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Intraoperative Ultrasound guided Palliative Radiofrequency Ablation of Unresectable Nonmetastatic Pancreatic Malignancies: A Pilot Observational Study

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ABSTRACT

Background & Aims: Radiofrequency ablation of unresectable pancreatic tumors represents a palliative method in selected patients. The lack of standardization of the technique used as well as the non-homogeneous immediate and long-term results from the reports in the literature made us evaluate in a pilot study the application of a standardized technique through a surgical approach, with the evaluation of the immediate and long-term results.

Methods: Ten consecutive patients diagnosed with unresectable nonmetastatic pancreatic adenocarcinoma were referred for radio-frequency ablation by surgical approach. For that, a UniBlate (AngioDinamics®) internal cooled electrode was used, under intraoperative ultrasound guidance. We analysed the morbidity, mortality and survival associated with this procedure. The median follow-up period was 12 months.

Results: Intraoperative ultrasound was essential for guiding the procedure. No mortality and no major postoperative complications after intraoperative tumoral ablations were noted. The median survival after the procedure was 7.5 months.

Conclusions: Radiofrequency intraoperative ablation of unresectable pancreatic tumors is a feasible procedure, with low morbidity and mortality if standardized, being noninferior to palliative chemotherapy alone in regards with survival. A larger study is necessary to demonstrate the potential benefits in survival, the role of multidisciplinary selection being also mandatory.

Key words: locally advanced pancreatic cancer – radiofrequency tumoral ablation – intraoperative ultrasound

Abbreviations: CEUS: contrast-enhanced ultrasound; CT: computed tomography; EUS: endoscopic ultrasound; FNA: fine needle aspiration; IO: intraoperative; IOTAB: intraoperative tumoral ablation; IOUS: intraoperative ultrasound; MRI: magnetic resonance imaging; PDAC: pancreatic ductal adenocarcinoma; OS: overall survival.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) stands as one of the most prevalent and frequently diagnosed malignancies affecting this organ, characterized by limited treatment options and grim life expectancy. Despite advancements in imagistic diagnostics and surgery, nearly 40% of patients are diagnosed with locally advanced disease, rendering them unsuitable for surgical intervention [1-3]. Thermal ablation techniques have emerged as a novel adjuncts in the comprehensive management of PDAC, serving as a cytoreductive measure often complemented by radiotherapy (external beem) or chemo-radiotherapy. This information is sustained by a systematic exploration of the PubMed database made by our team [4]. The literature review revealed that pancreatic ablative techniques are applicable in both open and laparoscopic surgeries, as well as via endoscopic ultrasound or percutaneous approaches [5]. While reports on the cytoreductive and immunomodulatory effects toghether with optimistic overall survival (OS) were identified [6, 7], the necessity for randomized studies to validate these findings was underlined [6, 8-10]. At the same time, the lack of standardized technical protocols and the relatively high rate of perioperative complications means that these techniques are not routinely used in specialized centers [7, 11, 12].

Taking into account the information from the specialized literature and the high rate of cases diagnosed with unresectable

pancreatic tumors in our service, we considered it important to try to implement a standardized program for the selection and thermal ablative treatment of patients at this stage. We assessed in a pilot observational study the application of a standardized intraoperative ultrasound guided palliative radiofrequency ablation of unresectable nonmetastatic pancreatic malignancies, with the evaluation of the immediate and long-term results.

METHODS

We prospectively enrolled the patients diagnosed with pancreatic locally advanced, unresectable, non-metastatic adenocarcinoma that were referred for intraoperative tumoral ablation (IOTAB), between November 2017 and September 2020, at the Regional Institute for Gastroenterology and Hepatology, Cluj-Napoca, Romania. Data of all patients were prospectively collected and retrospectively analysed. The procedures were performed with the patient hospitalized and all patients gave written informed consent before the procedure (we had a specific consent for the procedure, beside the usual consent of the institution).

