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Provisional chapter

Focal Therapy in Kidney Cancer

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Abstract

The widespread use of imaging has led to an unprecedented increase in the diagnosis of small renal masses. Incidence rate has increased worldwide and most notable in older population (more than 75 years). There has been an evident revolution in the management of patients with small renal masses. Treatment strategies include active surveillance, partial nephrectomy, radical nephrectomy and focal ablative therapies. Nephron sparing surgery for small renal tumours offers comparable cancer-specific survival and better overall survival when compared to radical nephrectomy. Nevertheless, complications related to extirpative surgery must be taken into consideration. Thermal ablative therapies were developed in an attempt to provide a reproducible treatment option with low risk of complications. Energy based renal ablation therapy offers treatment flexibility, technically less challenging procedure with acceptable oncological outcomes.

Keywords: small renal tumours, kidney cancer, cryoablation, radiofrequency ablation, microwave ablation

1. Introduction

A number of population based studies reported an increase in the incidence of diagnosed small renal masses ≤4 cm [1–2]. Nephron sparing treatment remains the recommended treatment for cT1a renal masses, especially in young healthy patients. Partial nephrectomy carries the same oncological outcomes to radical nephrectomy in treating patients with cT1a renal masses [3–6].

Over the last 2 decades, thermal ablation has emerged as alternative treatment option for the management of patients with renal masses <3 cm in size. Focal ablative treatment is associated with fewer complications and less morbidity. It offers a viable treatment alternative especially in patients whom might not be medically suitable for extirpative surgery.

Focal ablative treatment offers flexibility with treatment's approach. Tumours could be treated laparoscopically, percutaneously or less often open approach. The American Urological Association recommends percutaneous access over surgical approach whenever is feasible [8].

Focal ablative therapy is well tolerated and technically less challenging. Hilar dissection and clamping is not a prerequisite in focal ablative therapy. Renal parenchymal loss is minimal following ablative therapy.

2. Cryoablation

2.1. Mode of action

The therapeutic principle of cryotherapy treatment is selective destruction of tumour cells with minimal injury to the surrounding tissue. Argon and helium are the most commonly used freezing agents. New cryotherapy systems use the Joule-Thomson principle to generate lethal temperature down to −187.5°C. Very low temperature causes direct cellular damage during freezing phase and indirect reperfusion injury during the thawing phase.

Cellular changes secondary to cryotherapy treatment could be summarised in four main stages:

- Formation of extracellular ice crystals leading to hyperosmolar extracellular environment and cells shrinkage
- Formation if intracellular ice crystals causing cells damage
- Metabolic activity stops at −40°C
- Thrombosis and micro capillary damage leading to necrosis

To achieve the described cellular changes, it is essential to achieve the following aspects of the cryotherapy treatment [7].

2.1.1. Target treatment temperature

It is understood that irreversible tissue damage is achieved when cells are exposed to temperature between −20 and −50°C. Different structures of the kidney react differently to freezing temperatures. This behaviour is largely related to collagen and elastin content. Renal collecting system and renal vasculature tolerate cryoablation without real long term injuries. However, renal parenchyma is usually destroyed at −19.4°C. It is recommended to achieve temperature of −40°C or below to ensure killing tumour cells. Thermosensors are usually placed at the edge of the tumour to ensure adequate treatment temperature for the area of interest.

2.1.2. Double freeze-thaw cycle

The standard of care during renal tumour cryoablation is double freeze-thaw cycle. This concept has been established after an experiment on 16 female dogs. More adequate area of

treatment and liquefaction was achieved following two freeze-thaw cycles compared to dogs who had only one treatment cycle.

2.1.3. Satisfactory ablation area

It is recommended to perform cryoablation treatment for renal tumours under real-time imaging. The operator should aim for treatment area of 10 mm beyond the margin of tumour to ensure adequate treatment temperatures.

2.1.4. Duration of treatment

The duration of treatment should be balanced against risk of suboptimal treatment with short cycles or risk of tissue fracture and bleeding with long treatment. The optimal duration of freezing cycles is not well described in the literature. Two active cycles with initial freeze cycle of 8–10 min and a second freeze cycle of 6–8 min is considered the optimal.

