A review of prostate cancer focal therapies in general practice

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Background
Focal therapy is an emerging treatment modality for prostate cancer that aims to spare patients treatment-related side effects including erectile dysfunction and urinary incontinence associated with surgery and radiotherapy, which are the current standards of care.

Objective
In this narrative review, the authors aim to provide a focused summary of prostate cancer focal therapies for general practice including an overview of key underlying oncological principles, existing treatment modalities, their functional and oncological outcomes, and follow-up after treatment.

Discussion
Focal therapy is being increasingly established in the management of localised prostate cancer and is a promising alternative to surgery and radiotherapy in carefully selected patients. With a growing body of evidence in support of focal therapy, its potential in the future of prostate cancer management is clear.

PROSTATE CANCER is the most diagnosed cancer in Australian men and the second leading cause of cancer-related deaths.[1] Prostate cancer can be localised or metastatic, the former referring to cancer confined to the prostate and immediately adjacent tissues such as the seminal vesicles, bladder, rectum or pelvic side wall without spread to distant organs. Treatment considerations include the patient's age, overall health and preferences, institutional capabilities and access, prostate cancer stage and grade, and consideration of treatment side effects. Based on serum prostate-specific antigen (PSA) levels and pathological factors, localised prostate cancer can also be risk stratified into low, intermediate and high risk, which correlates with cancer-specific mortality.[2] Intermediate risk prostate cancer, which confers a favourable survival profile, encompasses almost half (49.5%) of all prostate cancers.[3]

Low-risk prostate cancer, which requires histopathological diagnosis of International Society for Urological Pathology Grade Group 1 disease, is typically managed with active surveillance (AS).[4,5] It is considered clinically insignificant, with no known cases of metastases and an exceedingly low risk of local invasion or extra-prostatic extension.

Although AS is used in select cases of intermediate risk prostate cancer, the possibility of disease progression, local invasion and metastases confers the need for active treatment. High-risk prostate cancer encompasses an aggressive group of cancers that stand to benefit the most from active treatment. The significant risks of treatment failure, local and systemic recurrence, and death in high-risk prostate cancer patients precludes AS. Whole-gland therapies such as radical prostatectomy (RP) and radiotherapy with androgen deprivation therapy remains the treatment paradigm for intermediate- and high-risk prostate cancer patients. However, recent data have also shown that although these treatments reduce cancer progression and metastases development when compared to AS, they might not result in a mortality benefit at 15 years of follow-up.[5] Therein lies the potential of prostate cancer focal therapy (FT), a minimally invasive, prostate-sparing modality of treatment, which aims to maintain oncological outcomes while sparing patients the significant morbidity associated with whole-gland treatment such as erectile dysfunction, bowel dysfunction, urinary incontinence and decreased quality of life.

In this narrative review, the authors aim to provide an overview of prostate cancer FTs including the underlying oncological principles, existing FTs and their oncologic and functional outcomes to date, and patient selection.

Oncological basis for focal therapy

Prostate cancer multifocality has been observed to occur in up to 90% of cases.[6] It is hypothesised that genetic predisposition results in a field effect, upon which carcinogen exposure then leads to cancer precursor lesions. These precursor lesions, known as prostatic intra-epithelial neoplasia, then undergo independent clonal expansion to evolve into spatially separated, distinct cancer foci. Subsequently, synchronous cancer foci can have different genetic alterations and clonal origins, leading to differing degrees of biologic aggressiveness.[7]

FT therefore aims to treat the prognosis-determining index lesion while sparing healthy tissues and avoiding comorbidities that significantly affect quality of life. Widespread adoption of PSA testing[8] and the advent of accurate prostate cancer localisation with multiparametric magnetic resonance imaging (mpMRI) has greatly facilitated FT. PSA screening has led to an increase in the diagnosis of localised disease amenable to FT. This has also led to notable reductions in mean tumour volume from 4.7–6.1 mL to 2.1–2.6 mL at diagnosis,[7] and an almost 50% absolute decrease in metastatic prostate cancer at diagnosis.[9] Increasing availability and use of mpMRI has also allowed for accurate detection of clinically significant prostate cancer foci, with over 90% sensitivity enabling precise targeting of lesions.[10]

Overview of focal therapies

FT represents an emerging form of minimally invasive treatment for prostate cancer. It represents a collective term encompassing a wide range of energy modalities including high-intensity focused ultrasound (HIFU), irreversible electroporation (IRE), focal laser ablation (FLA), photodynamic therapy, cryoablation, brachytherapy, radiofrequency ablation and prostatic artery embolisation.[11] Of these energy modalities, the most frequently used and available FTs for prostate cancer in Australia include HIFU, cryotherapy, IRE and FLA.