Indication for IOTAB were adenocarcinoma of the pancreatic head or pancreatic body, confirmed by biopsy done by preoperative endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) with histopathological examination or Tru-cut intraoperative biopsy with extemporaneous histopathological examination), with contraindication for resection (mesenteric artery invasion, portal or superior mesenteric vein invasion, without possibility for vascular reconstruction). Imaging staging for these patients included thoraco-abdominal and pelvic computed tomography (CT), EUS and in some cases nuclear magnetic resonance (MRI), where the CT examination was inconclusive. Preoperatively, the tumour marker CA 19-9 was collected. The contraindications of the procedure were: the presence of metastasis (hepatic, peritoneal, lymph nodes), the presence of metallic stent in common bile duct, ascites, severe coagulation disorders and no informed consent given. Previous surgery of the abdomen represented a relative contraindication.

Intraoperative Ablation Technique of Pancreatic Tumors

The intraoperative ablation was performed under general anesthesia, with the patient supine on the operating table, the approach being performed through laparotomy. First, a thorough exploration of the peritoneal cavity took place to exclude the presence of nodal, peritoneal and visceral (liver) metastases, which would contraindicate the continuation of the procedure. In addition to surgical exploration, intraoperative ultrasound (IOUS) of the liver was routinely used to scan the liver to rule out the presence of occult metastases (not detected on preoperative CT or MRI examinations). The exposure of the pancreas followed by sectioning the gastro-colic ligament and entering the omental bursa. The dissection of the lower border of the pancreas, with the exposure of the superior mesenteric vein and the portal vein, was necessary in patients with tumors located in the immediate proximity of these vessels, to increase the safety of the ablation needle insertion procedure. The dissection of the duodeno-cephalo-pancreatic complex from the posterior planes was routinely performed only in cases with cephalopancreatic tumors, for the same reason of safety. In situations where the histopathological result of malignancy was not established preoperatively, the next step consisted of Tru-cut ultrasound-guided biopsy, with extemporaneous histopathological examination. Once the indication of the tumor ablation procedure was confirmed, the anesthesia team inserted a nasogastric tube, whose distal end was later guided manually by the surgical team to the level of the second portion of the duodenum. On this tube, once actual ablation time started, continuous washing with cold physiological serum (2-8°C) was performed, in order to prevent thermal lesions of the duodenal wall.

For the ablative technique, the UniBlate RFA electrode with the 1500X generator (AngioDinamics®) was used (Fig. 1).

Fig. 1. The UniBlate RFA electrode (AngioDinamics®).

The electrode was internally cooled with saline solution. Intraoperative ultrasound established in all cases the intimate relationships of the tumor with the vascular structures in the vicinity (superior mesenteric artery and vein, portal vein, splenic artery and vein, superior mesenteric artery, gastroduodenal artery, hepatic artery) and with the Wirsung duct (Fig. 2).

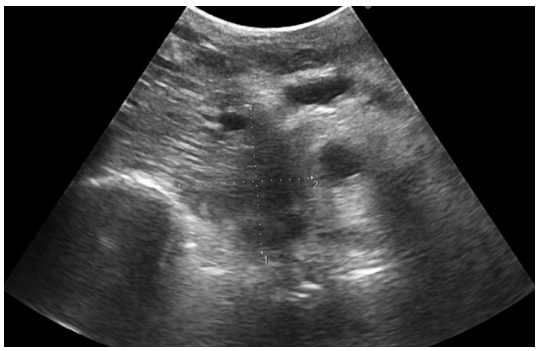

Fig. 2. IOUS aspect with the tumoral relations with surrounding structures. (star = superior mesenteric artery; dot = splenoportal confluent; TU=pancreatic head tumor).

The entire pancreatic parenchyma was scanned by ultrasound to exclude the presence of other simultaneous lesions, not detected by preoperative imaging. The insertion of the ablation needle was done under ultrasound guidance (Figs. 3A-B). The setting of the ablation time was made according to the size of the tumor (5-15 minutes), the intention being to produce a subtotal ablation, in the center of the tumor, without including its periphery, to protect the vascular and digestive structures nearby. The preset of radiofrequency power was 100 W for a temperature of 80°C.

In cases where the local extension of the tumor implied a clinically significant digestive or biliary invasion, digestive and bilio-digestive diversions were performed. Cholecystectomy was performed routinely in patients who did not have this done in their medical history. Drainage of the peritoneal cavity was

performed routinely at the end of the intervention: subhepatic space, omental bursa and Douglas pouch.

