—Commentary—

EUS-guided solid pancreatic tumor ablation

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INTRODUCTION

In recent decades, endoscopic ultrasound (EUS) has evolved from a diagnostic approach to an interventional apparatus; it is a safe and effective alternative therapeutic option for patients with tumors, especially for those unfit for surgery. Several case series and pilot studies have shown the feasibility and safety of EUS-guided tumor treatments, primarily in pancreatic tumors. Two different approaches of EUS-guided ablation can be distinguished based on the mechanisms of action. Direct mode techniques have a locoregional effect on the lesion and include radiofrequency ablation (RFA), photodynamic therapy (PDT), neodymium-doped yttrium aluminum garnet (Nd: YAG) laser ablation, and ethanol injection. In indirect modes, the antitumoral effect is achieved by a second mechanism, such as fine-needle injection of chemotherapeutic agents and immunotherapy factors such as lymphocyte cultures and oncolytic viruses that stimulate the immune system against the lesion, or the placement of fiducial markers that guide stereotactic radiation.[1-4] These methods regionally enhance the systemic effect of chemotherapy; they are often proposed for locally advanced pancreatic cancer due to poor surgical results and for anatomically resectable neoplasms for which a preoperative strategy is desirable.[5]

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ENDOSCOPIC ULTRASOUND-GUIDED RADIOFREQUENCY ABLATION

RFA induces a hyperthermal injury. It uses high-frequency alternating current as electromagnetic energy, which generates heat and results in coagulative necrosis and cellular apoptosis through direct and indirect mechanisms.[1,6] This technique takes advantage of the heat sensitivity of tumor cells compared to normal tissue, probably due to a different microenvironment pH and metabolic stress.[6] On histology after RFA or other hyperthermic ablation techniques, three areas can be distinguished depending on proximity to the probe. The central area has coagulative necrosis due to direct contact with the probe. The transitional area has sublethal damage due to the thermal conduction of the central area; cell apoptosis or complete healing is possible. The healthy external area is unaffected by the ablation.[6,7] The direct cellular injury depends on different aspects of the target tissues, including the thermal energy applied, the rate of application, and the thermal sensitivity.[6]

Indirect delayed damage is also possible, even after termination of thermal ablation; it includes apoptosis, vascular damage, cytokine release, and

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immunostimulation, with increased peripheral blood stream levels of neutrophils, macrophages, dendritic cells, and lymphocytes.[6-8] Pro-inflammatory cytokines and other cellular contents released after thermal damage could trigger a cascade of immune-mediated events with supplementary antitumoral action.[6]

The optimal treatment temperature, at which the high-frequency alternating current can induce cell injury through the onset of frictional heating, is between 60°C and 100°C.[6] Surprisingly, cell damage is not directly related to temperature. Temperature >100°C is less effective as the increased tissue impedance due to induced water vaporization reduces the electrical conduction of the tissue.[6]

Two different systems are available: monopolar and bipolar. The monopolar probe is a closed-loop system that includes an energy generator, an electrode, a dispersive electrode (ground pad), and the patient. High-current density energy heats the target tissue through the electrode. The ground pad closes the electric circuit and disperses the energy over a large area to reduce possible injury to the skin.[1] In a bipolar RFA system, a ground pad is not necessary since the current flows between two interstitial electrodes; both are usually placed in the needle probe. The heat sink effect (blood vessel perfusion-mediated cooling) is reduced in this system, but despite an overall minor ablative capacity, heat injury of the lesion occurs more quickly and there is less damage to the surrounding normal tissue.[1,6,7]

The currently available probes for the EUS-guided RFA of pancreatic tumors include the 19-gauge EUS-fine-needle aspiration (FNA) needle electrode (Radionics, Inc., Burlington, MA, USA), the Habib™ EUS-RFA catheter (EMcision Ltd., London, UK), and the EUSRA RF electrode (STARmed, Koyang, South Korea). These probes are similar to EUS-FNA needle and can have different gauges (14–19 gauge) and effector echogenic terminal tips of varying lengths, which should be inserted into the lesion under EUS-guidance.