High-intensity focused ultrasound

Initially developed for the treatment of benign prostatic hyperplasia, HIFU uses high-energy parabolic-focused ultrasound, which is absorbed and converted to heat, with subsequent tissue coagulation and coagulative necrosis. Mechanical effects of HIFU from the negative pressure of ultrasound waves also result in bubble formation within targeted cells, which cause cellular damage when the bubbles collapse.[12] HIFU, often a day-case procedure, can be performed using ultrasound devices designed specifically for prostate tissue ablation using a transrectal or transurethral approach.[13,14] Propensity-score matching between HIFU and robot-assisted radical prostatectomy demonstrated similar treatment-free survival at two years.[15] A 15-year follow-up demonstrated cancer specific survival rates of 95% and 89% for low- and intermediate-risk prostate cancer following HIFU, respectively.[16]

Cryotherapy

First described in the 1960s using transurethral and transperineally inserted liquid nitrogen cryoprobes guided by digital rectal examination,[17,18] cryotherapy involves ablation of tissues using freeze–thaw cycles that causes cell destruction via crystallisation of the extra- and intracellular fluid, cellular protein denaturation and secondary injury from the resultant inflammatory response.[19,20] In a study comparing cryotherapy and AS, cryotherapy appeared to increase time to radical therapy but did not appear to provide meaningful oncologic advantage, with 49% requiring radical treatment by 10 years. At a median follow-up of 85 months, metastasis-free and overall survival were 93.9% and 97%, respectively.[21]

Irreversible electroporation

Electroporation involves the creation of nano-sized pores in cell membranes through the application of an electrical current. Membrane permeabilisation can be reversible or irreversible.[22] Therapeutic electroporation began with the use of reversible electroporation to transiently increase cell wall permeability to facilitate the introduction of therapeutic agents into cells. IRE was initially seen as undesirable, as it resulted in cell death via apoptosis rather than an opportunity for treatment; however, in the early twenty-first century, the potential for IRE to treat cancer was explored through the principle that electroporation could be controlled to target cancerous tissue without compromising neighbouring structures.[22,23]

IRE systems involve a generator that delivers high-voltage electric current between electrodes placed transperineally, which surrounds the cancerous lesion. In an Australian study with five-years median follow-up, cancer-specific and overall survival was 100%, with failure-free survival rates of 83%. IRE was performed as a day-case procedure in this study, with patients discharged home with an indwelling catheter removed on day 5.[24]

Focal laser ablation

The use of laser energy for tumour ablation was first proposed in 1983 with the principle that laser light absorbed by tissues is converted to thermal energy, resulting in coagulation and tissue destruction.[25,26] FLA can be performed transrectally or transperineally with treatments delivered via a surgical diode laser. In a clinical trial for a novel, day-case cooled focal laser therapy (CFLT) system developed in Sydney, Australia, with three-years median follow-up, overall survival rates of 100% and failure-free rates of 88% were observed.[27]

Side effect profile of focal and whole-gland therapy

Whole-gland therapies are associated with side effects including erectile dysfunction, urinary and faecal incontinence. For select patients, treatment-related toxicities can be viewed as an unacceptably high cost when faced with whole-gland therapy.[28] Although the side effect profiles of various energy modalities for FT differ, functional data following these treatments consistently show very low rates of erectile dysfunction and incontinence (Table 1).[27]

Rectal injury or fistulas are also exceedingly uncommon (Table 1). Anorectal function, with parameters including anorectal pressures, capacity

Table 1. Focal therapies versus whole-gland treatments: A summary of the incidence of side effects

Side effect	Transrectal HIFU	Cryotherapy	IRE NanoKnife™	ProFocal-RX™	Radical prostatectomy	EBRT
Incontinence	2–7	0–5	5	0	30	3
Erectile dysfunction	2–7	0–50	0–35	5	80–85	50–74
Fecal incontinence	–	–	Nil	Nil	Nil	10
Urethral stricture	19	<1	2–5	Nil	1–3	10
Anatomy-limiting therapy	Yes	Yes	No	No	No	No

Data are presented as percentages.

