Cryotherapy

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16.1 Introduction

Cryosurgery has been applied in oncologic treatments for over 150 years (Arnott 1850), constantly evolving into the modern minimally invasive approach for the treatment of prostate cancer (PCa). Today, modern cryosurgery is an accepted option for both the primary and salvage treatment of localized PCa recognized by the international guidelines (Babaian et al. 2008; Heidenreich et al. 2011). Herein, we review the indications, procedure details, as well as contemporary results of cryotherapy for PCa.

16.2 Elements of Cryobiology

The basis of cryogenic injury is tissue destruction by subtraction of energy and achievement of nonvitally low temperatures. There are two main mechanisms that can be considered as the principal pathways of cryoinjury, and these consist of vascular-related injury on one hand and direct cellular damage on the other (Hoffmann and Bischof 2002).

Extreme temperatures mainly affect the small vessels, damaging the endothelium whereby vessel cell lining sloughs and blocks blood flow, thereby inducing a typical inflammatory response with permeability of the vessels, distention of vessel walls, thrombosis, ischemia, and necrosis of the supplied tissue (Hoffmann and Bischof 2002). Moreover, during the thawing phase of cryotherapy, reperfusion injury enhances endothelial

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damage stimulating the inflammatory response with release of oxygen radicals and augmenting tissue damage.

Direct cell injury relies on tissue water biophysics. The complex cryoinjury process can be summarized by two topographically distinct processes: intracellular and extracellular ice formation. Intracellular ice crystal formation occurs at high freezing rates typically seen in cryosurgery. These ice crystals mechanically disrupt and damage vital cell structures such as organelles and the membrane. Extracellular ice formation subtracts water from the extracellular environment and, aside from its mechanical damage, induces extracellular hypertonicity that in turn draws water from within the cells, dehydrating them and disrupting normal enzymatic processes and membranes properties (Mazur 1984; Theodorescu 2008). Achieving temperatures below −40°C as well as maintaining the exposure for longer times enhances tissue destruction as virtually all water is transformed to ice at these extreme conditions (Gage and Baust 2007; Klossner et al. 2007). Extracellular ice formation is likely the predominant injury mechanism during cryoablation; however, using high freezing rates as typically seen with modern devices, intracellular ice formation, and the associated mechanisms of cell damage certainly come into play potentiating the overall effect.

Moreover, during the thawing phase, additional injury mechanisms come into play. Specifically, when frozen tissue temperature rises above −40°C, smaller ice crystals fuse to form larger structures in a process known as recrystallization, and additional structural damage is inflicted upon cell structures. As thawing proceeds, extracellular ice melts and a hypotonic environment is created driving overloading water shifts into the cells (Theodorescu 2008).

Despite the same injury mechanisms coming into play, different cell types and cell lines respond differently to cryoinjury. PCa cells' response to cryoinjury has been extensively studied. Cryoinjury is a time-dependent process as cryoinjury progresses with freezing. Reaching temperatures below a −40°C threshold ensures effective PCa cell destruction (Tatsutani et al. 1996), although at the periphery of the ice ball, where temperatures are not as cold, cryoinjury may only be reversible (at temperatures −20°C to 0°C) or induce apoptosis (Gage et al. 2009). Apoptosis plays an important role in cryoablation of prostate cancer. It has been shown that cryoablation sensitizes cancer, but normal prostate cells, to pathways of apoptosis suggesting a potential role for combination strategies in PCa cryosurgery (Clarke et al. 2007; Kimura et al. 2010a; Santucci et al. 2011) to enhance targeted damage to cancerous tissue.

Along with local mechanisms of destruction, cryotherapy offers an additional perspective to cancer control. Since cancerous tissue is not removed by the procedure and cancer-specific antigens are left in situ, these can be recognized by the immune system and stimulate a cancer-specific immune response towards them. However, there is controversy regarding the nature of such immunologic response with conflicting data reported in the literature. While some studies support an anticancer response after cryoablation, others indicate that immunosuppression or tolerance to these antigens may be induced (Ablin 1974; Urano et al. 2003; Udagawa et al. 2006; Yamashita et al. 1982; Miya et al. 1987). It appears that the nature of the immune response depends on local and systemic factors such as cytokines, antigen-presenting cells, as well as the type of antigen presented that build up the immune system response (Sabel 2009).

