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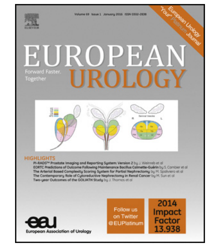

European Association of Urology

Platinum Opinion

Focal Therapy for Prostate Cancer: An "À la Carte" Approach

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1. Background and rationale

Over the past decade, enthusiasm regarding focal therapy (FT) for prostate cancer (PCa) has resulted in the development of several energy sources [1]. Newer energy modalities were designed to overcome the limitations of an existing technology but they often had a different profile of limitations and complications. Although the design of a single ideal energy modality is highly desirable, it may also be logical to find a meaningful pattern of clinical application for existing technologies on the basis of their merits.

Earlier FT energy modalities were scaled down from extensive whole-gland ablative experience for cryotherapy, high-intensity focused ultrasound (HIFU), and brachytherapy. Although there was a significant reduction in complication rates with focal ablation, the inherent differences for these modalities (mechanism of tissue damage, mode of delivery, limitations, and complication profile) could be further explored to potentially improve outcomes. There are limited clinical data for newer energy modalities developed primarily for focal ablation (laser and electroporation).

We have significant experience in using different energy modalities for PCa therapy (whole-gland ablation and FT) and propose a novel FT approach that we term an *à la carte* model. According to the limitations and complication profile, better selection of an energy modality depending on the PCa characteristics can improve oncologic and functional results, and represents a step towards personalized medicine.

2. What we know: FT energy modalities

2.1. Cryotherapy

The advantage of cryotherapy is easy accessibility via transperineal needles to all parts of the prostate including the anterior zone. Cryotherapy needs an extremely low temperature (–40 °C) for tumor cell lysis, which usually exists at least 5 mm inside the leading edge of the ice ball. The peripheral temperature is as high as 0 °C, which is ineffective for cancer cell damage (Fig. 1). Preclinical studies recommend advancement of the ice ball at least 10 mm beyond the intended border of tissue destruction. While treating posterior and apical tumors, the safety margin of 10 mm can entrap vital structures such as nerves and sphincters in the advancing ice ball. Collateral cellular damage can occur in normal tissue at –15 °C, and in neurovascular tissue autonomic dysfunction can occur at +3 °C and irreversible damage at –20 °C [2]. This is evidenced by erectile dysfunction rates of 90–100% following whole-gland cryotherapy and 10–35% following FT. Urinary incontinence rates dropped from 4–18% after whole-gland treatment to 0–1.5% after FT [1,3].

2.2. HIFU

HIFU offers more precise control over selecting the target area, and magnetic resonance fusion images are often used in defining the target location. This facilitates precise ablation of posteriorly located cancers, for which a cryotherapy ice ball with a 10-mm margin could cause collateral nerve damage. A specific limitation of HIFU is the dissipation of ultrasound waves over longer focal distances. When ablating an anterior-zone cancer, ultrasound waves need to travel over a longer distance to reach the focal point, and after a few initial passages the intervening prostatic tissue undergoes edema, which pushes the target area farther away (Fig. 2) [4,5]. Moreover, it has not been proved that HIFU ablation of apical tumors is incontinence-free. Some authors recommend a safety margin of 4–6 mm from the sphincter muscle because the apex region is subjectively defined by the treating urologist at the time of intervention,

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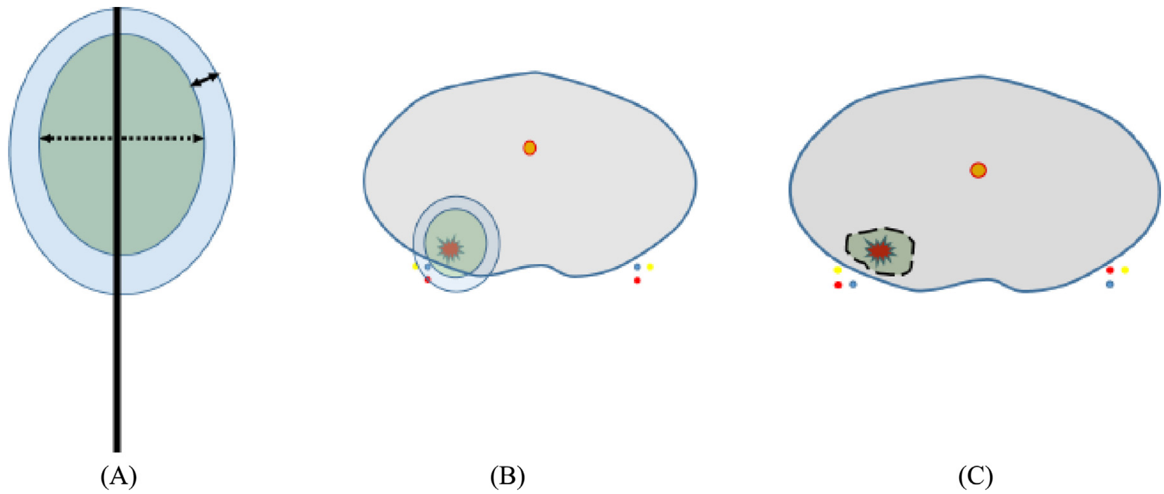