EBRT, external beam radiotherapy; HIFU, high-intensity focused ultrasound; IRE, irreversible electroporation; Nil, therapies where the side effect has not been reported; –, the rate of the complication is not reported in the literature but is known to occur in some cases.

Table 2. An example of oncological follow-up protocols used in trials of existing focal therapies

Oncologic follow-up protocols	HIFU[36]	Cryotherapy[35]	IRE NanoKnife™[34]	ProFocal-RX™[27]
Prostate MRI	10–14 days post ablation and at 6 months	12 months' post treatment	Within 3–10 days and at 6 months	Within 72 hours post ablation
Surveillance biopsy	MRI-TRUS fusion-targeted in-field biopsy at 6 months	MRI-TRUS fusion-targeted and systematic saturation biopsy at 12 months	MRI-TRUS fusion-targeted in-field biopsy at 6 months	MRI-TRUS fusion-targeted in-field and random out-field biopsy at 3 months
PSA	1, 3, 6, 9 and 12 months	1, 3, 6 and 12 months	6 weeks, then at 3, 6, 9 and 12 months	3 months

HIFU, high-intensity focused ultrasound; IRE, irreversible electroporation; MRI-TRUS, magnetic resonance imaging-transrectal ultrasound; PSA, prostate-specific antigen.

and volume at first urge on anorectal manometry also did not significantly change after HIFU FT.[29,30]

Initial reported functional outcomes following FLA were positive, with no significant change in urinary or bowel symptoms or patient-reported quality of life at 3–6- and at 12-months' follow-up.[27]

Psychosocial impacts of treatment are important to consider. In addition to the emotional distress caused by adverse urinary, bowel and sexual side effects, whole-gland therapies also necessitate absence from work, particularly shortly after treatment.[31] By virtue of their minimally invasive nature, FTs offer a benefit in terms of return to work and physical activity with a single-centre longitudinal study of 25 men treated with FLA reporting a median return to work and usual physical activity after 1.0 and 3.5 days, respectively.[32] Additionally, many FTs can be performed as day-case procedures and this therefore reduces hospital length of stay.[14,24,27]

Treatment considerations and limitations

Patient selection is essential to achieve optimal oncological outcomes with FT. Selecting potential candidates for FT is based on patient and disease characteristics. Multiple expert panels have been convened on this topic. Consensus opinions on appropriate FT candidates include patients who have a greater than 10-year life expectancy, have biopsy results that are concordant with MRI findings, and have low- and intermediate-risk disease.[33] Specifics of treatment follow-up and assessment efficacy also vary between expert panels; however, common recommendations include the use of PSA, MRI and staged prostate biopsy[27,34–36] with follow-up time frames and biopsy protocols varying in existing trials (Table 2).

Current evidence does not support the use of FT with high-risk prostate cancer, where treatment failure is observed to be higher. In light of this, FT in patients with high-risk prostate cancer is only recommended in trial settings; however, high-risk stratification of prostate cancer encompasses a heterogenous group of disease characteristics. In time, a better stratification in the setting of FT might be discovered, allowing a wider use case and optimal patient selection for those with high-risk disease.

Anatomy is also a factor to consider when choosing between modalities of FT (Figure 1). For example, thermal energy sources such as cryotherapy or HIFU are not best suited for treating tumours located near the prostatic apex because of the

