Review Article

Current Status of Focal Cryoablation for Small Renal Masses

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Focal cryoablation is an established minimally invasive technique for the treatment of small renal masses. Because of the lack of robust evidence, it is indicated in selected patients who have relative contraindications to extirpative approaches. With appropriate selection of patients, cryoablation is safe and effective. Main advantages are low risk for complication, minimal invasiveness, and good functional outcomes; oncological outcomes require further studies. The role of the percutaneous approach has been expanding because of its ability to reduce pain and hospitalization, the possibility of performing the procedure under sedation, and the fact that it is potentially more cost effective. UROLOGY ■■: ■■–■■, 2016. © 2015 Elsevier Inc.

The extensive use of ultrasound and computed tomography (CT) in recent years has increased the incidental diagnosis of small renal masses (SRMs) by 60%.[1] However, many such lesions are benign and are diagnosed in people over the age of 70 years or with severe comorbidity. Moreover, most of them behave in an asymptomatic manner, with a growth rate of 3-4 mm/year.[2] Active surveillance is an option in these cases even though this may entail a degree of anxiety for patients and also increased costs.

Partial nephrectomy (PN) has become the standard therapy for T1a renal cell carcinoma (RCC).[3] In this context, focal (CA) is an increasingly popular treatment option for SRMs in cases that are technically difficult from the surgical point of view and in patients who present relative contraindications to PN. The early reports on the effect of CA in SRMs demonstrated necrosis in renal tissue following application of a cryoscalpel at a temperature of −186°C.[4] Uchida et al were the first to describe CA in SRMs using liquid nitrogen.[5] Current CA systems are based on the Joule-Thomson principle which describes the change in temperature that accompanies expansion of a gas without exchange of heat with the environment. CA has increasingly been applied as a treatment option in SRMs, to the extent that in some reports it has been the most common thermoablative procedure.[6]

The last version of the European Association of Urology guidelines on RCC specifically concluded, however, that due to the low quality of available data, no recommendation can be made on CA.[3] On the other hand, the American Urological Association considers ablation techniques, including CA, as a third-line treatment option in patients with cT1a tumors associated with major comorbidities and increased surgical risk.[7]

This review summarizes the available evidence for use of focal CA for SRMs and assesses selection criteria, techniques and equipment, complications, and functional and oncologic outcomes based on the latest literature reports.

EVIDENCE ACQUISITION

A comprehensive review of the Medline literature was performed in April 2015. A search was undertaken by applying the following search terms: focal cryoablation, kidney cryotherapy, kidney cryosurgery, renal cryosurgery, kidney cryoablation, renal cryoablation, renal cryotherapy, kidney cancer, and renal tumors. Further references were identified from the reference lists of retrieved articles. Case reports and congress abstracts were not included. Articles selected were reviewed and approved by all authors. Eligibility criteria included specification of CA technique (percutaneous or laparoscopic), reporting of patients' selection criteria, reporting of complications, and presentation of oncologic results.

CRYOBIOLOGY

The necrotic effect of CA was first described by Cooper in 1964.[8] A lethal dose was defined as −20°C for 1 minute.

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More recently, −40°C has emerged as the target temperature based on several in vitro studies.[9] Also, in vivo-like tissue-engineered models for prostate and renal cancers indicate that exposure of cancer cells to −30° to −40°C for ≥1 minute using a double freeze-thaw protocol leads to complete cell destruction.[10] A double freeze-thaw cycle to −40°C is required because, while the majority of cancer cells die at this temperature, some have been shown to survive. The double freeze-thaw cycle amplifies the injurious events and leads to proper destruction of malignant tumors. Moreover, a significant increase in cell death was shown when the freeze cycle duration was increased from 5 to 10 minutes.[11] The cancer cell survival is further reduced by a slow thawing rate, which is performed passively. The mechanisms of cell death due to CA are initiated by extracellular ice crystal formation, which leads to hyperosmosis and water removal from the cells and subsequently denaturation. The ice crystal formation causes mechanical damage due to shearing forces affecting the cell membrane integrity; intracellular ice crystal formation leads to permanent injury of the cells. During thawing, a loss of blood supply is caused by vascular stasis in the previously frozen tissue.

