Emerging minimally invasive techniques for treating localized prostate cancer

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INTRODUCTION

Since the introduction of PSA as a clinical marker for prostate cancer in the late 1980s, more men are diagnosed with localized prostate cancer [1]. Currently, radical prostatectomy is the 'gold standard' treatment for localized prostate cancer. Although the operation is effective, it is a major procedure and may be associated with major morbidities [2]. External beam radiotherapy and brachytherapy achieve an encouraging PSA outcome, yet complications can be considerable [3]. In addition, most men in whom radiotherapy fails have higher grade cancer and radical prostatectomy in this situation is technically difficult and associated with significant complications [4].

Several minimally invasive procedures using different energy sources are under investigation as alternative therapeutic options for localized prostate cancer. These include: cryotherapy, high-intensity focused ultrasound (HIFU), photodynamic therapy (PDT), microwave and radiofrequency interstitial tumour ablation (RITA). The aims of these new techniques are to eradicate the tumour *in situ*, minimize complications, and shorten the hospital stay and time to return to routine daily activities. In this review we evaluate some of the new procedures in terms of development, technique, mechanism of action and results of recent trials.

CRYOTHERAPY

The first prostate cryosurgery was performed by Gonder *et al.* [5] in 1966 using a single transurethral liquid nitrogen probe. Complications were significant, mainly urethral sloughing and rectal fistula due to the inadequacy of precise probe placement and monitoring the ice-ball. This resulted in the abandonment of cryosurgery. The introduction of real-time TRUS-guided placement of the cryoprobes and continuous monitoring of the ice-ball progression in 1993 [6] resulted in the revival of interest in cryosurgery.

Various experiments have shown that −40°C or less is required for total cell death [4]. Cryosurgery causes tissue damage by two mechanisms; an immediate cellular injury and a delayed vascular effect [7]. Slow freezing to −20°C causes crystal formation in the extracellular space and the formation of an osmotic gradient across the cell membrane. This consecutively draws water from the cells, leading to cellular dehydration and high intracellular electrolyte concentration. However, rapid freezing to −40°C results in a more lethal intracellular ice-crystal formation, causing injury to cellular organelles and membranes [7]. Upon thawing, water will shift from the extracellular to the intracellular compartment, causing mechanical cell membrane rupture.

The vascular effect of freezing may be considered the main mechanism of tissue damage [7]. During freezing, vasoconstriction results in cellular anoxia and hypoxia. In the thaw phase, circulation is restored. However, the resulting endothelial damage leads to increased vascular permeability, excessive oedema formation, platelet aggregation, microthombi formation and vascular occlusion.

Multi-port high-pressure gas systems that use the Joule-Thompson effect (gas at high pressure changes temperature when released to an area of lower pressure) are currently used in cryosurgery. Argon gas is used for freezing, as the temperature decreases to −186°C when expanded; however, helium gas warms to +40°C according to the Joule-Thompson effect, and hence used for thawing [8].

The technique of cryosurgery involves TRUS-guided insertion of 4–16 cryoprobes transperineally into the prostate, using a brachytherapy-type template. Large prostates may not be sufficiently frozen, and men with a prostate volume of >50 mL should have their prostates downsized before cryosurgery, with neoadjuvant androgen deprivation [6]. A urethral warming catheter is placed to reduce sloughing [9]. Ice-ball progression is monitored by TRUS and thermosensors; up to five thermosensors are inserted at the external sphincter region, Denonvilliers' fascia, both neurovascular bundles and in the mid prostate. The temperature at the external sphincter area and Denonvilliers' fascia should remain >0°C to reduce the risk of incontinence and recto-urethral fistula, respectively [9]. Once the temperatures at the neurovascular bundles and mid prostate reach −40°C, argon flow is stopped and thawing begins, with delivery of helium gas. Two freeze/thaw cycles are used to induce more effective cell killing [7]. After completing the second cycle, the probes are removed and the urethral warmer left for 5–20 min. A urethral or suprapubic catheter is then placed, which can be removed after 2–3 weeks.

Results of recent studies of prostate cryosurgery are encouraging. Derrick *et al.* [10] reported that 80% of their 65 patients had a PSA level of <0.5 ng/mL 8 years after cryotherapy. Bahn *et al.* [11] published the largest series; they stratified 590 patients into three risk groups according to clinical characteristics: low (15.9%), medium (30.3%) and high risk (53.7%). Using the American Society for Therapeutic Radiology and Oncology definition of three consecutive PSA level increases, the 7-year actuarial biochemical disease-free rate (DFR) was 92%, 89% and 89% for the low-, medium- and high-risk groups, respectively.