2.2. Guidelines

The European Association of Urology guidelines state that, due to lack of high quality data, no recommendation can be made on cryoablation and radiofrequency ablation [9]. The American Urological Association (AUA) recently released its guidelines for management of patients diagnosed with small renal masses [8]. Focal ablative therapy should be offered as an option rather than standard treatment in high risk patients [8, 9].

Cryotherapy treatment offers a viable alternative to surgery especially in following clinical circumstances:

- Patients with multiple comorbidities
- Elderly patients
- Patients with multiple/bilateral renal tumours
- Patients with impaired renal function

Cryotherapy is usually recommended for small renal tumours (<3 cm in size). Cystic renal masses and hilar masses represent relative contraindications for cryotherapy treatment. Untreated coagulopathy is an absolute contraindication for cryotherapy treatment.

2.3. Modality of treatment

Cryotherapy treatment can be delivered percutaneously, laparoscopically or less often with open surgical approach.

Laparoscopic mobilisation of the kidney and accurate dissection of the tumour might provide an excellent exposure of the tumour. It allows treating anteriorly located tumours safely, thus avoiding injury to surrounding structures. Laparoscopic approach allows real time monitoring of ice-ball formation in cryotherapy treatment and confirmation of probes positioning.

Location of the tumour and surgical expertise would normally mandate the approach of laparoscopic cryoablation (transperitoneal or retroperitoneal). Standard three ports technique is used. Gerota fascia is incised. The kidney is mobilised and tumour is identified. The overlaying and surrounding fat might be excised to allow accurate assessment during the treatment. Histological confirmation with 18-gauge biopsy needle is advocated if no prior biopsies have been taken.

Cryoprobes are inserted percutaneously under direct vision. Laparoscopic ultrasonography is used to confirm the location of the probes and the margins of the tumour. Treatment is delivered with double freeze-thaw cycle. Cryoprobes are removed. Low pressure check is performed to check for any post-interventional bleeding.

Percutaneous cryotherapy can be performed as an outpatient procedure under conscious sedation or general anaesthesia. It might offer an advantage to laparoscopic approach especially patients requiring multiple procedures as in Von Hippel-Lindau (VHL) disease. The American Urological Association (AUA) recommends a renal biopsy prior to ablation to provide pathological diagnosis and minimise over treatment of benign conditions [8].

Following anaesthetic induction patient is positioned in the prone or flank position. Lesion is characterised following the administration of intravenous contrast depending on imaging technique (iodinated or gadolinium contrast). Tumour is localised with finder needle (20-gauge). A representative biopsy is taken with 18-gauge Try-Cut core biopsy needle under CT/MRI guidance. Positioning of cryoprobes and prongs are confirmed with repeat imaging. Cryotherapy treatment is carried out achieving the standard of care principles. Once treatment is completed; cryoprobes are removed. Post treatment imaging is performed to check treatment adequacy and evaluate for potential bleeding.

2.4. Follow-up and oncological outcomes

The absence of histological evidence for treatment success remains an inherent criticism for focal ablative therapy. The interpretation of a routine biopsy following cryotherapy treatment is highly controversial. Therefore, the determination of treatment success is solely reliant on radiological evaluation. Radiological evaluation of treatment success is interpreted by complete loss of contrast enactment of follow-up CT or MRI scan. Treated renal lesion is expected to shrink by >50% in size within the first year following cryotherapy treatment. Most of urological institutions recommend first CT scan or MRI scan with 3–6 months post cryotherapy treatment. Currently, there is no consensus on surveillance after RCC treatment. A six monthly CT scan is usually recommended within the first year of follow-up. Annual CT scan is recommended thereafter if favourable response to treatment has been established.

Selective post cryotherapy treatment biopsy should be sought in the following situations:

- If a lesion demonstrates persistent contrast enhancement following treatment (Incomplete treatment).
- If a lesion demonstrates enlargement following cryotherapy treatment and or new contrast enhancement (Local tumour recurrence or progression).