16.3 Indications for Cryosurgery

Cryosurgery for PCa is a recognized treatment option (Babaian et al. 2008; Heidenreich et al. 2011); however, there is no agreement to date upon the indications and contraindications for this approach, and international guidelines remain cautious in this regard.

In the setting of primary cryotherapy for localized PCa, both the European Association of Urology (EAU) and the American Urological Association (AUA) guidelines agree that cryosurgery is an option for patients who do not desire or are not good candidates for conventional surgery

(Babaian et al. 2008; Heidenreich et al. 2011). The AUA statement on cryosurgery recognized cryosurgery as an option for low, intermediate, and high-risk PCa (Babaian et al. 2008), albeit high-risk PCa patients may require multimodality treatment. The EAU guidelines identify the ideal candidates for cryosurgery as these patients having minimal extension beyond the prostate, gland size ≤40 cc (larger glands may present technical difficulties with probe placement and can be downsized with hormonal treatment prior to intervention), PSA < 20 ng/mL, and biopsy Gleason score < 7 (Heidenreich et al. 2011).

Without a doubt, patient and disease characteristics need to be taken into account when considering cryotherapy as an option for prostate cancer. The lack of homogeneous data in the literature, specific to low, intermediate, and high-risk disease, however, is translated into almost conflicting recommendations from the major guidelines. As long-term outcomes of primary cryosurgery become available, we are likely to see a refinement of the guidelines with stronger and more precise recommendations made.

There are several technical contraindications to cryosurgery that apply both in the primary and salvage settings. As large defects in the prostatic fossa may impair the effectiveness of the urethral warmer coaptation used during the procedure to safeguard the urethral lining and increase the chance of mucosal sloughing, a history of transurethral resection of the prostate or similar procedures should be considered relative contraindications. Additionally, major rectal pathology may be considered a contraindication. Moreover, extensive counseling is needed for potent patients expecting to maintain erectile function as potency is typically impaired following whole-gland cryoablation. Large prostate glands (>40 cc) may be difficult to treat due to sheer size alone or interference of the pubic arch. The latter obstacle can be overcome with either manual positioning of the probes that is void of transperineal grid constraints or extended lithotomy position of the patient. For larger prostates, gland downsizing using hormonal agents can be utilized prior to intervention.

Cryotherapy in the salvage setting represents an attractive alternative to salvage prostatectomy offering reduced morbidity and technical challenge (Kimura et al. 2010b). Salvage cryosurgery has been used both after external beam radiation and interstitial radiotherapy, along with other failed primary therapies such as cryoablation, high-intensity focused ultrasound, etc. Therefore, patients with local biopsy-proven recurrence of prostate cancer after radiation or other primary therapy with no evidence of metastatic disease represent potential candidates for salvage cryotherapy. Due to a higher chance of seminal vesicle invasion, we recommend considering seminal vesicle biopsies and lymph node sampling in the evaluation of potential high-risk candidates.

Several studies have suggested factors associated with greater success of salvage cryotherapy, and these can be summarized as favorable disease characteristics: low PSA nadir after primary treatment, low PSA presalvage cryotherapy (<4 ng/mL), PSA doubling time >16 months, as well as the Gleason grade of the recurrent disease (Ng et al. 2007; Spiess et al. 2006; Ismail et al. 2007).

In summary, although cryoablation is a recognized option both in the primary and salvage settings for the treatment of localized prostate cancer, there is difficulty in reaching a consensus on selection criteria and to define ideal candidates for this approach. This is mainly due to the paucity of data in the literature and is likely to resolve in the near future as more studies on cryoablation add their results to the pool of available information. There is agreement that currently cryoablation should be considered as a treatment option for patients that are not willing or are not good candidates for conventional surgery.