Once the tip is in place within the margin of the lesion, energy can be delivered. Some echogenic bubbles are seen around the needle as proof of ongoing treatment. The generator can be switched off automatically due to a change in tissue impedance, or manually, depending on the system used. The size of the ablation depends on the wattage and treatment duration as well as on the system used. The treatment can be repeated in multiple sessions, and in case of large lesions, the probe can also be placed in different areas.[1,9] Although RFA is already well established in other clinical settings, the treatment of pancreatic lesions is still under evaluation. Several animal studies and small human clinical series are assessing the feasibility and safety of different systems and settings to limit adverse events due to thermic damage, acute pancreatitis, stomach and duodenal transmural burns, perforations, and bleeding.

Goldberg *et al.* first reported EUS-guided RFA of a normal pancreas in 13 pigs in 1999.[10] They evaluated the potential benefit of a thermal injury in pancreatic lesions. A radiofrequency current of 285 ± 120 mA was delivered transgastrically for 6 min to obtain a temperature of 90°C. Pathological analysis was performed immediately (n = 5), 1–2 days after ablation (n = 2), and 2 weeks after the procedure (n = 6). The results showed discrete, well-demarcated, spherical foci of coagulation necrosis measuring 8–12 mm in diameter surrounded by a 1–2 mm hemorrhagic rim; there was radiologic-pathologic correlation within 2 mm between pigs examined immediately and 1–2 days after ablation. The authors also reported a retraction of the coagulated focus in 4 of 6 (67%) pigs examined on day 14 and a 1–3-mm fibrotic capsule surrounding the coagulated tissue in the other pigs. They also observed gastric (n = 3) and intestinal (n = 1) burns not associated with perforation, and one case of mild hyperlipasemia with focal pancreatitis and subsequent fluid collection.[10]

Since the publication of Goldberg *et al.*, several other animal studies assessing the feasibility and safety of different probes have been published.[11-13] These evaluations provided the initial information to be considered for the EUS-RFA settings used in patients with pancreatic lesions. Recently, Alvarez-Sánchez and Napoléon[14] reviewed the published data of EUS-RFA; they analyzed seven case series that included a total of 42 patients with different indications treated with different systems.

RFA has also been proposed as a treatment for lesions other than adenocarcinomas, such as cystic neoplasms and neuroendocrine tumors (NETs). In a pilot study, Pai *et al.* assessed the feasibility and safety of the Habib EUS-RFA probe in eight patients with cysts (n = 6) or NETs (n = 2); two cases showed a complete resolution

of the cysts, three cases showed a 48.4% reduction in size, and the remaining two (NET) cases showed a change in vascularity with a central necrotic area.[15] Lakhtakia *et al.*[9] reported the successful treatment of three symptomatic NETs, while Armellini *et al.*[16] reported the complete resolution of a G2 NET, and Waung *et al.*[17] reported the resolution of a symptomatic insulinoma that was nonresponsive to other treatments.

Overall, although limited, the published experience showed that EUS-guided RFA can be considered a feasible and safe tool for the treatment of different unresectable pancreatic neoplasms. It is a useful locoregional antitumoral technique and provides the option for real-time treatment control, which reduces the risk of complications.

CRYOTHERM ABLATION

Cryotherm ablation is a hybrid bipolar technique combining the thermal injury of RFA with the cooling effect of a cryogenic gas. The blending of the two different energies could overcome the limits of bipolar systems, which provide less collateral heat damage than monopolar systems despite a lower overall ablative capacity and may increase the effect of the two single modalities.[7,18] The currently available probe for EUS-guided cryotherm ablation was developed by Erbe Elektromedizin GmbH (Tübingen, Germany). This probe uses an EUS-FNA needle with a sharp distal tip containing two interstitial electrodes that form the current closed system. The electrically active section is 26 mm long with a gauge of 1.8 mm. This fixed length requires a lesion with a minimum diameter of 28 mm. A Teflon sheet covers the device, and it can easily pass through the operative channel of a therapeutic EUS scope once the tumor has been identified. The probe is connected to the energy generator and the CO_2 source. Different parameters including energy power, time of application, and gas pressure can be set separately. Treatment can be controlled manually unless tissue impedance changes, and the generator will stop automatically to avoid adverse events.