Fig. 1 – Graphical representation of the ablation volume with for cryotherapy and high-intensity focused ultrasound. (A) A cryo probe with an ice ball. The dotted arrows show the kill zone and the solid arrow shows the safety margin. (B) Cryoablation of a posterior lesion for which the safety zone for the ice ball extends beyond the prostatic capsule. (C) More precise control of the ablation zone with high-intensity focused ultrasound.

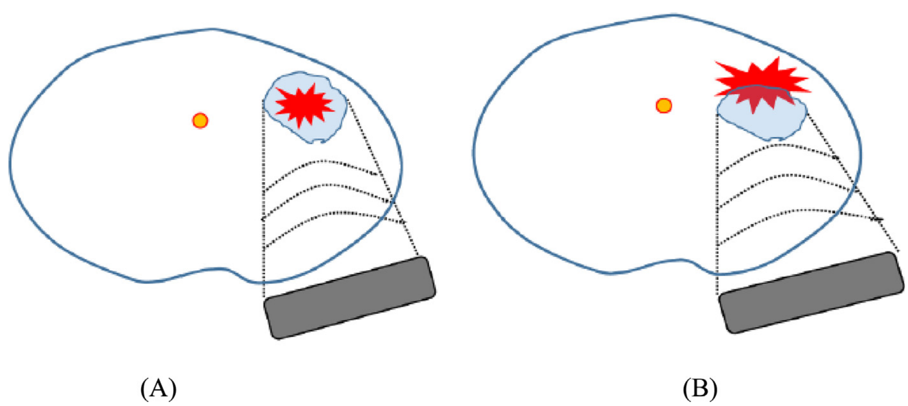

Fig. 2 – Graphical representation of anterior displacement of lesion during high-intensity focused ultrasound (HIFU). (A) Cancer within the HIFU target at the beginning of the treatment. (B) Prostatic edema along the HIFU pathway pushes the lesion anteriorly away from the target region.

which could result in inappropriate ablation of sphincters. The above reasons could explain the relatively low impotence rate of 28–66% for whole-gland HIFU, which further decreased to 5–15% for focal HIFU. Incontinence rates were for $<$1–35% for whole-gland HIFU and $<$1–10% for focal HIFU [6–8].

2.3. *Brachytherapy*

Although brachytherapy is widely used for whole-gland radiation, FT experience is very limited. The specific advantage of brachytherapy is the rapid fall-off in radiation dose and eventual effects over a few millimeters around the radiation seeds. Hence, only cancer cells adjacent to the seeds are killed, and vital structures adjacent to the prostate are spared [9]. The literature on brachytherapy reveals large heterogeneity in the dose used and in toxicity reporting (urethral and sexual toxicity). Although studies on oncologic outcomes after focal brachytherapy are awaited, the functional outcomes that have been published are promising. Incontinence rates are consistently very low at 0–1.3%, with only one study reporting 8%. However, incomplete treatment of the apex is a concern, and cancer control needs to be balanced with functional outcomes. Impotence rates range from 3.9% to 71% [1,9,10].

3. Our proposal: an à la carte model

While intensive research to identify an ideal energy modality for focal ablation is ongoing, available techniques can be utilized according to their merits to improve FT outcomes and limit side effects. We propose an à la carte model for FT according to intraprostatic tumor location.

3.1. *Posterior cancers*

The most common posterior tumors are in close proximity to the rectum and laterally to the nerves. HIFU appears have more advantages for this location considering the shorter focal distance and more precise contouring of the target area. Moreover, HIFU is the least invasive of all the available energy modalities, and hence should be offered when feasible.

3.2. Anterior cancers

The ease of accessibility via transperineal needles and established oncologic efficacy make cryotherapy more desirable for cancers in anterior locations.

3.3. Apical cancers

Both of the commonly used thermal-based energy modalities appear to induce varying degrees of sphincter damage. However, results for brachytherapy show superior continence rates, so this approach may be more appropriate for apical cancers very close to the sphincters.

It is important to consider these options when initial FT with one energy modality fails and in decision-making for salvage procedures.

4. Conclusions

The selection of an energy modality for FT according to intraprostatic cancer location is a novel concept that needs to be verified in terms of oncologic and functional outcomes in prospective comparative trials. Each energy modality appears to have a specific limitation or complication profile, and it is wiser to personalize FT according to the merits of each technique until we identify an ideal energy source.

Conflicts of interest: The authors have nothing to disclose.

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