





HANDBOOK OF **FOCAL THERAPY FOR PROSTATE AND RENAL CANCER**

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3 Focal therapy as an alternative treatment for prostate and renal cancer

Christopher Hartman, Sandeep Gurram, Ardeshir R Rastinehad

Introduction

Diagnosis and treatment of genitourinary cancers has evolved rapidly in the past two decades. The advent of prostate specific antigen (PSA) testing has allowed for earlier diagnosis of organ-confined prostate cancer (PCa), and the increased use of computerized tomography (CT) imaging has allowed for earlier detection of renal masses (Volpe et al. 2004). Additionally, minimally invasive surgical techniques have allowed the urologist to progress from treating both neoplasms of the prostate and kidney with large, open surgeries, to focused surgical resection. More recently, renal and prostate ablative techniques have emerged as focal therapies for treating these cancers while reducing the morbidity associated with surgical extirpation. The following discussion examines the progression from surgery aimed at radical whole-organ removal to renal and prostate ablative techniques and how these therapies can become recognized as mainstream treatments for these malignancies.

The progression from surgery to renal ablative techniques

Earlier diagnosis of small renal masses has allowed the standard of care for these tumors to progress from radical nephrectomy to partial nephrectomy. This has been made possible not only due to the earlier diagnosis of small renal masses that are amenable to focused resection, but also because of the understanding of the benefits of partial nephrectomy as compared to radical nephrectomy. These benefits include greater preservation of renal function, greater overall survival, and delayed or averted dialysis in patients with bilateral renal masses or a renal mass in a solitary kidney (Thompson et al. 2008; Zini et al. 2009). Although the goal of preserving renal function and avoiding dialysis is important in planning surgical approach, it is paramount to first ensure good oncologic outcomes. To this end, studies have demonstrated that the oncologic outcomes of partial compared to radical nephrectomy are similar, arguing that a partial nephrectomy should be attempted for all patients with small renal masses that are amenable to nephron-sparing surgery (Lau 2000; Leibovich et al. 2004). Additionally, studies have shown that partial nephrectomy results in > 95% cancer-specific survival in these patients (Gill et al. 2007).

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Disadvantages of partial nephrectomy as compared to radical nephrectomy include the greater potential for postoperative complications, as well as the greater surgical skill required to perform nephron-sparing surgery. This is particularly evident in the comparison of laparoscopic radical versus partial nephrectomy, and results in fewer surgeons who are able to perform the procedure. Postoperative complications, including urinary leak, significant bleeding, renal arteriovenous malformations, and pseudoaneurysms are almost exclusively encountered after partial nephrectomy as compared to radical nephrectomy. These complications have led some to propose that in cases in which a patient has a relatively complex renal mass and a normal contralateral kidney, the benefits of a partial nephrectomy may be outweighed by the complications.

Alternatively, renal ablative techniques offer a minimally invasive approach to address low-stage renal tumors. Two principal techniques have emerged as effective renal-ablative procedures – cryoablation and radiofrequency ablation (RFA). Other ablative therapies including stereotactic radiotherapy, microwave therapy, irreversible electroporation, and laser ablative therapies have all been utilized, though to a lesser degree (Castro 2013; De Meerleer et al. 2011). Proponents of renal ablative procedures advocate that these techniques offer less morbidity to the patient than extirpative techniques while still providing adequate treatment to the patient (White 2011).

Renal cryoablation employs an argon gas-based system to freeze renal tumors and effect cell death. This may be achieved either laparoscopically with direct vision of the tumor and ultrasonographic guidance, or via percutaneous access and CT, magnetic resonance imaging (MRI), or ultrasonographic guidance. The critical temperature below which renal tumor necrosis effectively occurs is at approximately -40^0C, and modern cryoprobes typically freeze tissues to -130^0C or lower. During freeze–thaw cycles, direct cellular membrane damage occurs via the formation of intracellular ice crystals; while extracellular ice formation results in an osmotic gradient that promotes fluid shifts, cellular membrane rupture, and cell death. Conversely, thaw cycles result in reperfusion injury that further produce tumor necrosis. Whether performed via a laparoscopic or percutaneous approach, real-time monitoring is imperative to confirm that the zone of ice ball formation extends at least 5–10 mm from the margin of the tumor. This ensures that temperatures within the tumor are adequately low to result in cell kill (White 2011; Gill et al. 2000).