2.5. Treatment outcomes

Currently, there are no RCTs comparing treatment outcomes of PN with focal ablative therapies for small renal masses. The CONSERVE trial was a feasibility multicentre RCT attempted to compare PN with CA and RFA. The study was however unable to recruit the desired number of patients [10].

Rai and colleagues [11] performed recent meta-analysis in which they compared outcomes of partial nephrectomy and cryoablation. This study highlighted significantly lower recurrences rates following RAPN. The overall recurrence rates in the CA cohort were 11.5% compared with 0% in the RAPN cohort. Similar results were concluded from met analysis of 13 studies comparing laparoscopic and RAPN with LCA; 9.4 vs. 0.4% respectively [12]. The analysis suggested LCA might be associated with improved peri-operative outcomes. These meta-analyses found that impact on oncological survival and mortality outcomes was profound. These results should be carefully evaluated, as it might reflect the short oncological follow-up [11, 12]. A retrospective review of more than 800 patients reviewed the intermediate oncological outcomes of LCA. The 5 and 10 year disease survival was reported at 90.4 and 80.0% respectively; however the 5- and 10-year overall survival in the study was 83.2 and 64.4% [13].

2.6. Complications

Cryotherapy is relatively safe procedure with low risk profile. Percutaneous and laparoscopic cryotherapy have similar overall complication rates [14, 15]. As one might expect, the length of in hospital stay following percutaneous cryoablation is shorter when compared to laparoscopic cryoablation [15, 16]. A recent systematic review reported the overall rates of complications following cryoablation therapy range from 7.8 to 20%. Zargar and colleagues [17] found that complications rate for percutaneous cryoablation are lower than laparoscopic cryoablation (2.8–12.9% vs. 15–20% respectively). The incidence of major urological complications following cryotherapy is 4.9% (3.3–7.4%).

Post-operative haemorrhage is the common reported complication. Other reported complications are ureteric injury and obstruction, peri-renal abscess and haematuria. Other minor non-urological complications include pain and paraesthesia at the probe site, urinary tract infections and self-limited haematuria. Reintervention following cryoablation therapy is reported at 2.6%.

3. High temperature ablative techniques

Cancer cells are very sensitive to both very high and low temperature. Radiofrequency and microwave energies use the concept of high temperature (above 55°C). Thermal ablation causes denaturation of cellular proteins and vascular necrosis of tumour cells resulting in instantaneous cellular death.

3.1. Radiofrequency ablation

3.1.1. Mode of action

Electric current passes through radiofrequency ablation (RFA) probe/electrode into tumour creating closed loop circuit with a generator and grounding pads. The current triggers disruption of intracellular ions and friction between molecules producing heat. The electromagnetic field generates high temperature typically above 55°C. The generated heat results in cytotoxic effect and instantaneous cell death occurring with temperature reaching 60°C [18].

3.1.2. Technique

Small renal masses (≤3 cm) can be treated with single cycle of RFA. However, larger tumours (up to 5 cm) might be suitable for treatment using overlapping cycles technique. RFA achieves excellent results in treating exophytic and endophytic tumours.

RFA is carried out under general anaesthetic or conscious sedation. Different types of RFA electrodes could be used including; single tip, multi-tined expandable electrodes, or a cluster tip electrode. RFA electrodes are inserted into the tumour under CT/MRI or ultrasound guidance. Hydro-dissection can be used if the tumour is adjacent to bowel segment.

Once electrodes are positioned; a 12 min cycle is delivered. Some RFA systems use internal cooled electrodes to avoid adjacent tissue carbonization. This method might have an impact on heat distribution to distant area of the tumour and subsequently might affect the efficacy of treatment [19, 20].

3.2. Microwave ablation

3.2.1. Mode of action

Microwave ablation uses the same concept of thermal ablation as RFA technique. Thermal ablation results in coagulative necrosis of tumour cells. Microwave ablation uses different energy source. It produces an electromagnetic spectrum with frequency of 900–2450 MHz. The oscillating microwave field causes polarisation of molecules resulting in increased kinetic energy producing heat.

Microwave ablation has several advantages over radiofrequency ablation. It is possible to treat larger tumours without the need of overlapping treatments. Microwave ablation does not cause charring effect. Skin pads are not required during microwave ablation treatment; therefore the risk of skin burns is minimal.