16.4 Cryoablation Procedure

Herein, we describe the general steps of the procedure using third-generation cryotechnology that utilizes the Joule–Thompson principle of gas expansion and therefore heat delivery and subtraction by means of ultrathin needle-like cryoprobes. Translating the physical principle into

practice, as compressed gas is delivered to the tip of the cryoprobe in a closed circuit and allowed to expand through a minute opening, gas pressure falls, and it changes its physical properties (internal state). For argon gas, the change of state subtracts energy resulting in reduction of the temperature and freezing. The opposite is true regarding the properties of helium gas that upon expansion releases energy to the environment, thereby generating heat that translates into active thawing. The opposite effects of helium and argon derive from differences in attractive and repulsive forces of the molecules (internal energy) of these gasses. A newer cryotechnology that has been introduced relies on argon gas as the sole cryogen, whereby both freezing and thawing phases are achieved by regulating the properties of this gas, since Joule–Thompson coefficients of gasses vary with pressure and temperature. At pressures of 3,500 PSI, expansion of argon gas results in temperature drop and thus freezing. Allowing this gas to expand under lower pressures (200–500 PSI), when Joule–Thompson coefficient of argon is very low and only negligible cooling takes place, the gas is used to heat the needle shaft by spreading the heat generated by an electrical heating source embedded in the needle. This technical modification allows for the use of a single gas (argon) for both freezing and thawing during cryoablation.

Several cryoablation platforms are commercially available, and these consist of a console for treatment planning and monitoring that receives information from the probes and regulates the freezing/thawing phases. The console is connected to peripherals such as a urethral-warming catheter, a transrectal ultrasound mounted on a stepper, cryoprobes, and temperature sensors. Gas tanks (argon with or without helium) are connected to the system. On the console monitor, the information from the treatment planning is integrated with ultrasound imaging in real time which allows for precise monitoring of the procedure as well as input from temperature sensors and cryoprobes. For treatment planning, the desired ice coverage can be precisely sculptured by varying the configuration of the probes as well as by using different probes generating different shapes and sizes of ice balls. The probes are positioned in the gland through a transperineal grid template under ultrasonographic guidance to produce a series of overlapping ice balls that cover the entire gland.

Typically, cryoablation is performed as an outpatient procedure under spinal, locoregional, or general anesthesia. With the patient in lithotomy position, cryoprobes are positioned under transrectal ultrasonographic guidance using both sagittal and transverse views. In addition to cryoprobes, temperature sensor probes are placed to allow for precise monitoring of ice ball development. These thermocouples can be positioned in Denonvillier's fascia, the urethral sphincter, and/or the neurovascular bundles to monitor the freezing process and avoid injury to adjacent structures. Once the probes are in place, flexible cystoscopy is used to verify the integrity of the urethra and bladder and to place a superstiff guidewire for the introduction of the urethral-warming catheter. A dual freeze/thaw cycle is performed and monitored by ultrasonography and readings from the temperature probes. At the end of the procedure, the urethral-warming device is replaced with a urethral catheter, although some prefer placing a suprapubic cystostomy to ensure adequate bladder drainage in the postoperative period. Acute swelling and inflammatory processes following cryoablation typically resolve within 1–2 weeks. In our experience, most patients are able to void spontaneously by 1 week after treatment.

16.5 Primary Cryotherapy: Complications

Cryoablation of the prostate is a minimally invasive surgical technique, and its morbidity profile has been extensively studied. Table 16.1 provides a summary of the reported complications. The majority of the postoperative events reported in the literature are self-limiting. Transient penile and scrotal swelling and paresthesia have been reported to occur within 2–3 weeks in up to 10% of patients and typically resolve in 2–6 months (Wake et al. 1996; Ghafar et al. 2001). Major

Table 16.1 Complication rates after primary cryoablation of the prostate using third-generation technology