Radiofrequency ablation, alternatively, employs alternating radiofrequency currents between 450 and 1200 kHz to effectively generate heat and kill tumor cells. Ionic friction is created within tissues exposed to radiofrequency waves between these frequencies, and results in cellular agitation and heating. At temperatures greater than 60°C, irreversible cellular damage occurs via coagulative necrosis. Thus, in RFA procedures, tissues are typically heated to a mean of 105°C, ensuring adequate cell kill. As opposed to cryoablation and

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the formation of an ice ball, RFA does not result in significant tissue contrast differences on imaging. This prevents the use of real-time image guidance to monitor the zone of cell kill. For this reason, the ablation zone must be estimated during RFA. Typically, a zone approximately 5–10 mm beyond the renal tumor is preferred to ensure adequate tumor destruction. Like cryoablation, RFA is possible via either a percutaneous or laparoscopic approach (White 2011; Gill et al. 2000). **Table 3.1** shows a comparison between cryoablation and RFA for renal neoplasms.

Advantages of ablative focal therapy for renal tumors include preservation of renal function, reduced morbidity, shorter recovery times, and fewer complications as compared to extirpative surgical procedure (Desai 2005). This is especially relevant for patients with small renal masses who are otherwise unable to undergo definitive treatment, such as those with significant comorbidities precluding surgical intervention. Additionally, local ablative techniques are generally technically easier to perform than extirpative procedures and allow patients to return to work and normal activities as soon as the day following the procedure.

Disadvantages of ablative focal therapy for renal masses stem from the inability to remove tissue, whether benign or neoplastic. The recent American Urological Association guidelines on follow-up for clinically localized renal neoplasms recommend that all patients have a diagnostic biopsy prior to undergoing treatment (Donat et al. 2013). Up to 20% of small renal masses may be benign, and thus the lack of tissue for pathologic analysis in ablative procedures prohibits a tissue diagnosis of cancer from being made (Remzi et al. 2006). More importantly, oncologic efficacy of ablative procedures has not been definitely established. A number of studies have been performed, however, with cancer-specific survival demonstrated to be 95.2% for cryotherapy and 98.1% for RFA (Novick et al. 2015). Additionally, metastatic recurrence-free survival has been found to be relatively good at >95% for stage 1 renal masses, and was not found to be

Table 3.1 Comparison between cryoablation and radiofrequency ablation for renal tumors

Parameter	Cryoablation	Radiofrequency ablation
Temperature change	Freezing	Heating
Method of cell kill	Argon gas-based freezing	Alternating radiofrequency currents between 450 and 1200 kHz
Temperature at which cell kill occurs	-40°C	60°C
Typical temperature employed	-130°C	105°C
Access to tumor	Laparoscopic or percutaneous access	Laparoscopic or percutaneous access
Monitoring	Possible via ultrasound visualization of ice ball	Not possible

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significantly different from that of extirpative procedures (Novick et al. 2015). Nonetheless, a thorough discussion of the risks and benefits of focal therapies should be undertaken with patients contemplating local ablative procedures for renal masses.

Guidelines on the treatment of kidney cancer

Both the American Urological Association (AUA) and the National Comprehensive Cancer Network (NCCN) have outlined guidelines for the treatment of renal neoplasms (Novick et al. 2010; Motzer RJ et al. 2015). After a thorough evaluation to exclude sites of distant metastases, treatment decisions should proceed based on renal tumor characteristics as well as patient-based factors. Generally, in patients with a relatively short life expectancy, and especially in those unfit for surgical intervention, more invasive treatment options should be dismissed in favor of less morbid options. Currently accepted options in the management of renal neoplasms include surveillance, tumor ablation, focused tumor resection, and radical nephrectomy.

Both the AUA and NCCN guidelines recommend an initial history and physical exam, as well as dedicated abdominal imaging in the form of a CT scan or MRI in patients with a suspected renal neoplasm. In patients with exceedingly large renal masses not amenable to localized treatment, such as those greater than 7 cm in diameter (≥ T2 renal masses), radical nephrectomy remains the gold standard of treatment in patients who are able to undergo surgery. In patients with tumors that are less than 7 cm in diameter (T1a and T1b tumors), a myriad of options exist for treatment.

