New technologies for ablation of small renal tumors: current status

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The diagnostic rate of small, "incidental" tumors which are amenable to local excision or ablation has increased significantly due to widespread use of non-invasive body imaging tests. The role of nephron-sparing tumor-ablative surgery has expanded beyond the traditional circumstances of neoplasms in solitary/functionally solitary kidneys or tumors present bilaterally. Due to technologic advances, possible therapeutic options now include open surgery, laparoscopic, percutaneous and extraciorporeal approaches, in addition to surveillance in some cases. This review will concentrate on the new energy sources available for tumor ablation rather than the different surgical approaches, with a detailed review of renal cryoablation, radiofrequency and high intensity focused ultrasound. The emphasis is on the experimental data and the limited clinical data available to date, and challenges and current limitations of the various modalities.

Key Words: minimally invasive, renal tumor, cryoablation, radiofrequency, high intensity focused ultrasound

Introduction

Nephron-sparing surgery for renal tumors traditionally has been applied to solitary or functionally solitary kidneys containing neoplasms. Novick et al[1] have popularized the selective use of partial nephrectomy even in the presence of a normal contralateral renal unit. With the widespread use of non-invasive body imaging [ultrasonography (US), computerized tomography (CT) and magnetic resonance imaging (MRI)] the diagnostic rate of "incidental renal masses" has increased substantially. These tumors are often smaller (less than 3 cm diameter), unifocal, peripherally located and remote from the renal hilum and the collecting system. Thus, they are often amenable to local excision or extirpation, sparing the majority of an otherwise normal kidney. The local recurrence rate is acceptably low for these "favorable" tumors.[1-4] Furthermore some data suggests that tumors less than 3 cm in diameter are usually slow growing with low risk of progression[5,6] and thus watchful waiting may also be a viable option in selected cases. Recent refinement in renal laparoscopic surgery along with advances in ablative techniques that entail varying degrees of "invasiveness" have broadened the options for management of small renal tumors. Possible therapeutic approaches now include open surgery, laparoscopic, percutaneous, and extracorporeal approaches. This review will concentrate on the new ablative energy sources and not on the different extirpative approaches. Cryosurgery, or cryoablation

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(Cab), and radiofrequency (RF) are the prevailing modalities at present and will be discussed in depth. Other energy sources under development will be briefly reviewed. The emphasis will be on experimental and clinical data available to date and challenges and limitations of the various modalities.

Cryoablation

Mechanisms of action

Liquid nitrogen circulated through vacuum insulated probe(s) and more recently, pressurized argon gas forced through a small aperture at the tip of the probe (thereby creating an endothermic reaction) are the two cryogenic energy sources commonly used. Rapid freezing, achieving temperatures of -196°C with liquid nitrogen and -140°C with argon, causes intracellular and extracellular ice crystal formation. Crystals in the interstitial space (including the microvascular bed) result in hyperosmolar extracellular "brine". Water is then drawn from within cells into the extracellular space, leaving a higher intracellular osmotic concentration, which is deleterious to the cells. Rewarming (usually by circulating helium at room temperature through the same cryoprobe aperture with the argon system) results in restoration of the circulation. Irreversible endothelial cell damage leads to interstitial edema and thrombosis of the microcirculation. Coagulative and ischemic necrosis ensues. For prostates, the use of two freeze-thaw cycles has been shown to have superior cytocidal action compared to a single cycle.[7,8] Data on renal tumors are lacking in terms of the optimal number of freeze-thaw cycles.

Experimental data

Uchida et al reported that renal cell carcinoma cell lines needed temperatures below –20°C to achieve adequate cell kill[9] with a canine model. This was confirmed in a porcine model. Based on thermosensor measurements, Campbell et al[10] found the iceball had to extend several millimetres beyond the apparent sonographic tumor boundaries to ensure adequate cell kill. Histologically, a similar discrepancy had been reported in the prostate cryosurgery literature.[11] Within hours after cryosurgery, the renal tissue shows a clear demarcation between the haemorrhagic and congested tissue and untreated tissue. These changes are followed by central coagulative necrosis and subsequently, repair and fibrosis at 3 months.[12] These histologic findings mirror those from serial prostate biopsies after Cab.[13] A porcine model has been used by Nakada et al, corroborating many of these findings.[14] Nakada's group also used a VX-2 rabbit renal tumor model to confirm the efficacy of cryoablation compared to nephrectomy.[15,16]