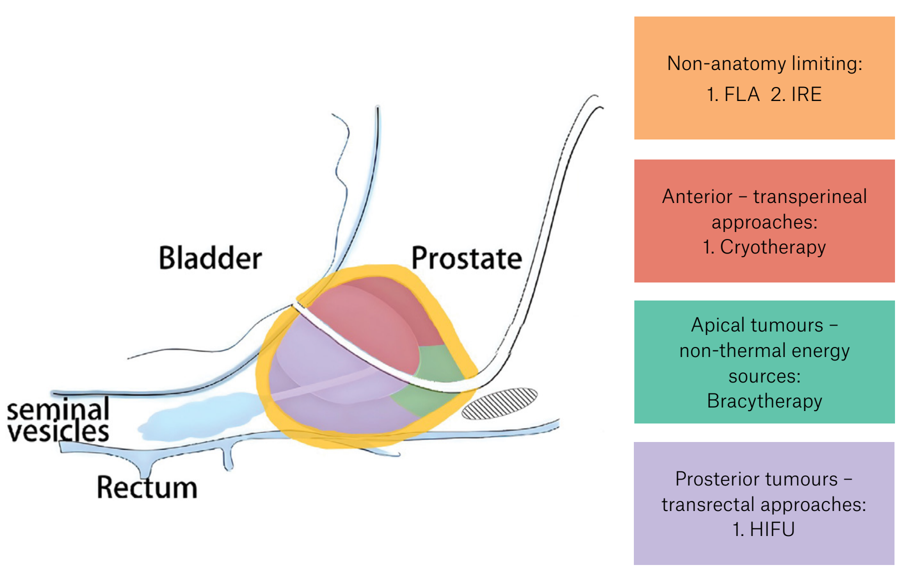

Figure 1. Anatomical considerations for focal therapy.

FLA, focal laser ablation; HIFU, high-intensity focused ultrasound; IRE, irreversible electroporation.

Adapted from Liu W, Kadier A, Shen D, et al. Combined MRI-TRUS fusion targeted and systematic biopsy versus systematic biopsy alone for the detection of prostate cancer: Protocol for a prospective single-centre trial. BMJ Open 2024;14(3):e080593. doi: 10.1136/bmjopen-2023-080593, with permission from BMJ Group under Creative Commons CC BY-NC 4.0 licence. Modifications include colour-coding regions of the prostate and addition of a table of focal therapies on the right-hand side of the image.

risk of damage to the urethral sphincter.[37] Anteriorly located tumours are more readily accessible by transperineal treatment approaches such as FLA and cryotherapy, whereas posteriorly located tumours might be more easily reached transrectally, such as with HIFU.[37]

Beyond anatomical and oncological considerations, other factors might be involved when selecting patients for FTs. Patients with contraindications to MRI might be unsuitable for certain FT protocols that rely on MRI-based surveillance for follow-up. Transrectal treatments such as HIFU might not be suitable in patients with significant anorectal disease or patients at risk of fistulae formation such as inflammatory bowel disease or previous anorectal surgery.[14,27]

It is important to acknowledge that FT as a treatment modality remains an emerging technology and is not yet accessible through the Australian public health system. Prospective and comparative trials of FT against standard of care whole-gland treatment, while underway, are not currently available, nor are there any long-term follow-up outcomes for several energy modalities. Additionally, to improve oncological outcomes, areas that require further research include advancements in imaging and management of treatment failure. Although MRI demonstrates high sensitivity in diagnosing index, large and high-grade lesions, poorer sensitivity can be observed with secondary lesions, which might be clinically significant.[38] FT treatment failure can also occur, and optimal salvage treatments, which might include re-treatment with FT or salvage whole-gland treatments, also remain unclear.

Conclusion

FT is a modality of treatment that has become increasingly established in the management of clinically localised prostate cancer. It is a promising alternative to whole-gland therapies in selected patients, particularly those with intermediate-risk prostate cancer. Long-term data from randomised trials are needed to allow the integration of FTs into standard-of-care prostate cancer management.

Key points

- Historically, prostate cancer treatment involved whole-gland therapy (RP and radiotherapy). Whole-gland therapy is associated with significant adverse effects including erectile dysfunction and urinary incontinence.
- The prognosis of prostate cancer is driven by an index lesion, defined as the tumour with highest grade and size.
- FTs encompass multiple energy sources including HIFU, IRE and FLA that are used to treat index lesions, with the aim of maintaining functional outcomes without compromising oncological outcomes.
- At present, FTs in Australia are only accessible through the private healthcare system or in clinical trial settings, but not through the public healthcare system.
- Knowledge of FTs as an emerging alternative to whole-gland therapy for appropriately selected patients with prostate cancer, available energy modalities and potential adverse effects are valuable for general practitioners (GPs) managing patients with prostate cancer. This will facilitate initial discussions regarding treatment, and to identify potential side effects or psychosocial distress during follow-up. GPs are also vital in ensuring patients adhere to surveillance protocols and specialist appointments and are not lost to follow-up.

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