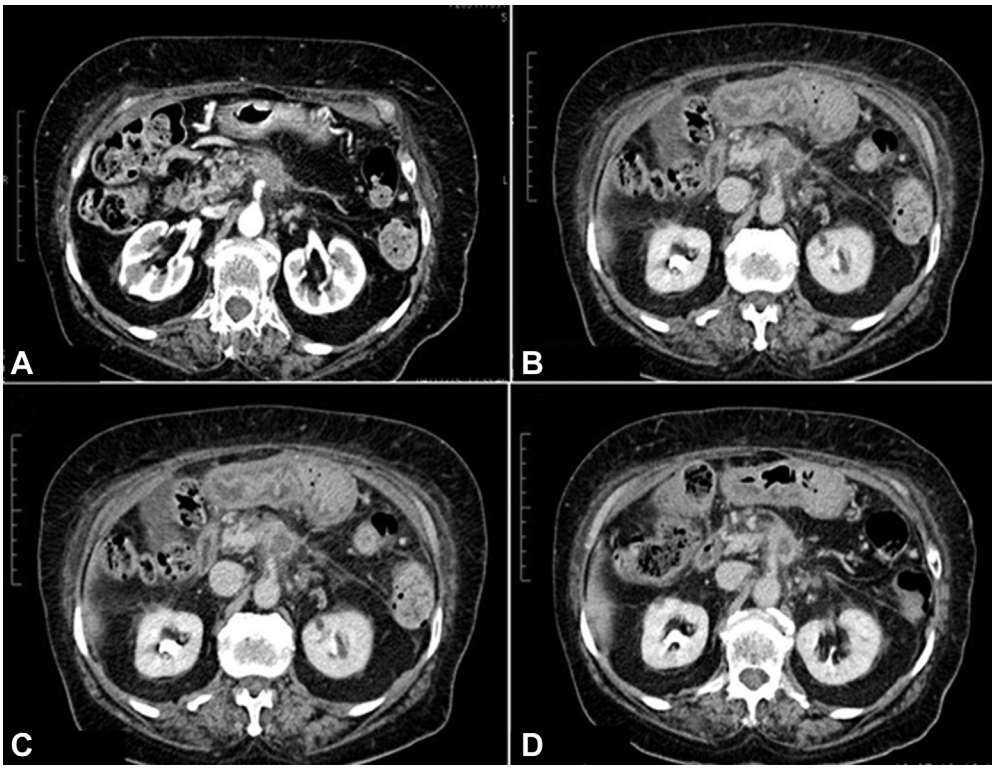

Figure 4. A, CT scan: pretreatment arterial phase showing a focal lesion of the pancreatic body, adjacent to the mesenteric artery with infiltration signs. Delayed phase showing the coagulation area in the body of the pancreas, well demarcated by a rim of postcontrast enhancement at 24 hours (**B**), 7 days (**C**), and 30 days (**D**). Power setting, 4 W, 1000 J, 250".

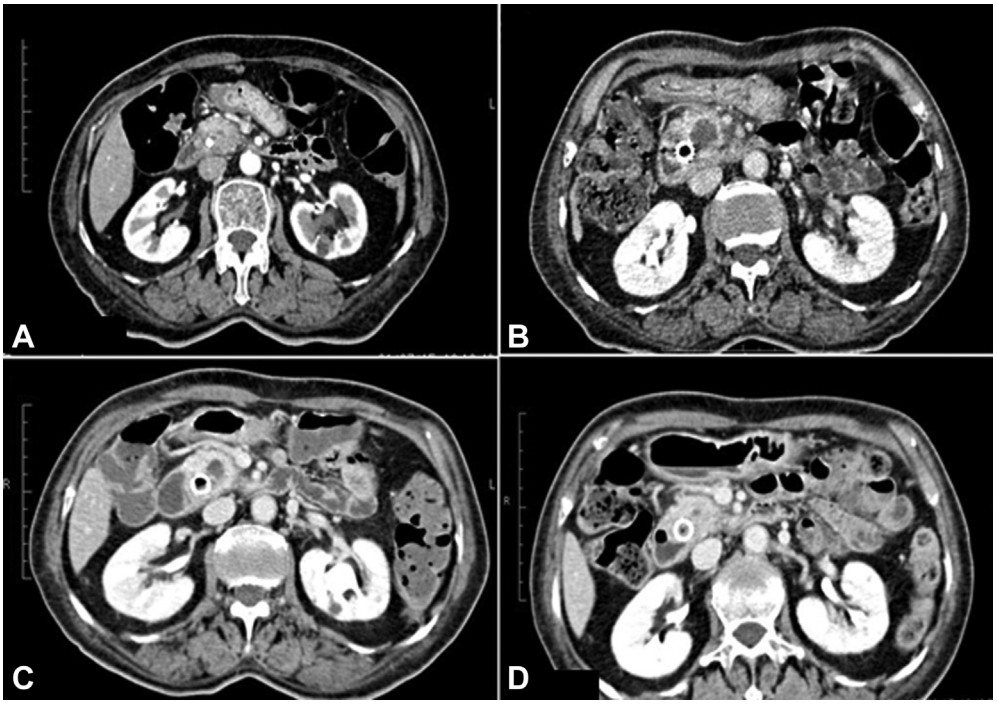

Figure 5. A, CT scan: pretreatment arterial phase showing a pancreatic head focal lesion. Delayed phase showing the coagulation area adjacent the biliary metal stent, with a well-demarcated rim of postcontrast enhancement at 24 hours (**B**), 7 days (**C**), and 30 days (**D**). Power setting, 3 W, 800 J, 270".