The AUA guidelines on the management of T1 renal masses divide patients into one of 4 categories: those with T1a (primary tumor ≤ 4 cm in diameter) tumors and who are healthy, those with T1a tumors who have significant comorbidities and an increased surgical risk, those with T1b (primary tumor > 4 cm but < 7 cm) tumors and who are healthy, and those with T1b tumors who have significant comorbidities and an increased surgical risk. They also classify treatment options as (1) the standard of care, (2) alternative recommendations, and (3) other options for treatment.

Standard care for patients with T1a tumors who are healthy is localized surgical resection with partial nephrectomy. This may be accomplished via either an open or laparoscopic approach based on surgeon and patient preference as well as tumor location. Alternatively, a radical nephrectomy may be elected in patients with tumors that are technically not amenable to partial nephrectomy, such as those that are predominantly endophytic, abutting or entering the collecting system, or in a location that is difficult to access. Radical nephrectomy is presented as an alternative standard of care. In these patients, the AUA guidelines recommend as an option for treatment either cryoablation or RFA, after a thorough discussion of the risks and benefits of these

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procedures. Active surveillance (AS) may also be considered as an option in patients not wishing to undergo surgery.

In patients with T1a tumors who are poor surgical candidates and who have significant comorbidities, the AUA guidelines list either radical nephrectomy or partial nephrectomy as standard of care. The guidelines list local ablative procedures as an alternative recommendation in patients who wish to undergo treatment but who are unfit to undergo surgical resection. Additionally, in patients with significantly reduced life expectancy, AS is listed as an alternative recommendation in order to avert the morbidity associated with surgical procedures.

In patients with T1b tumors who are healthy, the AUA guidelines present either partial or radical nephrectomy as the standard of care based on contralateral renal function and primary tumor characteristics. In patients who are unwilling to undergo surgery, the guidelines recommend the option of discussing ablative techniques as an alternative to surgery, though this may be suboptimal in a healthy patient and result in greater rates of local recurrence.

In patients with T1b tumors who have significant comorbidities and are poor surgical candidates, the AUA guidelines present radical nephrectomy as standard of care. In patients with a poorly functioning contralateral kidney, a partial nephrectomy may be considered and is listed as an alternative recommendation, though it can be associated with increased morbidity in this patient population. AS is an additional recommendation for care, especially in patients with a limited life expectancy. The AUA guidelines recommend ablative techniques as an option in patients who wish to undergo treatment but who are unfit for surgery (Novick et al. 2015).

In contrast to the AUA guidelines, the NCCN guidelines do not stratify recommendations based on surgical risk. For T1a tumors, possibilities for treatment include partial nephrectomy, which is the preferred option, radical nephrectomy in cases in which a partial nephrectomy is not feasible, cryoablation or RFA in patients who are not surgical candidates, or AS in selected patients, such as those with a high surgical risk. Options for treatment of T1b tumors are limited to partial or radical nephrectomy. In patients for whom AS or ablative techniques are being considered, the NCCN guidelines recommend considering a biopsy of the renal mass in order to confirm malignancy and further guide treatment, though a biopsy is not necessary prior to surgical extirpation (Motzer et al. 2015).

Surveillance of patients who have undergone focal therapy for renal tumors

Though recommendations for follow-up in patients who have undergone focal therapy for renal tumors is widely variable amongst different groups, a number of key components exist, including the need for repeat abdominal imaging after therapy as well as interval history

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and physical examinations. One of the most extensive sets of guidelines for surveillance has been defined by the NCCN. A brief description of these guidelines follows.

In patients with surgically resected tumors that are confirmed to be benign, ongoing surveillance is generally unnecessary. Alternatively, for patients with a confirmed neoplasm or in patients who have undergone ablative procedures and do not have a tissue diagnosis, different surveillance protocols are recommended.

The NCCN guidelines recommend follow-up with a history, physical exam, and comprehensive metabolic panel every 6 months for the first 2 years after treatment, then annually up until 5 years in all patients who have undergone a partial nephrectomy or ablative procedure. Among patients who have undergone either cryotherapy or RFA, abdominal imaging in the form of a renal mass protocol CT scan or MRI is recommended within 3–6 months after the procedure. Thereafter, a CT scan, MRI, or renal ultrasound (US) should be obtained annually to complete 5 years of follow up in these patients. Chest imaging, such as a chest X-ray or CT scan of the chest, should be performed annually for 5 years. In patients who demonstrate either new enhancement in the ablated tumor, progressive growth of the tumor, or new nodularity in the treated zone, a repeat biopsy should be performed.