Reference	Number of patients	Complication rates (%)							
		Slough	Perineal pain	Urinary retention	UTI/sepsis	Urethral stricture	Fistula	Incontinence	ED
Bahn et al. (2002)	210	NR	NR	3	NR	NR	2.4	9	41
Shinohara et al. (1996)	102	NR	3	23	3/3	NR	1	4 (15[a])	86
Han et al. (2003)	106	5	2.6	3.3	0	NR	0	3	87
Wake et al. (1996)	100	1	NR	20	NR	2	0	8	NR
DiBlasio et al. (2008)	78	NR	NR	NR	NR	1	NR	7.7	84.6
Cohen (2004)	98	2	NR	NR	NR	NR	0	0	NR
Prepelica et al. (2005)[b]	65	NR	0	3.1	NR	NR	0	3.1	NR
Hubosky et al. (2007)	89	2	6	4	1/0	NR	1	2	NR
Donnelly et al. (2010b)	117	NR	NR	15.4	NR	NR	NR	32.5	70.9
Chin et al. (2008)[c]	33	NR	32	NR	NR	NR	NR	7	29
Lian et al. (2011)	102	4.9	NR	0	NR	0	0	4	64.1

UTI urinary tract infection, *ED* erectile dysfunction, *NR* not reported
[a]Including patients who underwent transurethral resection of prostate following cryoablation
[b]High-risk patients
[c]Locally advanced disease

complications are rare with a reported incidence of rectourethral fistula ranging from 0% to 2.4%, urethral sloughing occurring in <5% with the use of urethral-warming devices, and incontinence requiring pads being reported in less than 10% with most cases resolving spontaneously. It remains unclear whether urge or stress incontinence is the predominant type, since most studies did not distinguish between the types of incontinence. Similarly, episodes of urinary retention have been reported in <5% of patients following cryoablation (Hubosky et al. 2007; Han et al. 2003), albeit the definitions of urinary retention vary and most of retention episodes are transitory and resolve within several weeks of surgery. Urethral stricture rates are approximately 2.5% (compared to 8.4% with radical prostatectomy) (Elliott et al. 2007).

Incontinence and erectile dysfunction are among the most widely used measures of functional outcomes following treatments for localized PCa. For cryoablation, erectile dysfunction occurs in most patients treated with whole-gland ablation although some studies report that a majority of patients remained potent (Table 16.1). A recent study using the Surveillance Epidemiology End Results (SEER) database reported on complications of primary cryotherapy derived from Medicare claims (Roberts et al. 2011); the authors estimate 20.1% of erectile dysfunction following cryotherapy, along with 9.8% incontinence.

An accurate assessment of the rates of erectile dysfunction and urinary incontinence is hampered by the varying definitions of these outcome measures and only scattered use of validated instruments to adequately identify these conditions. For future studies, it is of paramount importance to use validated tools (e.g., questionnaires) to evaluate both erectile function and continence.

Kimura et al. used validated tools to assess urinary function after cryoablation and found that while urinary function and bother scores dropped immediately following cryoablation, they recovered steadily and persistently in a 12-month period (Kimura et al. 2010c). Another study reported excellent voiding function outcomes with no apparent change in urinary function scores after primary cryoablation (DiBlasio et al. 2008). Malcolm and colleagues reviewed quality of life outcomes comparing brachytherapy, robotic and open radical prostatectomy, and cryotherapy (Malcolm et al. 2010). These authors have shown that cryotherapy, as well as brachytherapy, were associated with a better health-related quality of life, especially that related to the urinary function and bother along with sexual bother as assessed by validated tools. When directly compared to brachytherapy,

Table 16.2 Complication rates after salvage cryoablation using third-generation cryotechnology

Reference	Number of patients	Complication rates (%)							
		Slough	Perineal pain	Urinary retention	UTI/sepsis	Urethral stricture	Fistula	Incontinence	ED
Ng et al. (2007)	187	NR	14	21	10	2.1	2	40	NR
Han and Belldegrun (2004)	29	NR	NR	NR	NR	NR	0	7	NR
Ismail et al. (2007)	100	2	4	2	NR	NR	1	13	86
Pisters et al. (2008)[a]	279	NR	NR	NR	NR	NR	1.2	4.7	69.2
Ghafar et al. (2001)	38	0	39.5	0	2.6	NR	0	7.9	NR
Cresswell et al. (2006)	20	NR	NR	4	NR	NR	0	4	86
Bahn et al. (2003)	59	NR	NR	NR	NR	NR	3.4	8	NR

UTI urinary tract infection, *ED* erectile dysfunction, *NR* not reported
[a]Series includes a portion of cases treated using second-generation technology

cryoablation resulted in worse sexual function scores for up to 12 months while urinary scores were similar; however, after 18 and 24 months, cryoablation has shown consistently better urinary domain scores compared to brachytherapy (Hubosky et al. 2007).