Clinical data

Cryoablation has been employed with open surgical exposure, laparoscopically and percutaneously. Gill et al have reported on 32 patients with exophytic tumors under 4 cm treated laparoscopically.[17] A follow-up MRI at 12 months was available on 20 patients. Percutaneous CT-guided needle biopsy at 3 to 6 months did not reveal recurrent tumor in any of 23 patients. One patient did present with a tumor recurrence at 1-year follow-up and underwent nephrectomy. No deleterious effects on renal function, blood pressure, or urinary components for lithogenic tendencies were found.[18,19] Rukstalis et al[20] performed open renal Cab on 29 patients. There was one positive biopsy at 3 months, manifested by enhancement of the mass on contrast CT study. Rodriguez et al reported on seven patients using both open and laparoscopic Cab and reported no local recurrences.[21] Shingleton et al[22,23] performed Cab percutaneously with needle probes using MRI for probe-placement guidance and for treatment monitoring. Their experience included five tumors in four patients with Von Hippel Lindau (VHL) Syndrome, with tumor diameter up to 5 cm. Follow-up in this small cohort of up to 23 months reported no evidence of tumor recurrence. A recent modification of the argon-based system consists of a ray of small cryoprobes. The system was designed to create numerous small "ice seeds" instead of one or two ice balls with the earlier design. The "ice seeds" design supposedly provides better conformation to the shape of the target organ or lesion. However, preliminary data in prostate cancer show sub-optimal results with a lower than desired negative biopsy rate.[24] Data on renal lesions are unavailable with this modified system.

Challenges

The cytocidal action of Cab has been well studied. Although there have been some elegant animal studies on Cab in renal tumors which reported on safety and efficacy, the data cannot be extrapolated with impunity to the clinical setting, especially the data on "chronic effect" and cancer control. The ideal cryogenic probe system and the optimal mode of delivery (open, laparoscopic, or percutaneous) have yet to be defined. The foremost technical challenges are cryoprobe placement and real time monitoring of the freezing process. Intracorporeal ultrasonography, used in both open and laparoscopic cryosurgery, is still an evolving technology and its accuracy is dependent on the skill and experience of the operator. Discrepancy between the ultrasonographic boundaries of the freezing and extent of subsequent cytocidal effect, a lesson learned from the prostate Cab experience[11] and from canine studies correlating intra-renal temperature data and ultrasound appearance,[10] suggests technical adjustments with cryoablation are still needed. Gill et al[17] routinely allow the expanding iceball to extend 1 cm beyond the ultrasonographic tumor boundary, to ensure adequate cell kill. Using thermosensors for monitoring the effect of Cab intraoperatively, another technique learned from prostate Cab, the operator also has to contend with the fact that the kidney is one of the most vascular organs in human, although this monitoring modality is probably superior to reliance of visual assessment of iceball progression alone.

The second major challenge is the appraisal of clinical results. The series reported to date all have a median follow up of less than 18 months. Limited post-Cab imaging and biopsy data have been reported. Lack of enhancement and absence of growth (with or without obliteration or downsizing of the tumor mass), has been accepted as the surrogate indicator of successful tumor ablation. There is controversy regarding the significance of "atypical enhancement" on MRI or CT. Routine follow-up biopsy has been advocated by some[20] although to date only 6-month biopsy data are available. Serial biopsies would be preferable although follow-up biopsies are still subjected to sampling errors and an optimal follow-up biopsy schedule has yet to be determined.

One other significant problem with Cab is the lack of tissue for accurate diagnosis and the inability to assign pathological grading and staging with certainty. Pre-Cab biopsy is the obvious answer but there are inherent problems with such biopsies including potential tumor seeding and bleeding.