Among patients who were treated with a partial nephrectomy, a baseline CT scan, MRI, or US should be obtained within 3–12 months of surgery. If this initial imaging study is negative for residual disease or recurrence, one of the three previous imaging studies may be performed at yearly intervals, based on surgeon preference and individual patient risk factors, for a total of 3 years. Chest imaging should also be performed at yearly intervals for a total of 3 years. In any patient who has previously been treated with focal therapy, pelvic and head imaging, as well as bone scans should be performed as clinically indicated (Motzer et al. 2015).

Current difficulties with prostate cancer

For some time, urologists were plagued by the difficulties of detecting clinically relevant PCa. The lack of a highly sensitive and specific biochemical marker have led some to believe that patients were being over-biopsied and consequently over treated. There was an overriding belief that prostate cancer by its very nature was a heterogeneous disease and that, instead of developing from a local focus, arose insidiously throughout the entire gland.

Since this time, significant strides have been made in understanding both the natural history of PCa and the risk factors predisposing to its development. These developments ultimately have led to sophisticated risk calculators which assist the urologist in making a much more evidence-driven decision for a higher yield diagnostic biopsy. However, patient specific information regarding tumor volume, extra-prostatic extension, and lymph node involvement are limited to

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statistical probabilities, which may limit interpretations and planning for oncologic outcomes.

The latest difficulty lay with inadequacies of the transrectal ultrasound (TRUS) guided biopsy and its inability to effectively obtain a representative sample of the tissue of concern. This led to the development of multiparametric MRI, which has significantly improved cancer detection and diagnostic yield with MRI targeted biopsies (Maxeiner et al. 2015; Meng et al. 2015; Salami et al. 2015). Currently, patients with localized PCa are forced to choose between whole gland therapy and AS or watchful waiting. Now, with the ability to effectively and consistently localize clinically significant prostate cancer, there is a concerted effort to explore providing localized therapy in order to preserve prostate tissue without sacrificing oncologic outcome.

In summary, there is evidence that PCa is over treated and over diagnosed. Focal therapy appears poised to fill a gap in the treatment algorithm between patients who are candidates for AS and others requiring whole gland therapy. One limitation is that focal therapy needs to demonstrate an oncologic impact on cancer-specific survival. When patients with low-grade and low-volume disease are selected for treatment, it will be difficult to demonstrate efficacy. For focal PCa therapy to become an accepted part of the treatment algorithm, we must address three specific areas:

- First, improvements in initial clinical staging will allow the physician to set specific inclusion criteria for patients considering focal therapy, which should include patients with clinically significant disease
- Second, evaluation and optimization of the treatment approach must be undertaken
- Third, an acceptable post-treatment follow-up schedule in patients undergoing focal therapy should be determined, which can include quality of life questionnaires and cancer specific outcomes

Rationale behind focal therapy for prostate cancer

As screening methods have become more sophisticated, a shift in the patient population being treated for PCa has occurred (Huland and Graefen 2015). More men with less advanced disease are being discovered considerably earlier, yet they are being treated based on the knowledge accrued at a time when men had a significantly worse disease burden. This knowledge has led physicians to make more informed decisions in regards to whole gland therapy, but now more patients with PCa are being discovered at an earlier stage. These patients are seeing similar risks and morbidities as their counterparts with more advanced disease, but with decreased benefits in treating their low-risk disease. It is at this stage now where patients are looking toward AS for these lower risk diseases. However, there still remains a large gap between AS and whole gland therapy. Focal therapy may offer a middle ground, affording the low-to-intermediate risk patient

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a lower treatment morbidity while providing adequate oncologic outcomes.