Kimura and colleagues (2011) assessed erectile function outcomes using validated questionnaires and found that 77.4% of patients had moderate to severe erectile dysfunction following cryoablation and suggested that the use of erectile aids may assist in recovery of potency to preoperative levels. Similarly, Ellis et al. (2007a) have suggested that penile rehabilitation strategies (regular use of vacuum devices and oral agents) after cryoablation may increase potency rates. In fact, the authors report steady recovery of erectile function over time with over 50% of preoperatively potent patients regaining erections sufficient for intercourse over a 4-year follow-up (Ellis et al. 2007a). Despite encouraging reports, more studies are needed to determine the appropriate strategies to enhance both urinary and sexual function in men undergoing cryoablation.

16.6 Salvage Cryotherapy: Complications

Complications profile of salvage cryotherapy for radiorecurrent prostate cancer appears to be similar to that in the primary setting with higher rates of events (Table 16.2). Urethral mucosal sloughing remains a rare event using third-generation technology and has been reported in <2% of patients. Specifically, fistula rates appear to be higher, up to 3.4%, as well as incontinence rates that remain in most series under 10%. In the few series reporting erectile function outcomes, only a minority of patients regain potency. These results favorably compare to conventional salvage radical prostatectomy series (Kimura et al. 2010b), suggesting that salvage treatment with cryosurgery may be considered as a relatively low morbidity option.

16.7 Primary Cryotherapy: Oncological Outcomes

Oncological outcomes reported in the literature are summarized in Table 16.3. The various definitions of biochemical recurrence make it very challenging to adequately compare the different series emphasizing the need for a consensus on the matter. Conventional criteria of biochemical failure adopted for radical prostatectomy are most likely not suitable for cryoablation since a portion of PSA-producing tissue is spared periurethrally due to the use of urethral-warming devices, and therefore undetectable PSA levels are not always achievable. Similarly, biochemical failure criteria used in radiation oncology are likely not suitable as well, since an effective ablation of the entire gland is carried out and most of PSA-producing tissue is destroyed. Despite the obvious difficulties with diverse definitions of failure, the currently

Table 16.3 Oncologic outcomes of primary cryoablation

Reference	Number of patients	Definition	bDFS 1 year	bDFS 3 years	bDFS 5 years	bDFS 7 years
Hubosky et al. (2007)	89	ASTRO	94%	–	–	–
		≤0.4	70%	–	–	–
DiBlasio et al. (2008)	78	ASTRO	97.9%	95.7%	71.1%	–
Prepelica et al. (2005)[a]	65	ASTRO	83.3%[b]	–	–	–
Cresswell et al. (2006)	31	≤0.5	60%	–	–	–
Donnelly et al. (2010b)	117	Nadir+2	–	82.9%	75%	–
Bahn et al. (2002)[c]	590	ASTRO	–	–	–	89.5%
Jones et al. (2008)[c]	1,198	ASTRO	–	–	77.1%	–
Lian et al. (2011)	102	<0.5	92.2%[b]	–	–	–

bDFS biochemical disease-free survival
[a]High-risk patients
[b]Median follow-up of 30–35 months
[c]Contains a proportion of patients treated with earlier-generation technology

available literature shows that in most series over 80% of patients remain disease free at 1 year. Biochemical disease-free survival has been reported at 5 years in three studies, showing consistent results of approximately 75% of patients using similar definitions borrowed from radiation oncology (DiBlasio et al. 2008; Donnelly et al. 2010a; Jones et al. 2008).

Oncological outcomes of primary cryoablation are strongly dependent on disease characteristics. Favorable disease characteristics translate to better bDFS rates. Clinically low-risk patients have better outcomes compared with intermediate and high-risk ones (Hubosky et al. 2007; Bahn et al. 2002). Caso et al. (2010) have evaluated predictors of biopsy-proven recurrence after primary cryotherapy and found that, on multivariate analysis, only time of undetectable PSA (TUPSA) was associated with both biochemical and biopsy-proven disease-free survival, suggesting that TUPSA may be used as a potential informative tool during follow-up. As the experience with primary cryotherapy matures, we are likely to be able to identify additional factors associated with oncologic outcomes and produce predictive models as well as more accurate recommendations on patient selection for this approach.