Cryosurgery has emerged as an attractive alternative salvage treatment for recurrent prostate cancer after radiotherapy. Katz *et al.* [12] described their 6-year experience with 67 patients who had salvage cryoablation. At 12 months, 72% of their patients had a PSA level of <1 ng/mL. The longest follow-up was presented by Bahn *et al.* [13], who followed 59 patients for 7 years; the DFR was 59% using a PSA threshold of 0.5 ng/mL.

Complications after cryosurgery have declined significantly with advances in technology and modifications of technique [2]. Recent series reported incontinence rates of 1.3–7.5% and 6.7–11% for primary and salvage cases, respectively [4,14]. Patients with a history of TURP may be at greater risk of incontinence after cryosurgery [15]. Erectile dysfunction is the commonest complication of cryosurgery, with most studies reporting a >70% incidence, although late recovery has been reported [16]. The incidence of recto-urethral fistula was recently reported at 0–0.5% [14].

HIFU

Experiments in the early 1990s showed that HIFU is capable of destroying prostate cancer cells implanted in adult male rats [17]. Further studies showed the feasibility and safety of HIFU to destroy the prostate in a canine model [17]. The first clinical trials using HIFU for treating localized prostate cancer began in 1993 [17].

The principle of HIFU involves focusing high-energy ultrasonic waves emitted from a transducer into a small site within the prostate. This results in a sharp focal temperature rise to 70–100°C within a few seconds, leading to protein denaturation and eventually coagulative necrosis [17].

The HIFU is delivered with the patient under general or spinal anaesthetic. A suprapubic catheter is inserted and the ultrasound probe placed transrectally inside a balloon-shaped latex cooling device containing degassed coupling liquid. The cooling device keeps the temperature of the rectal wall to <37°C throughout the procedure, and maximizes coupling of the acoustic waves at the probe–rectal wall interface. Using the imaging mode, the boundaries of the treatment area and the position of the rectum are first defined. The distance between the rectal mucosa and the posterior prostatic capsule is also measured. Once the data have been entered, the computer places the firing head in the target region and treatment proceeds automatically. A beam of focused ultrasound is emitted from the transducer intermittently. Each shot lasts for 3–5 s followed by a 5–6-s gap, during which the transducer changes position. The shot creates an elliptically shaped elementary lesion which is ≈2 mm thick and 10–18 mm long. The treatment continues layer by layer until the whole area is covered; it takes <3 h to treat a 25-mL prostate [18].

The HIFU systems have security features to protect the rectal wall, in addition to the cooling device. These include: rectal wall temperature monitoring; continuous rectal wall reflectivity index (indicating tissue change) measurements; patient motion detector (to stop the procedure if the patient moves) and real-time measurement of the transducer-rectal wall distance with automatic readjustment of the focal point.

Like in cryosurgery, prostates of >50 mL should be reduced with neoadjuvant androgen deprivation before HIFU [18]. Other limitations of HIFU include a rectal wall thickness of >6 mm [19] and significant prostatic calcifications or stones, which cause acoustic shadowing.

Early results of the European multicentre study were published [19], in which 602 HIFU sessions were delivered in 402 patients with T1-2N0-XM0 prostate cancer. The mean PSA nadir was 1.8 ng/mL, and after a mean follow-up of 407 days, 87% of the men had negative biopsy results.

Results of longer follow-up studies are also available. Poissonnier *et al.* [20] used HIFU on 230 men; all had clinical T1–2 disease with a baseline PSA of ≤15 ng/mL, Gleason score ≤7 and a prostate volume of ≤40 mL. Using treatment-failure criteria of a positive biopsy or three consecutive PSA rises, the 5-year DFR was 65%. The same group reported on the efficiency and safety of HIFU as a salvage therapy after radiation failure [21]; 106 patients were included in the study, with a mean (range) follow-up of 15.7 (3–99) months. The 40-month DFR was 40.5%, but complication rates were not insignificant; 22% of patients developed incontinence and the rates of bladder-neck stenosis and recto-urethral fistula were 17% and 5%, respectively.

Chaussy *et al.* [22] evaluated the role of combining TURP and HIFU in reducing comorbidity in men with primary prostate cancer. There was a significant improvement in the median postoperative catheter time from 40 to 7 days; incontinence rates declined from 15.4% to 6.9%, and the men had a significantly lower IPSS than those treated with HIFU alone. Other reported complications of primary cases include recto-urethral fistula in 0.9% and erectile dysfunction rates of 22% and 69% [17].