Difficulties with current prostate biopsies

The 12 core TRUS biopsy is the current standard for prostate biopsies, although there are significant limitations, including high false-negative rates, incorrect risk stratification, detection of clinically insignificant disease, and the need for increased sampling. The TRUS biopsies are random biopsies and thus are limited in efficacy by the fact that PCa is often heterogeneously interspersed between prostatic stroma. This property has led to the fact that these biopsies can under-sample and not detect up to 30% of clinically significant cancer on initial biopsy. This under-sampling rate is multiplied in larger glands, presumably due to the decreased ratio of tissue sampled to tissue present (Serefoglu et al. 2012).

Another concern is the fact that standard TRUS biopsies may improperly risk stratify patients. It is presumed that this is secondary to the idea that the portion biopsied may only be at the periphery of the mass and therefore may not accurately portray a representative sample of the tumor. Conti et al. demonstrated that in only 62% of patients did the Gleason grade on biopsy correlate with that on prostatectomy specimen, and that 28% of patients with Gleason 6 disease on biopsy were upgraded to grade 7 or greater (Conti et al. 2009). This has far-reaching implications given that a considerable number of patients with Gleason 6 disease on prostate biopsy are now opting for AS. The ability to accurately stratify these patients will improve the overall success of these protocols by removing those who have more advanced but previously hidden disease.

In order to overcome sampling error, template-mapping biopsies have been proposed as a solution (Valerio et al. 2014). However, increased random sampling has also led to increased detection of clinically insignificant cancer. A more controversial issue is the method in which repeat biopsies are taken. The use of extended or saturation biopsies by their very nature can increase detection of smaller cancers, but also carry with them the inherent risk of detecting clinically insignificant tumor (Ukimura et al. 2013).

Multiparametric MRI and focal therapy for prostate cancer

Unlike standard TRUS biopsies in which sonographic characteristics do not normally differentiate between a potential cancerous lesion and normal prostate tissue, multiparametric MRI (mpMRI) may be able to more accurately detect clinically significant areas of PCa, such as those of a high Gleason score (Salami et al. 2015). When MRI-guided biopsies are performed, they can substantially enhance cancer detection rate as well as the rate of detecting clinically significant PCa. The use of mpMRI in conjunction with a targeted biopsy has increased the

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detection rate of clinically significant PCa in patients with MR visible lesions (Rastinehad et al. 2014; Wysock et al. 2014). This alleviates the limitations associated with mpMRI alone, including poor sensitivity and specificity with lesions <5 mm and Gleason pattern 3 disease (Turkbey et al. 2011). Thus, MRI-guided fusion US biopsies have the ability to decrease false negative rates and improve accuracy with risk stratification (Bjurlin et al. 2014).

Patient selection and risk stratification for focal therapy

Many consensus statements have been made in order to determine who is the appropriate patient to receive focal therapy. Originally a conservative approach was used, and only patients with low volume and low risk cancer were considered candidates. However, newer consensus statements have shifted over to treating intermediate-risk patients. They state that results so far are showing promise and that treatment of low-risk, low volume patients would be overtreatment for a group that is best served with AS (van den Bos et al. 2014).

Others have argued that patients who qualify for AS are prime candidates for focal therapy. Generally, patients who have risk factors for recurrence after radical therapy are excluded from these programs. Men without these risk factors have more favorable outcomes and thus would benefit from some form of therapy. Many of these men also decided to opt into the AS protocols because they fear the side effects of radical therapy. Focal therapy offers these men definitive treatment with a significantly decreased side effect profile, which tailors to this specific patient population (Ahmed et al. 2007).

Focal therapy for prostate cancer

Focal therapy, in the past, has been deemed inappropriate for PCa treatment because of the overriding belief that this malignancy is multifocal and therefore cannot be adequately addressed with focal ablation or resection. However, inspection of whole-gland post-surgical specimens has shown that there is a significant portion of disease that is confined to a local area. Mouraviev et al. have shown that in their analysis of 1184 radical prostatectomy specimens, 19.2% of patients had tumor completely localized to one-half of the prostate. Therefore, with hemiablation, approximately 1 out of every 5 men in that series would have had the entirety of their PCa treated (Mouraviev et al. 2007).