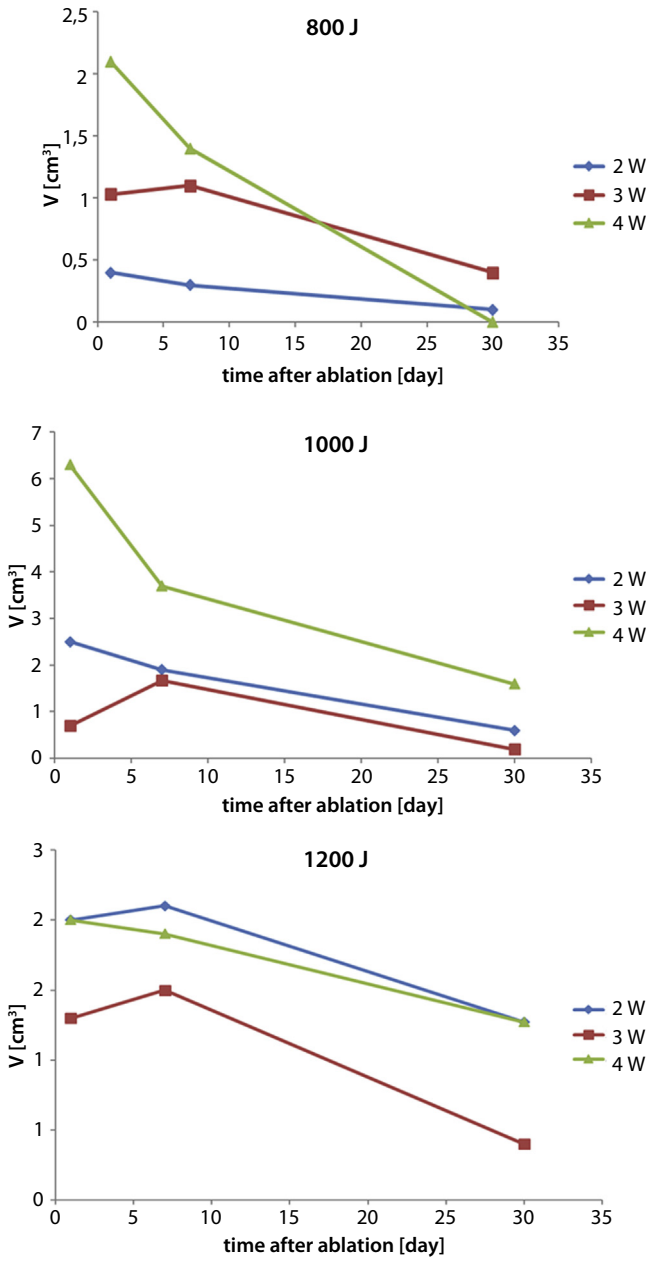

Figure 6. The changes of ablation volume on CT scan expressed in cm^3 in relation to observation time at 24 hours, 7 days, and 30 days after EUS-guided laser ablation.

the short-term follow-up for end-stage pancreatic disease of the recruited population. Moreover, the aim of our study was not to ablate the whole tumor, and therefore only a single treatment for each patient was performed.

In conclusion, in this preliminary experience EUS-guided LA was a feasible and well-tolerated procedure. The use of thin fibers enabled their insertion into standard 22-gauge EUS needles to obtain a selective ablation of pancreatic adenocarcinoma. If future studies will demonstrate superiority of current standards of care, then this minimally invasive technique could become an interesting alternative in the management of patients with locally advanced pancreatic tumor.

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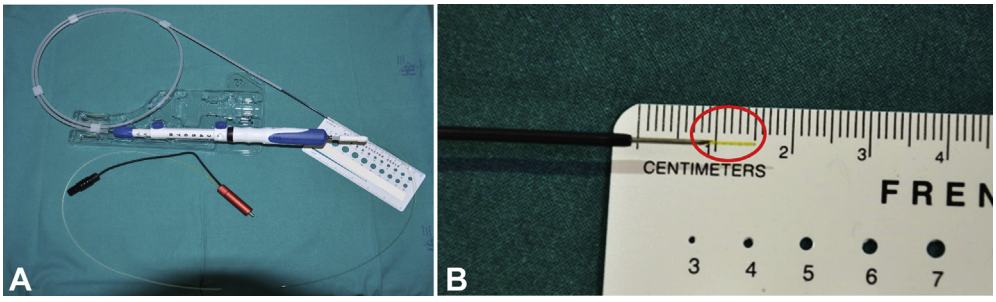

Supplementary Figure 1. A, A 22-gauge Needle Flex from Boston Scientific preloaded before the procedure. **B,** The fiber out from the tip of the needle (5 mm).