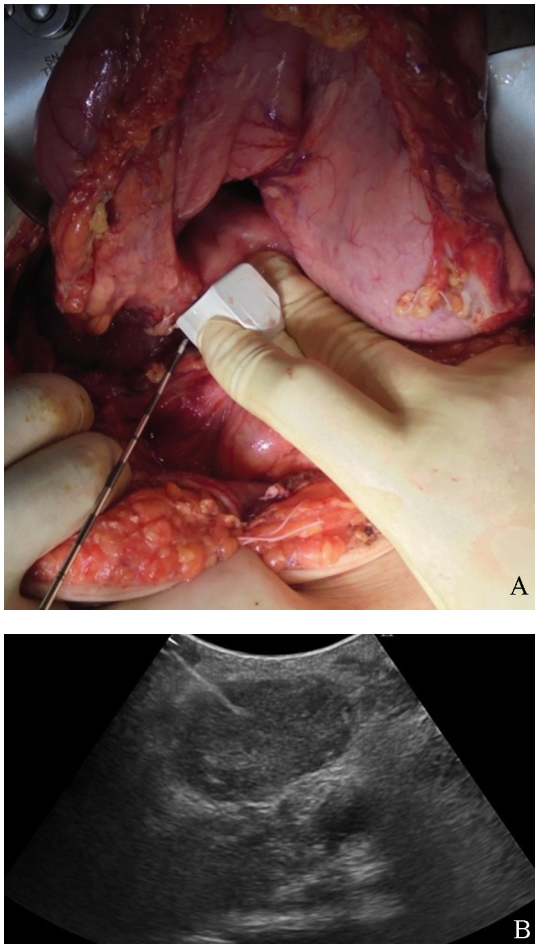

Fig. 3A-B. IOUS guided insertion of the RFA electrode: intraoperative aspect (A); IOUS aspect (B).

Post-operative Follow-up

Postoperatively, the patients were monitored for 24 hours in the intensive care unit, after which they were transferred in the surgical unit. Laboratory tests (complete blood count, serum lipase, serum amylases, CA 19-9 tumoral marker) were performed at 24 h after the procedure, and repeated when indicated. An ultrasound examination of the abdomen was performed at day 1 after surgery, to assess the abdominal cavity for free liquid or hematomas. Contrast-enhanced CT was performed at day 1 after surgery to check the local treatment outcome and to exclude any adverse events (portal thrombosis, hematoma). Starting from 1 month after surgery, imagistic examination was repeated in our service or by the oncologist, for the same reasons. Technical success was defined by achieving tumoral subtotal ablation (the presence of a markedly hypodense area inside the tumour). The median follow-up period was 12 months. The monitoring visits at 3 months interval consisted of clinical, biological, and imaging assessment.

RESULTS

We included 10 consecutive patients (8 women and 2 men, with a median age of 62.5 years), diagnosed with locally advanced, non-metastatic pancreatic adenocarcinoma. The presence of visceral or peritoneal metastases represented an absolute exclusion criterion, due to the influence on the survival by the systemic disease. Among the included patients, in 5 patients the tumor was in the head of the pancreas and in 5 patients at the level of the isthmus and pancreatic body. All patients presented clinically characteristic neoplastic pain syndrome due to invasion of the solar plexus. The unresectable criteria were established preoperatively in all patients, by CT imaging and endoscopic ultrasound: arterial invasion in 7 patients and venous invasion without the possibility of reconstruction in 3 patients. In 3 patients, the histopathological diagnosis of malignancy was confirmed intraoperatively by extemporaneous examination.

Five patients had obstructive jaundice preoperatively. Among them, 4 benefited from endoscopic biliary stenting, being indicated the installation of a plastic and not metallic stent, which could create thermal injuries during the ablation. Two patients had a biliary-digestive diversion (choledoco-duodeno-stomy) performed preoperatively. Intraoperative (IO) contrast enhanced ultrasonography (CEUS) done for diagnostic purposes was performed in 2 patients, in whom the intraoperative ultrasound (B mode) and palpation raised the suspicion of multicentric neoplasia, refuted by the procedure. Intraoperative CEUS to check the area of post-ablation necrosis was performed in all patients (Fig. 4).