Radiofrequency energy

Mechanism of action

Radiofrequency (RF) energy is based on high frequency current flowing from a generator via (a) single or multiple needle electrode(s) to the tissue in which it is in contact. The electric current agitates ions, leading to accelerated friction, an exothermic process. Tissue temperature is usually targeted at between 80-100°C, achieving coagulative necrosis of the tissue. A grounding pad on the patient completes the electrical circuit, allowing the RF energy to be released into the targeted lesion. Temperature-based systems utilize thermosensors to monitor the heating process, which usually utilize power of 26-200 W at a frequency of 460-500 kHz. Monopolar and bipolar electrodes are both available, with a variety of needle number and configuration (multiple hooks displayed from a single shaft once the needle is satisfactorily positioned). With this "dry" RF system, desiccation and charring from the high local temperature results in high electrical impedance, limiting the size of the therapeutic target. An alternative dry RF probe utilizes an internal cooling mechanism with circulating chilled water to prevent charring around the probe. Clinically, this probe creates a more uniformed thermal lesion in both the liver and kidney.[25] Based on the same theory, a "wet" RF system involves infusion of hypertonic saline solution into the tissue, preventing desiccation and charring. Lower local tissue impedance results in a wider extent of tissue necrosis and ablation.[26] Thermosensors are a crucial component of this technology in terms of treatment monitoring.

Laboratory data

Collyer et al[27] performed RF with the porcine model reporting a single "dry" needle and a multi-tine Leveen created renal lesions of 6-10 mm and 25-45 mm respectively. Polascik et al, using a VX-rabbit renal tumor model, tested "wet" RF with tissue pre-infusion of hypertonic saline and delivery of 50 W at 500 kHz for up to 45 seconds.[26] The kidneys were harvested acutely and the preliminary report indicated satisfactory necrosis although no firm conclusion could be drawn comparing "wet" and "dry" RF in the pig model. However, Collyer et al documented a two- to three-fold increase of lesion size created by the respective electrodes with the "wet" system.[27] Of note is that skipped areas of viable cells were noted and complete necrosis was not generally achieved.[27] Patel et al reported large lesions could be safely and quickly reproduced in the rabbit kidney although they did not comment on "skipped" lesions.[28] Rendon et al created 22 lesions in seven pig kidneys by applying RF energy via open surgical exposure and percutaneous routes, documenting the anticipated changes with thermal injury and ischemic necrosis in wedge-shaped lesions. They reported thermal ablative damage to adjacent organs (duodenum, psoas, distended bladder) in their initial experiments. They then described a novel protective maneuver with either hydro-dissection (30-60 cc's normal saline) or gaseous dissection (500 cc's CO_2) into the perinephric space. The technique appeared to provide protection to other intra-abdominal structures in their remaining experiments.[29] Miao et al[30] using a "cooled-tip" RF system reported favorable results in rabbit VX-2 tumors using MRI for assessment of results.

The gross appearance of RF-created kidney lesions generally showed a clear demarcation of induced lesions and the adjacent normal parenchyma. A central cavity is seen, surrounded by a grey-colored zone of necrosis.[31-33] Histologically, kidneys harvested acutely have revealed severe stromal and epithelial edema with hyper-eosinophilia and pyknosis. As with cryoablative effects, microvascular thrombosis and coagulative necrosis are the early results. "Chronic lesions" were non-specific.

Further advances in solid organ ablation include the pharmacological manipulation of blood flow to decrease the "steal phenomenon" of adjacent blood vessels in the procine liver model.[34] Larger coagulative areas were created with the use of agents to modulate hepatic blood flow. Others have recently published the combination of RF and intratumoral injection or liposomal delivery of chemotherapeutic drugs in a breast cancer model with improved outcomes.[35,36] Clearly, this is an exciting field with tremendous potential.

Clinical data

The volume of clinical data on RF for kidney lesions is even more limited than that for Cab. Zlotta et al[31] treated the clinical feasibility of "RITA" (radiofrequency interstitial tumor ablation) with both in vivo and ex vivo bipolar and monopolar RF application in conjunction with open nephrectomy. The documented RF can be clinically delivered under US guidance and local anesthesia. Rendon et al also performed partial or radical nephrectomy either immediately (five patients) or 1 week after RF treatments (six patients). Significantly, residual viable tumor, albeit small volume, was found in four of five tumors excised immediately after RF and in three of six tumors in the delayed excision group.[37] No significant complications were observed in nine of 10 patients.