Further investigation has shown that the disease can be localized to an even more specific focal entity, the index lesion. The index lesion theory refers to the site of the largest tumor focus and is the primary entity which influences disease progression and other characteristics. Further support for this model shows that non-index lesions tend to be smaller, better differentiated, and less likely to have a prognostic impact (Karavitakis et al. 2011). These non-index lesions tend not to

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play a strong role in the progression of disease, while progression of the index lesion correlates with biochemical failure (Wise 2002). The presence of this focal disease-driven entity empowers focal therapy to be effective, provided that the lesion can be accurately localized. However, one should maintain objectivity when basing therapy decisions on the index tumor theory, which is still in its infancy and requires further scientific validation. The newer aforementioned advancements in multiparametric MRI and biopsy schemes have created the path to accurate discovery of these lesions. Currently, the standard of care to both localize the index lesion and to map the entirety of the prostate is by use of transperineal biopsy. The use of the 5 mm interval brachytherapy template allows for accurate prostate three-dimensional mapping though more protocols are now endorsing multiparametric MRI as a viable option in localizing disease (Ahmed et al. 2007; Donaldson et al. 2014). **Table 3.2** offers a review of the advantages and disadvantages of focal therapy for prostate cancer.

Cryotherapy as a treatment for prostate cancer

Cryotherapy of the prostate utilizes a brachytherapy-like stepper that contains a grid template. This allows cryoprobes to be placed through the perineum under ultrasonic visual guidance. Similar to renal cryotherapy, pressurized argon gas is transmitted through a cryoprobe for cooling. The size of the ice ball can be adjusted based on the number and location of cryoprobes used. In order to assess the extent of the ice ball, thermocouples can be placed in the mid gland, by Denonvilliers fascia, by the neurovascular bundle, and at the level of the external sphincter. The thermocouples at the mid gland and the neurovascular bundles are used to ensure that the temperature is at least less than –40°C while those at the external sphincter and Denonvilliers fascia are used to prevent incontinence and rectourethral fistulas. A flexible cystoscopy is performed to assess the urethra and the bladder neck for misplaced cryoprobes and a urethral warming catheter is placed to prevent urethral sloughing. Two freezing cycles are performed and slow thawing is suggested due to increased cell death. Allowing the ice ball to extend 2–4 mm laterally into the periprostatic tissues allows for adequate necrosis of prostatic tissue (Miller 2011).

Advantages of cryotherapy include its minimally invasive nature, it bypasses the need for radiation or surgical risk, it can be used in a focal

Table 3.2 Advantages and disadvantages of focal therapy for prostate cancer

Advantages	Disadvantages
Organ sparing	No final whole gland pathology or disease staging
Can be used as salvage therapy	Complicated salvage therapy
Minimally invasive	No established surveillance method
Rapid recovery postoperatively	Mixed oncologic outcome results
Intermediary between radical therapy and surveillance	Should not be used on high risk patients
Can be performed multiple times	

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manner, it can be used as salvage therapy, and it can be performed multiple times. A major disadvantage is that there is no consensus definition for biochemical recurrence. Currently, the American Society for Therapeutic Radiology and Oncology (ASTRO) and Phoenix criteria are generally used, though they are poor substitutes for ablative therapy (Catalona 2011).

The use of focal cryotherapy has been studied in two trials assessing the use of hemiablation for presumed unilateral disease. Both trials showed promising results with 92–94% stable PSA via ASTRO criteria and approximately 90% potency rate. Both recruited patients from a specially selected population of patients who had disease limited to one lobe (Bahn et al. 2006; Onik 2008). Though there are many limitations to each of these studies, the results are promising enough to warrant further investigation.

HIFU as a treatment for prostate cancer

High intensity focused ultrasound (HIFU) has also emerged as a new technique aimed for localized therapy for PCa. Like other focal therapeutic strategies, it has considerably decreased morbidity compared to whole gland resection and it has proven itself to have acceptable short to intermediate-term cancer control. The mechanism of tissue destruction through HIFU involves both hyperthermic damage and acoustic cavitation (Cordeiro 2012). An ultrasonic transducer with a parabolic configuration allows for focusing of powerful ultrasonic waves to a focal zone approximately 3–4 cm from the transducer. This energy intense area undergoes coagulative necrosis as the surrounding tissue can be heated to over > 80°C, much greater than the > 43°C needed for protein denaturation. This small area of intense energy can be used for focal gland ablation or can be extended to whole gland therapy by focusing on multiple points to cover the entirety of the gland (Catalona 2011; Cordeiro 2012). Cavitation effect also imparts a significant release of energy at the sonicated tissue. As microbubbles are affected by the ultrasound wave, they oscillate and collapse, spreading energy to the surrounding tissue.