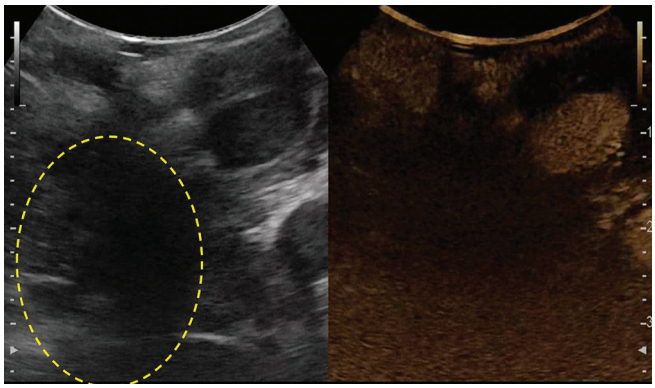

Fig. 4. IO-CEUS, after the ablative procedure. (PV: portal vein; TU: tumor; SMA: superior mesenteric artery).

Tactical cholecystectomy was indicated in 4 patients. Biliary-digestive derivations were performed in 3 cases.

Postoperatively, the patients received subcutaneous treatment with sandostatine for 3 days.

Postoperative complications included: lower digestive hemorrhage (n=1), portal vein thrombosis (n=1), obstructive jaundice (n=1), hemoperitoneum (n=1). For the case with hemoperitoneum, emergency re-intervention was necessary, the other complications being resolved non-surgically: conservative treatment, anticoagulant treatment in the therapeutic dose and respectively endoscopic biliary stenting. According to the Clavien-Dindo classification, we recorded 1 grade 3b complication and 3 grade 2 complications.

The CA 19-9 values collected preoperatively and postoperatively did not show significant differences (Fig. 5).

The control CT performed routinely on postoperative day 1 indicated in all cases the area of tumoral necrosis

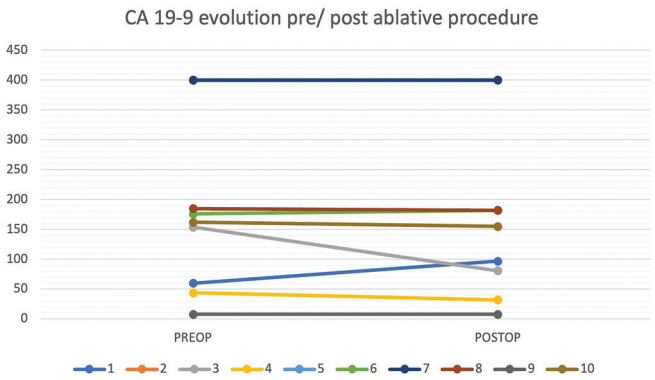

Fig. 5. The perioperative CA 19-9 values.

(subtotally), according to the therapeutic protocol. At the CT imaging control at 1-month post-procedural, 1 patient was diagnosed with an intra-abdominal abscess (clinically confirmed) which was treated by ultrasound-guided percutaneous drainage. At the 3-month follow-up, 1 patient was diagnosed with 3 hypodense liver lesions, suspected of liver metastases, interpreting the case as neoplastic disease in systemic evolution. At 6 months postoperatively, 1 patient presented imaging regression of the neoplastic disease (CT scan and RVS ultrasound), with description of complete necrosis (Fig. 6).

All analyzed patients had the pain syndrome described preoperatively controlled postoperatively only by non-opioid drug treatment.

The median survival was 7.5 months (min 4.5 - max 10 months; IQR=5.5), with a survival rate of 80% at 3 months, 60% at 6 months and 10% at 12 months (Fig. 7).