Percutaneous ablation of small tumors with CT[38,39] and MRI[40] guidance has been reported in several small series. Pavlovich et al have the largest experience to date, having reported on 24 ablations in 21 patients.[41] Amongst these patients, 19 had VHL (clear cell tumors) and two had hereditary papillary renal cell carcinoma. No major complications were encountered and most of the procedures were conducted with the patients under sedation. Gervais et al[42] applied RF on nine thermal tumors in eight patients who were not surgical candidates on account of medical co-morbidities. Several lesions required repeat RF due to evidence of residual tumors. With a 10- month follow up, seven of the nine high-risk patients appeared to have undergone successful tumor ablation. The study shows that the procedure can be repeated if necessary. This group has also expanded the eligibility patient criteria for RF in renal tumors. Pautler et al[43] reported on a case of RF administered by retroperitoneoscopy for renal tumors in a VHL patient.

Challenges

The main advantage of RF is the relative simplicity of the technology. As with Cab, data have documented a tissue ablative capacity. It should be emphasized that several groups have reported on successful creation of "lesions" by RF in normal kidneys, i.e., they were mainly feasibility studies. The dynamics and tissue response may be different in various malignant tissues. The documentation of residual viable cancer, albeit in only a small percentage of the total tumor volume, should sound a loud cautionary note regarding the current state of this technology.

The effect of organ perfusion on the success of RF has been well documented in the hepatology and radiology literature. The so-called "steal phenomenon" can lead to inadequate heating and compromised results. In Pavlovich's series of percutaneous renal RF ablation, failures were predicted by the treating physician because of the inability to achieve a sufficient temperature for tumor destruction, likely due to the heat sink of adjacent large vessels.[41] The relationship of blood flow to the success of RF has been studied with renal hilar occlusion[44] but the intrarenal and tumor vascular dynamics have not been elucidated. In this study, an increase in damage to the entire renal unit was observed with hilar occlusion.

Although real time ultrasound has been successfully used by several groups for needle placement, its ability to provide real time monitoring of the development of RF lesions is not established. Furthermore, follow-up has been universally short. Optimal tracking of the renal tumors and documentation of sustained response has been an on-going debate. Serial CT scanning with intravenous contrast post-RF should indicate total non-enhancement in the case of complete tissue necrosis and destruction. However, there has been documented residual cancer in cases where CT did not show contrast enhancement post-RF.[37] As with other minimally invasive techniques, one other major problem is the inability to provide adequate tissue sampling for staging and grading of renal cell carcinoma. Lastly, the safety of RF is still unresolved. Reported adjacent organs sustaining significant damage[37] is worrisome. At present the ideal patient for RF on renal tumors are those patients with VHL or other hereditary problems with multiple renal tumors. Patients with severe co-morbidities may also be candidates, obviating a more extensive extirpative procedure.

High intensity focussed ultrasound (HIFU)

Mechanism of action

A concave transducer, composed of a piezoelectric element, causes a high intensity ultrasound beam to converge and focus on the targeted tissue. The bursts of energy (750-4500 W/cm^2 lasting for milliseconds or seconds) are absorbed at the focal point of the transducer, resulting in a temperature rise in the tissue approaching 90ºC. Tissue destruction theoretically occurs by two mechanisms, thermal or cavitational damage, with resultant cellular protein degradation. Thermal damage is thought to be the result of lower intensity energy delivered over a longer duration (1 second), whereas cavitational effects are derived from high intensity energy exposed over a brief period. The latter process results from "bubbles" developing and expanding rapidly until they burst at high pressures (20 000-30 000 bars), inflicting tissue damage locally. In theory, at least, the transducer can focus the ultrasound energy, avoiding "collateral" tissue damage.

Experimental data

HIFU has been applied to rat and canine kidneys, producing lesions with coagulative necrosis or cavitation, based on the intensity and duration of exposure.[45] Histologic changes of HIFU-induced lesions were studied in the rabbit VX-2 tumor model[46] and the authors reported separation of affected cells, with pale eosinophilic cytoplasm. Accurate localization of the tumors for tissue destruction was problematic in the earlier studies.[46,47] A corollary to the difficulty of target localization is the problem of damage to adjacent organs, possibly attributed to mis-focussing. Significant damage in abnormal organs was noted in 13 of 16 dogs in a study by Chapelon et al,[45] whereas lesions in the targeted organ, i.e., kidney, was achieved in only 10 of 16 animals. A target shift from ventilatory motions also contributed to the localization difficulties.[46] Similar difficulties with targeting were reported by Watkin et al.[47]

Clinical data

Clinical experience with HIFU has been more extensive with the prostate in both benign and malignant conditions, compared to that for the kidney. Susani[48] applied HIFU in two renal cell carcinomas prior to the patients undergoing nephrectomy and reported difficulty in delineating the treatment lesions from the pre-existing tumor necrosis. Kohrmann et al[49] reported on US waves targeted to renal tumors, focussing to a target size of 10 mm x 3 mm at a depth of 10 cm. Preliminary experience on 25 patients with different target organs, including the kidney, has been satisfactory using MR for follow-up assessment.