There are some distinct advantages of HIFU, one of which is the ability to permit both localized and whole gland therapy with minimal energy spread to tissue outside the treatment map. Once the physician outlines the area of interest, the automated system will focus the beam and progress to non-adjacent areas, therefore minimizing the effect of conductive heat spread outside of the treatment map. Much like other localized treatment therapies, HIFU can be used effectively as both a repeat therapy and as salvage therapy in patients who underwent radiation therapy. Another advantage is the low rate of rectal injury with active cooling of the rectal mucosa with cooled water.

The most important disadvantage is a lack of ability to monitor success and recurrence with HIFU. Much like cryotherapy, those who practice HIFU have become accustomed to using the ASTRO criteria

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to assess treatment success and recurrence. The consensus panels who created both the ASTRO and Phoenix criteria have expressly stated that these guidelines are not to be used as criteria for thermal ablative therapies. Another variable that has been used to assess efficacy was a post-treatment biopsy, however this is plagued by the same inadequacies as mentioned previously, such as high false negative rates. What has been shown is that lower risk groups have significantly improved outcomes in these short to intermediate-term follow-ups. Currently, the INDEX trial, an intermediate-term follow up, multicenter trial, is underway. It proposes to use HIFU to treat the hemigland containing the patients' index lesions, and will have a follow-up period of 36 months.

The use of emerging modalities in the treatment of prostate cancer

Both HIFU and cryotherapy have been available for clinical use for the last 15 years. Newer developments in the field are now emerging and include radiofrequency ablation, irreversible electroporation, laser therapy and photodynamic therapy. What is most important to note is that many of the studies performed assessing the efficacy of these modalities are meant to assess them as a replacement to whole gland techniques. Patients with high-volume and high-grade disease will not benefit from these modalities, as oncologic efficacy still remains inferior to whole-gland extirpative techniques. Instead, these modalities offer focal zones of therapy that allow for decreased genitourinary morbidity while effectively treating the targeted area. Therefore, newer studies need to be performed in low to intermediate risk patients who will benefit from both decreased morbidity of partial gland therapy and decreased anxiety and burden of an AS regimen, while retaining acceptable oncologic outcomes.

Difference between renal and prostate focal therapy

When considering focal therapy, renal tumors are considerably different from PCa. They are more easily and accurately localized and have a lower false negative rate of detecting a mass. In addition, long term oncologic and survival data are available for both open and minimally invasive techniques of partial nephrectomies, and were deemed satisfactory. Therefore, the next step in management was to create further minimally invasive techniques to target renal masses. PCa has some marked differences in comparison to renal cancer, the most important of which is accurately localizing and stratifying the tumor. It is unclear whether the significant number of AS patients who later seek whole gland therapy is secondary to disease progression or under-staging on initial prostate biopsy. Under-sampling and under-staging errors with current biopsy techniques can falsely decrease the efficacy of both focal therapy and AS and undermine their true degree of oncologic efficacy. For focal therapy to evolve into a mainstream

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FOCAL THERAPY FOR PROSTATE AND RENAL CANCER

Focal therapy has emerged as a preferred treatment choice thanks to its highly targeted action which minimizes damage to surrounding tissue, reduces unwanted side effects and improves clinical outcomes.

Handbook of Focal Therapy for Prostate and Renal Cancer provides an accessible overview of the ablation methods used to treat cancers of the prostate and kidney. It describes the various techniques, the selection criteria, benefits and limitations of each one, and offers advice on the management of side effects.

The book is arranged into three sections; the first covers the principles and mechanisms of focal therapy while sections two and three discuss its clinical application in the treatment of prostate and renal cancer, respectively. Written in a practical, clinically-oriented style, *Handbook of Focal Therapy for Prostate and Renal Cancer* is the ideal reference for urologists, radiologists and radiation oncologists wishing to employ the latest focal therapy techniques in the care of their patients.

- Highlights established technologies such as cryoablation and radiofrequency ablation and introduces emerging techniques such as high-intensity focused ultrasound and interstitial laser ablation
- Provides guidance on the management of side effects and emphasizes the importance of follow-up after focal treatment
- Includes contributions from a global team of experts who summarize latest best practice and current evidence

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