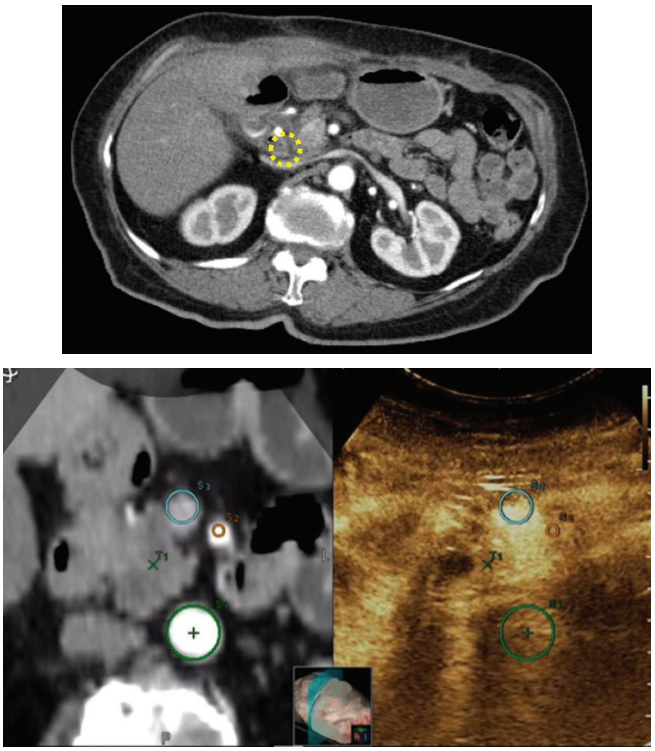

Fig. 6. Stabile total necrosis at CT (left) and RVS ultrasound (right) at 6 months after RFA ablation.

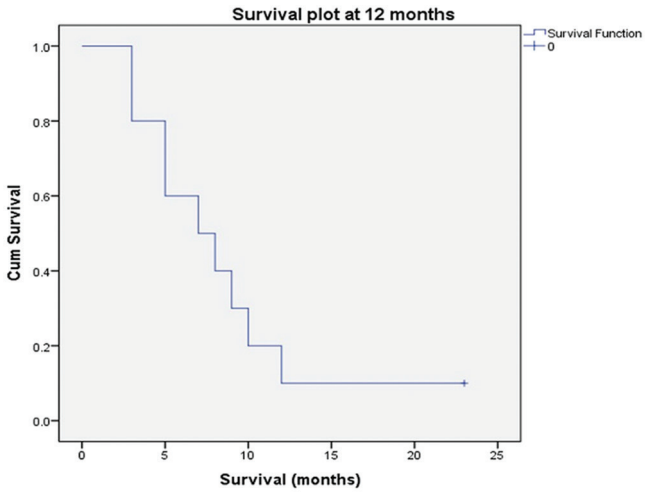

Fig. 7. Survival at 12 months after the ablative procedure.

DISCUSSION

Pancreatic adenocarcinoma, despite the progress made in medicine in general and in surgery in particular, remains a pathology accompanied by a poor prognosis [13]. Even more so when we discuss about unresectable pancreatic cancer, when the median survival does not exceed 2-11 months, regardless of the palliative oncological treatment followed [14]. The latter is the only treatment indicated as standard of care in international guidelines, both for unresectable locally advanced cases and for metastatic ones [15, 16]. All these in the context where there is evidence in the specialized literature that indicates the thermal ablation of pancreatic tumors as a feasible palliative option, with the potential to increase the survival of patients with unresectable but non-metastatic tumors [17-19]. The reasoning and utility underlying the indication of these ablative techniques for pancreatic tumors is the intention to perform a cytoreductive treatment that stabilizes an aggressive neoplasm and stimulates the immune system, acting like an anti-tumor vaccine [20-22].

The use of the UniBlate radiofrequency ablation device offered greater safety intraoperatively compared to the Starburst electrode, the ablation area being easier to control and thus avoiding damage to the neighboring vascular or digestive structures, with the final goal of obtaining an area of subtotal tumoral necrosis, with the preservation of a safety zone in the periphery [23]; The UniBlate RFA electrode provides linear, scalable ablations from 1 to 3 cm in length and 1 to 2.5 cm in diameter [24].

In all patients, we used IOUS to confirm the unresectable criteria, to perform an ultrasound-guided biopsy (where necessary) and to guide the insertion of the ablation needle. If for the ablation of liver metastases or hepatocarcinoma, in order to ensure that no post-ablation tumoral tissue remains, we routinely use IO-CEUS with SonoVue [25] in cases of unresectable and non-metastatic pancreatic tumors where we intend to obtain a cytoreduction, we consider that this ultrasound technique (adding contrast) does not demonstrate its practical utility. Thus, although we performed post-ablation IO-CEUS on all patients, this did not bring us useful information that would change our therapeutic strategy.

The use of pancreatic tumor ablative techniques in patients who require concurrent palliative surgery (biliary-digestive or digestive derivations) was considered in the literature to be feasible, with a potential positive impact on survival [19]. In 3 cases we performed such palliative interventions, simultaneously with the ablative technique, without negative impact on the complication rate.

The specialized literature indicates that CA 19-9 values after IOTAB decrease significantly in 50% of cases [26, 27]. We did not find this conclusion in our initial study, which may be due to the small number of cases.