3.2.2. Technique

Two microwave antennae are inserted under CT or ultrasound guidance. A fibre-optic thermal sensor inserted at the periphery of the tumour to provide continuous temperature monitoring. It is recommended to delivers 3 cycles achieving temperature of 60°C. Each cycle lasts for 20 min [21].

3.3. Possible side effects of high thermal ablative techniques

- Heat sink effect: kidney is well perfused organ. this may result in unequal distribution of the heat particularly close to the larger vessels.
- Thermal injury to neighbouring structures such as bowels, ureter, genitofemoral nerve and psoas major muscle.
- Post-ablation syndrome: the syndrome is usually self-limiting. Patients might suffer symptoms of low-grade fever (37.5–38.5°C), delayed pain, nausea, vomiting, malaise, and myalgia.
- Haematuria and peri-nephric haematoma are usually self-limiting.
- Hyper adrenal crisis is very rare. This might be secondary to adrenal thermal injury.
- Skin burns (mainly with radio-frequency ablation).
- Calyceocutaneous fistulae.
- Infection and abscess formation.
- Acute tubular necrosis and decreases overall renal function [22].

3.4. Oncological efficacy

Few studies have evaluated the short and intermediate oncological outcomes. The technical success rate has been reported to be 95.5–98.5%. The average need for repeat treatment is thought to be around 3%. Small renal tumours (<3 cm) and exophytic location were independent factors for successful treatment. The overall 5 year survival rate was reported between 65–85% and cancer specific survival rate of 88–97.9% [23–25].

3.5. Monitoring and follow up

Most urological institutions recommend contrast enhanced CT scan at 3 months to evaluate treatment success. Follow-up CT scan is suggested every 6 months for the first 2 years. Annual CT scan is suggested thereafter for a period up to 7 years.

4. Investigational and experimental treatments

4.1. Laser interstitial thermal therapy (LITT)

This treatment modality is currently being evaluated for treatment of solid tumours including brain, pancreatic, breast, thyroid and prostate cancer. LITT utilizes image guided low voltage laser probes to deliver heat and destroy target tissue. Optical fibres are inserted directly to the target tissue. Laser light delivers heat that is converted to heat. The emitted light energy from

laser fibres is absorbed and converted to heat. This would result in thermal destruction of the cancer cells [26]. Neodymium: yttrium-aluminium-garnet (Nd:YAG) laser has been used to treat small renal tumours. All reports are based on small number of treated patients with short follow up [27, 28]. LITT remains an experimental treatment.

4.2. Extracorporeal high-intensity focused ultrasonography (HIFU)

The therapeutic use of the ultrasound to treat cancer was established in the 1970s. The mechanism of HIFU involves mechanical and thermal effects. Some of the acoustic wave is converted to heat once absorbed by the tissue. The thermal phenomenon causes cell death by coagulation necrosis once tissue temperature exceeded the 65°C. The mechanical effect causes micro-streaming, cavitation and radiation force [29].

HIFU offers completely trackless non-invasive ablative technology. Treatment session can be lengthy. Several studies reported incomplete treatment when renal tumours were excised following HIFU treatment. Skin burns were reported up to 10% of the patients. Respiratory movement and acoustic interference could impede on delivering treatment accurately. Other limitations to HIFU treatment include limited focal zone depth and inability to monitor treatment progression in real life [30–32]. Recent studies investigated the role of magnetic resonance-guided high intensity focused ultrasound. The results are promising, however it remains experimental [33, 34].

Laparoscopic HIFU has recently evolved to overcome the challenges related to respiratory movements, targeting tumours and acoustic interference.

HIFU is considered to be experimental treatment. It could be considered in some selected cases.

5. Conclusion

In conclusion, ablative therapies have emerged as an alternative option to extirpative surgical treatment. Percutaneous focal ablative therapies represent a valid treatment option especially for high risk patients. Randomised controlled trials are needed to compare treatment outcomes of PN with focal ablative therapies for small renal masses.

Conflict of interest

None declared.

Notes/thanks/other declarations

None.

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