PDT

PDT involves administering a photosensitizing drug i.v. followed by delivery of light of an appropriate wavelength to the target area, in the presence of oxygen. The resulting photochemical reaction produces various oxygen species [23] that are highly toxic and known to react with many vital structures, including cellular organelles, proteins and nucleic acids.

The first therapeutic potential of PDT using haematoporphyrin derivative (HpD) as the photosensitizer to destroy transplanted malignant gliomas in rats was reported in 1972 [24]. *In vitro* experiments in the mid-1980s showed photo-induced toxicity of HpD on Dunning R3327 rat prostate cancer cells [25]. Windahl *et al.* [26] reported the first PDT on two men with localized prostate cancer after TURP in 1990. They used HpD for the first case and Photofrin^{TM} for the second. Laser light of 628 nm was used to illuminate the prostatic cavity 48–72 h later. Five months later the PSA levels decreased from 10 and 6 ng/mL to 2.5 and 0.2 ng/mL, respectively. These photosensitizers have two main limitations: (i) they absorb light at a short wavelength, meaning that the light used cannot penetrate deep into the tissue; and (ii) they cause prolonged skin photosensitivity and patients should be protected from direct sunlight for several weeks [27].

These properties have encouraged many urologists to study new photosensitizers. Selman *et al.* [28] injected dogs i.v. with tin ethyl etiopurpurin dichloride. After 24-h they illuminated the prostate with laser light at 660 nm via two optical fibres placed in the prostate transperineally. The outcome was acute haemorrhagic necrosis of the prostate. 5-aminolaevulinic acid (5-ALA) has been used successfully to destroy Dunning R3327 tumour when sensitized by 630 nm laser light [27]. 5-ALA is not a photosensitizer, but metabolises to fluorescent protoporphyrin IX, which is the active photosensitizing agent. Nathan *et al.* [29] assessed the safety and the efficacy of the photosensitizer meso-tetrahydroxyphenyl chlorine in 14 men with recurrent localized prostate cancer after radiotherapy. Patients were injected with 0.15 mg/kg meso-tetrahydroxyphenyl chlorine i.v., then kept in low light. Three days later, several 19 G needles were placed in the prostate transperineally 1–2 cm apart, under TRUS or MRI guidance. Laser fibres were passed through the needles to deliver a diode-laser light at 652 nm. The initial results of this phase I study are encouraging; nine patients had a decline in PSA levels and five had no viable tumour on biopsy. Contrast-enhanced CT or MRI showed necrosis in up to 91% of the prostate cross-section. In terms of morbidity, four patients developed stress incontinence, four of seven had sexual impairment and none had direct rectal complications. Five patients had mild self-limiting skin photosensitivity.

A novel photosensitizer, palladium-bacteriopheophorbide WST09 (Tookad^{TM}) has been assessed in canine prostate, with promising results [30]. This second-generation photosensitizer acts on the vascular bed, causing endothelial damage, vasoconstriction and thrombosis. WST09 has a short half-life and absorbs light at longer wavelengths (763 nm). These features allow patients to resume normal activity rapidly, and result in larger lesions (3 cm) than the 1 cm diameter lesion caused by Photofrin^{TM} using a single interstitial fibre [30]. Gertner *et al.* [31] reported on the safety and preliminary efficacy outcome of WST09 in 24 patients with locally recurrent prostate cancer after radiotherapy failure. They concluded in this phase I study that Tookad-based PDT is easily delivered, safe and associated with minimal urinary or bowel complications. A phase II study is currently underway in Europe and Canada, evaluating the ability of the treatment to safely and completely eradicate residual cancer in similar group of patients.