Related to the idea of downstaging towards resectability, emphasized in some publications as occurring in 4% of the cases that benefited from IOTAB [7], among our patients one female patient presented an imagistic regression of the pancreatic tumor (at 6 months) but the patient did not show up for radical surgical treatment due to the contraindications given by the associated comorbidities.

Regarding the postoperative results in patients who have benefited from pancreatic tumor ablative techniques, reports in the literature indicate a mortality between 0 and 25%, a morbidity of up to 28% and a median survival between 3 and 33 months [7, 11, 19, 28-32]. The most common specific complications are acute pancreatitis, pancreatic fistula, and portal vein thrombosis [7, 11, 29].

The complication rate in our pilot study falls within the literature limits, with 4 postoperative complications out of 10 operated patients (Clavien-Dindo 2-3b). Our initial results indicate a median survival of 7.5 months, within the range reported by other authors, and we think a larger number of cases are needed to demonstrate the potential for increased survival compared to palliative systemic chemotherapy alone.

An important aspect is related to the analgesic effect that can be achieved through ablative strategy that the neoplastic pain syndrome through the invasion or compression of the solar plexus significantly affects the quality of life of patients with locally advanced, unresectable pancreatic cancer. Some authors indicate this analgesic effect in 50% of cases [32]. In our pilot study, we consider that the analgesic effect was present in all 10 patients, who did not require opioid analgesia in the postoperative period, until discharge. An extended study, on a larger number of patients and with follow-up over a longer period would be useful to draw firmer conclusions on this subject.

The literature does not indicate that the prophylactic administration of sandostatine could influence the morbidity in pancreas surgery [33, 34]. However, considering the high rate of pancreatic fistula described in the literature as being present after ablative techniques [35], we considered it useful to associate sandostatine in subcutaneous administration to all patients. In our initial study, no patient developed a pancreatic fistula, which is why we consider that we cannot yet conclude whether the routine use of sandostatine could be beneficial for pancreatic ablative techniques.

Another important aspect discussed in specialized literature is the optimal moment for performing the ablative technique: before or after chemotherapy? It seems that survival is not influenced by this sequence [36]. Considering the effect of immune stimulation that the ablative technique seems to have [37], it could precede chemotherapy, in order to potentiate its effect. But considering the general risk of metastatic, systemic disease, of pancreatic adenocarcinoma, chemotherapy performed before the ablative technique could help in a better selection of patients, for maximum results on survival. It is certain that at the present time there is no consensus in this direction, future studies being necessary to conclude. In the case of our study, following multidisciplinary discussions, all patients underwent systemic chemotherapy before the ablative technique, without being able to conclude that this influenced the immediate results or survival.

For our study, the patients benefited from the pancreatic tumor ablative technique through a surgical approach (laparotomy), which gave us possibility for surgical exploration, with the dissection of the peripancreatic structures and the exposure of important vascular structures (eg: portal vein), for a safer inserting of the ablation needle into the tumor. Currently, there are several possibilities to perform the ablation of unresectable pancreatic tumors, except the radiofrequency technique: irreversible electroporation, microwave ablation, electrochemotherapy [38-40]. There is still no consensus regarding the optimal technique. Similarly, for the way of approach: percutaneous approach, endoscopic EUS-guided approach, laparoscopic approach [41-44].

CONCLUSIONS

Our initial results indicate the feasibility of introducing tumoral ablative techniques into the palliative therapeutic algorithm of unresectable non-metastatic pancreatic cancer, which is emphasized by the lack of perioperative deaths or major complications and the advantages brought over pain therapy and the association with other palliative surgical procedures. Although IOUS is essential in guiding these techniques, routine performance of IO-CEUS is not necessary. Obtaining a non-inferior survival compared to palliative systemic chemotherapy only indicates the need to continue the study on a larger number of patients, with special attention to the development of a multidisciplinary patient selection algorithm and approach option.

Conflicts of interest: None to declare.

Authors' contribution: I.I. and A.B. drafted the manuscript; I.I., A.C., S.B., L.C., P.C. collected the data; A.B. performed the surgery/ablative tehnique; I.I., A.C., S.B., C.B., L.C., P.C. managed the patients; N.AH. critically revised the paper. All the authors approved the final version of the manuscript.

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