Coagulative necrosis occurs due to the damaged endothelium cell lining of the microvasculature, and increased cellular permeability leads to edema and inflammation. Infiltration of inflammatory cells occurs in response to the release of cytokines from damaged cells. Thereafter, the necrotic tissue is removed by the phagocytic activity of these inflammatory cells. Finally, both intrinsic and extrinsic apoptosis have been recognized to increase cell death in cryogenic lesions.[10]

TECHNIQUES AND EQUIPMENT

CA of renal tumors can be performed by open, laparoscopic (LCA), or percutaneous (PCA) approach. The latter is recommended for tumors located more posteriorly, thereby avoiding proximity of the ice ball to neighboring organs.[12] Open CA, LCA, and PCA can all be guided by intraoperative ultrasound, CT scan, or magnetic resonance imaging (MRI). Before starting CA, an intraoperative biopsy of the lesion should be obtained for histologic examination. Depending on the company and the type of cryoprobes used, it would be necessary to warm the skin entry points to avoid collateral damage to the skin.[13] The number and type of cryoprobes are chosen to achieve an optimal coverage of the tumor. To ensure technical success, defined as complete tumor ablation with a margin of healthy renal parenchyma, probes must be ideally placed as more perpendicular as possible with no more than 1 cm distance between them to obtain an adequate overlap and a uniform low temperature.[14]

It is important not to remove the cryoprobes too early after the thaw process to avoid postoperative hemorrhage from the probe paths.[15] In the case of LCA, argon beam coagulation and hemostatic sealants may be used; also, single port access has been successfully adopted for LCA. In the case of PCA, conventional CT or real-time CT fluoroscopy may be used to intraoperatively monitor the ice ball formation. MRI, however, affords special probes adapted to the magnetic field.[15] To safely displace adjacent organs, hydrodissection or cargo dissection (CO_2 insufflation) is frequently applied.[13]

Probes

The probes used for CA typically range from 1.47 to 8 mm in diameter. With use of a 5-mm argon probe, the temperature 1 cm inside the ice ball is approximately −40°C.[12] Probes can be selected in several shapes. The standard 17-gauge cryoprobe creates an ice ball of 18-27 mm in diameter; other options include the elliptical probe and the bulb-shaped probe, which create ice balls of 32-56 mm and 32-60 mm in diameter, respectively.[15]

Coolant

Temperatures at the tip of the cryoprobe can be as low as −190°C.[16] These temperatures are achieved by insufflation of argon gas into the probes. The thawing process may be accelerated by the use of helium gas.[15,16]

Access Sheath

Some authors recommend the use of an access sheath to approach the tumor.[16] Once the access sheath has been placed, it can be used for multiple entries (biopsy, cryoprobes) without the need for additional punctures and reducing the risk of incorrectly targeting the lesion.

PATIENT SELECTION

When selecting the therapeutic option in patients with SRMs, there is a need to balance the treatment benefit, the life expectancy, and the willingness of the patient to undergo a particular treatment. Currently, there is no overall consensus on the best patient and tumor selection criteria; nonetheless, some main indications can be outlined. Peripheral, enhancing, and well-circumscribed SRMs with a size ≤3 cm represent ideal lesions for this treatment modality, especially in patients who would benefit from nephron-sparing surgery but who are not ideal surgical candidates; larger tumors between 3 and 4 cm may also be treated with CA by combining multiple cryoprobes.[17] Due to higher reported rates of recurrence and treatment failure for CA, nephron-sparing surgery still represents the gold standard for younger and minimally comorbid patients with a life expectancy exceeding 15 years. CA is instead currently predominantly offered as a reliable treatment option to older or frail patients and those with comorbidities such as diabetes, hypertension, or congestive cardiac failure.[18]

CA may also represent the preferred treatment option in certain specific subsets of patients, including those with a history of von Hippel-Lindau disease, tuberous sclerosis, or other inheritable familial renal tumors: these patients are at higher risk of induction of renal insufficiency by surgery, owing to the recurrent nature of their diseases, and CA can be offered as a first-line treatment option