Challenges

The obvious advantage of HIFU is its minimally invasive extracorporeal approach. As with other modalities already discussed, lesional localization and targeting require refinement. Improvement in imaging capacities, especially if coupled or integrated into the HIFU technology, would be a significance advancement, both for targeting and monitoring during treatments.

As with other modalities, the most reliable modality for assessment of the efficacy and completeness of tumor ablation is still being researched. Safety issues in terms of avoiding collateral tissue damage with HIFU are of paramount importance and have to be resolved satisfactorily before wider clinical application is advised.

Other modalities in development

Microwave thermotherapy

From the 300-3000 MHz range of the electromagnetic spectrum, microwave energy when transmitted from an antenna through tissue causes oscillation of the electromagnetic field and resultant polarization of molecules. Heat is generated by the resultant increased kinetic energy, which in turn causes coagulated tissue necrosis and hemorrhage. In contrast to prostate diseases, pre-clinical experience with renal tumors has been limited to implanted VX-2 tumors in rabbits.[50,51] Nakada et al reported equivalent survival in the group treated with microwave thermotherapy and in the nephrectomy group.[51] Clinical experience has been limited to preliminary feasibility assessment in conjunction with open partial nephrectomy.[52] One major drawback with this technology is the inability to monitor the treatment process sonographically or radiographically. Instead, thermosensors are needed. One advantage is that the microwave antennae are flexible, rendering the technology more versatile in terms of instrumentation compatibility and ready access to the target lesions.

Interstitial laser therapy

Both Diode (830 nm-980 nm) and Nd:YAG (1040 nm) lasers have been used as tissue ablative tools in the kidney.[53] The laser fibres inserted into the target tissue cause a thermal action and coagulative necrosis in the tissue. Experimental work in a porcine model has been described with an Nd:YAG laser inserted via a laparoscope. Unlike the prostate where some experience has been reported on benign prostatic hyperplasia,[54] very limited clinical experience is available on renal tumors. Ten patients with renal cell carcinoma have been treated with interstitial Diode laser followed by open radical or partial nephrectomy.[55] Satisfactory histologic changes, i.e., coagulative necrosis at a temperature near 85°C, were reported. The group also showed that real time ultrasound monitoring was feasible. Using a different system, deJode et al[56] used a Nd:YAG laser via a water-cooled applicator system on three patients with inoperable renal cell carcinoma. Thermo-lesions were monitored at real time with a color-thermometry sequence and then post-operatively with MRI to assess the extent of necrosis and completeness of treatment. No further reports on this promising approach have been forthcoming thus far.

Summary

The area of new ablative energy sources and the whole field of alternative ablative treatment modalities for renal tumors is evolving rapidly. Several common themes have emerged from the available data. The clinical experience to-date has been limited and follow up has been short. Technical challenges include difficulty with the imaging for probe placement and target localization. There is also difficulty with intra-operative monitoring of "treatment-lesions", whether they are iceballs or heat-induced tissue damage. There are safety issues, especially with HIFU, in terms of collateral tissue damage. There is unresolved controversy regarding the assessment of tumor-ablative efficacy in terms of the imaging modality and the interpretation of results. By the very nature of these treatment modalities that are potentially ablative rather than extirpative, a potential problem with accurate pathological staging and grading remains. Unquestionably though, there is tremendous appeal with these technologies in terms of their minimal invasiveness. There is general consensus that currently treatment with such technology should be limited to small, peripherally-located, preferably exophytic, lesions. The ideal candidates, with the current state of technology, are those with multiple tumors, especially in genetically predisposed individuals. Older patients with co-morbidities who are not ideal for radical extirpative surgery may also be candidates. □

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