In the preliminary study, Carrara *et al.* evaluated the feasibility, safety, and efficacy of cryotherm ablation on normal pancreatic tissue using a porcine model.[19] The authors treated 14 pigs with an energy output of 16 W and a simultaneous cryogenic effect, with CO_2 at 650 psi applied for 120–900 s. The treatment was clearly visible in real time as a hyperechoic elliptic area around the probe tip. They reported a direct correlation between the microscopic findings and the application time and could demonstrate a positive correlation between lesion size measured by the EUS during the treatment; the duration of application reflected dose-dependent adverse events. No mortality was reported although morbidity included one major complication of necrotic pancreatitis and an overall minor complication rate of 43%.[19] Arcidiacono *et al.* first evaluated the feasibility and safety of cryotherm treatment in a pilot prospective study using patients with locally advanced pancreatic adenocarcinoma after standard chemoradiotherapy failure.[20] The treatment was feasible in 16/22 patients (72.8%) because fibrosis and desmoplastic reaction of the lesion and gastroduodenal wall blocked probe insertion. No severe complications were reported during or immediately after the procedure. Early mild complications included abdominal pain with hyperamylasemia (n = 3) and mild duodenal bleeding (n = 1), which was treated endoscopically. Late complications could be related to tumor progression. The study showed a direct correlation between application time and the treated area. Although a computed tomography (CT) scan follow-up was performed in all patients, the tumor margins after ablation were clearly defined in only six patients, and the tumor was smaller than the initial mass (P = 0.07).[20]

ENDOSCOPIC ULTRASOUND-GUIDED PHOTODYNAMIC TREATMENT

PDT is a well-established technique that uses a noncytotoxic agent excited by an appropriate wavelength of light as a photosensitizer to develop cytotoxic substances that induce selective cellular apoptosis.[21] Benefits of this ablative method include tissue necrosis, and several studies have also reported a synergic action with chemotherapy, reinstating sensitivity in drug-resistant cells. PDT experience in the gastrointestinal tract primarily concerns esophageal neoplasms and cholangiocarcinomas. Recently, PDT was also proposed for the treatment of pancreatic cancer. Preliminary animal evaluation was limited to the distal pancreas due to a stiff laser-light catheter.[22,23] With the advent of a second-generation photosensitizer, a chlorine-6 derivative (Photolon®), and a novel flexible catheter, Choi *et al.* have proposed new perspectives in their feasibility and safety study of four patients with locally advanced pancreatobiliary tumors.[24] The authors treated patients for 330 s with a power density of 300 nW/cm and an energy

dose of 100 J/cm; patients included two with cancer in the caudate lobe of the liver, one in the distal common bile duct, and one in the tail of the pancreas. The median volume of necrosis produced by PDT was 4.0 cm^3 (range, 0.7–11.3). The disease remained stable in all four patients during a median follow-up of 5 months (range, 3–7) with no treatment-related complications.

ENDOSCOPIC ULTRASOUND-GUIDED NEODYMIUM-DOPED YTTRIUM ALUMINUM GARNET LASER ABLATION

A Nd: YAG laser has been proposed as a novel minimally invasive tumor ablation technique for hepatocellular carcinoma, colorectal cancer, liver metastases, and malignant thyroid nodules. A high rate of necrosis associated with a well-defined ablation area and a short application time are the primary potential benefits of this method compared to other laser-induced treatments.

Recently, Di Matteo *et al.* applied this technique to pancreatic tissue. They evaluated the *in vivo* feasibility and safety of EUS-guided Nd: YAG laser ablation of normal pancreatic tissue in a porcine model.[25] The authors punctured the normal tissue of the body and tail of the pancreas of 8 pigs with a 19-gauge probe carrying a quartz optical fiber and delivered a total energy of 500 or 1000 J continuously. The same group continued their experience on *ex vivo* porcine pancreatic tissue. Pancreatic specimens from 60 pigs were treated with an Nd: YAG laser beam and the ablation volume (Va) and central carbonization volume (Vc) were measured. Authors observed that the optimal laser output power to obtain a similar Va with smaller Vc was the lowest; it reduced the risk of thermal injury to the surrounding tissue.[26] Di Matteo *et al.* reported a case of a 46-year-old woman with a recurrent pancreatic NET. Application of an Nd: YAG laser under EUS-guidance at 4.0 W for 300 s, they observed a well-defined coagulative necrotic area at the posttreatment CT scan, and no metabolic activity was seen on ^{68}GA-DOTA-NOC PET at a 1-year follow-up.

CONCLUSIONS

EUS could provide feasible, safe, and effective locoregional ablation modalities complimentary to systemic chemotherapy for pancreatic solid tumors. As the population treated in the published experience was small, prospective randomized controlled trials are needed to confirm the efficacy and settings for wider, multidisciplinary acceptance.

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