MICROWAVE

The aim of this treatment method is to heat the whole prostate to a temperature of 55–70°C without damaging the rectum, bladder and urethra [32]. In the early 1980s, Yerushalmi *et al.* [33] were the first to propose the use of transrectal microwave hyperthermia to treat BPH symptoms. Several animal experiments were carried out evaluating prostatic and periprostatic tissue responses to various thermal doses [34]. Clinical trials showed that microwave thermoablation is safe and effective in treating men with BPH [35]. The first report of using microwave energy to treat prostate cancer was published in 1996 [36]. In this pilot study, five patients with locally recurrent prostate cancer after radiotherapy were treated with interstitial microwave therapy. Multiple proprietary microwave antennas were inserted into the prostate transperineally under TRUS guidance. The prostate was heated to 70°C for 20 min; 3 months later, four of the patients had a PSA level of <0.8 ng/mL. None of the patients had significant side-effects. In a slightly larger scale phase I/II study, Sherar *et al.* [32] showed that microwave thermotherapy was safe and with acceptable side-effects in 25 men with localized prostate cancer recurrence after radiation failure. The technique involved the transperineal insertion of five helical-tip antennae under TRUS guidance. The geometry of the prostate and the periprostatic structures was determined using TRUS; the temperature distribution and the thermal dose were then calculated. Six thermosensor probes were placed to monitor the temperature in the prostate and the surrounding tissues. Throughout the procedure, both the urethra and rectum were continuously protected from heat; cool water was circulated through a modified Foley catheter placed in the urethra, and the rectum was protected by injecting sterile saline into the space between the prostate and rectum, and by using a custom-designed cooling tube. Once the cooling systems were in place, power was delivered to the antenna manually, aiming at a target temperature of 55°C at the prostatic boundary for 15 min.

McCann *et al.* [37] reported that brachytherapy seeds had a negligible effect on the temperature distributions and rates of temperature rise in a phantom model. This suggests that the seeds are not a technical obstacle when testing interstitial microwave therapy to treat patients with localized prostate cancer recurrence after brachytherapy.

RITA

This is the most recently developed treatment method, and involves heating the tissue to 100°C with radiofrequency (RF) energy. Heat is produced by the molecular agitation and collisions induced by the RF electrical field, resulting in areas of coagulative necrosis.

For many years, RF has been used to treat various conditions, including osteoid osteomas and hepatocellular carcinoma [38]. Transurethral needle ablation of the prostate was the first application of RF in prostates, to treat BPH [39]. Two needles were inserted into the prostate under vision and low-frequency RF applied for 5.5 min per lesion. Numerous areas of coagulative necrosis were produced. This resulted in scar tissue formation and an improvement in BPH symptoms.

The size of the lesion depends on the total delivered energy, application time and tissue thermal conductivity. Too high an energy causes rapid tissue desiccation, leading to a rise in impedance at the tissue-needle interface. Therefore, the energy level should be appropriately balanced to produce the optimum results [38]. Heat loss by convection through blood flow has been shown to affect the lesion size considerably from one patient to another [40].

Zlotta *et al.* [38] reported on their initial experience of RF to treat localized prostate cancer in 15 men scheduled for radical prostatectomy. Under TRUS guidance, needle electrodes were placed into the prostate transperineally according to the predicted location of the tumour. The electrodes were connected to a RF generator with a supplying power of up to 50 W at a frequency of 480 kHz. Temperatures at the tip of the electrodes and in the rectum were continuously monitored using thermosensors. They concluded that RF can produce reproducible necrotic lesions in the prostate of ≈2 × 2 × 2 cm per needle. There were no complications and the procedure was well tolerated. The same group assessed the correlation between MRI and histopathological examination in 10 patients [41]. They revealed that RF lesions are predictable in size and location. These lesions were accurately visualized and verified using endorectal MRI, unlike on TRUS, where the changes appeared as transient hyperechoic 'snowflakes' that were not correlated with the zone of necrosis. This suggests that TRUS is not helpful in monitoring RF lesions.

CONCLUSIONS

Since the development of TRUS the opportunities for minimally invasive treatment options have increased. For these new techniques to become acceptable options they should have equivalent oncological outcomes and cause less morbidity than the current standard options.

Cryotherapy has been in clinical use for >15 years; the recent technological advances and technical modifications resulted in encouraging intermediate-term outcomes with acceptable morbidity (excluding potency), particularly in men with localized prostate cancer recurrence after radiotherapy.

HIFU is relatively a new technique and the initial results are less impressive, but the optimization of methods and refinement of techniques are still ongoing. For both cryosurgery and HIFU, longer-term data are required before final conclusions are made.

PDT, microwave and RITA have been studied only in animal models or small pilot studies. These techniques can induce tumour necrosis safely but their ability to eradicate prostate cancer effectively is still under investigation, and hence they should be considered experimental at this stage.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **HIFU**, high-intensity focused ultrasound; **PDT**, photodynamic therapy; **RITA**, radiofrequency interstitial tumour ablation; **RF**, radiofrequency; **5-ALA**, 5-aminolaevulinic acid; **DFR**, disease-free rate; **HpD**, haematoporphyrin derivative.