It is also important to compare cryotherapy to other well-standardized approaches for the treatment of localized PCa. Two randomized clinical trials comparing cryosurgery to radiation were published yielding conflicting results. Chin et al. (2008) found cryoablation to be inferior to external beam radiation in bDFS. However, a similar trial by Donnelly et al. (2010a) concluded that the two approaches have comparable oncological efficacy. This discrepancy may be due to differences in study designs; in fact, while Chin et al. included only patients with locally advanced PCa and had small sample size, Donnelly and colleagues excluded bulky disease from their study and benefited from a larger sample size.

To date, only two studies reported long-term oncological outcomes following primary cryoablation (Cohen et al. 2008; Cheetham et al. 2010). Both studies are based on early cohorts of patients (1990s) and therefore may not represent accurately the outcomes of third-generation technology. Cohen et al. (2008) reported on biochemical disease-free survival with in 370 men treated with primary cryosurgery before 1999. The authors have found that in low, intermediate, and high-risk groups, bDFS at 10 years were 80.5%, 74.2%, and 45.5%, respectively. Cheetham et al. (2010) focused on overall and cancer-specific survival. They report on 25 patients treated between 1994 and 1999 with 10 years of follow-up where only two patients died of prostate cancer compared to eight deaths attributed to other causes. This is clearly preliminary data, and conclusions should not be hasted, but it establishes the basis for future reports on long-term outcomes.

Table 16.4 Oncologic outcomes of salvage cryoablation

Reference	Number of patients	Definition	bDFS 1 year	bDFS 3 years	bDFS 5 years	bDFS 7 years
Ng et al. (2007)	187	Nadir + 2	–	–	56%	–
Ghafar et al. (2001)	38	Nadir + 0.3	86%	74%	–	–
Ismail et al. (2007)	100	ASTRO	83%	59%	–	–
Cresswell et al. (2006)	20	≤0.5	66.7%	–	–	–
Bahn et al. (2003)[a]	59	≤0.5	–	–	–	59%
Pisters et al. (2008)[a]	279	ASTRO	–	–	59%	–

bDFS biochemical disease-free survival
[a]Includes earlier-generation technology

It appears from the available data that the oncological outcomes of primary cryotherapy are acceptable and competitive with other primary treatments for PCa. Yet, it is paramount to emphasize the need for agreement on the definition of biochemical failure and encourage further outcome data to be evaluated.

16.8 Salvage Cryotherapy: Oncological Outcomes

The data on oncological outcomes following salvage cryotherapy for radiorecurrent PCa is affected by the same difficulties of lack of consistency in the definition of biochemical failure and therefore inability to perform an effective comparison between the published results. The summary of the literature is provided in Table 16.4.

Despite various definitions of biochemical failure, it is apparent that bDFS at 1 year can be as high as 86%. Long-term data suggests that with a strict definition of PSA, ≤0.5 ng/mL following salvage cryosurgery, 59% of patients are disease free at 7 years (Bahn et al. 2003), and these results are comparable to >55% bDFS at 5 years from other studies (Ng et al. 2007; Pisters et al. 2008). Recently, Cheetham et al. (2010) reported on 10-year data regarding outcomes after salvage cryoablation focusing on overall and cancer-specific survival. In their report, 8 out of 51 patients (15.7%) who underwent salvage cryotherapy died of PCa over 10 years. Williams et al. (2011) reported on 176 men undergoing salvage cryotherapy with long-term follow-up; the authors found that 47%, 39%, and 39% of patients were disease free at 5, 8, and 10 years, respectively. This study has also evaluated metastasis-free survival, indicating 87% at 5 and 82% at 10 years.

Several studies attempted to identify prognostic factors associated with the outcome of salvage cryoablation. A report from the COLD (Cryo On-Line Data) registry analyzed 455 patients and found that PSA nadir levels <0.6 ng/mL after salvage cryotherapy were associated with better cancer control outcomes offering 80% bDFS at 1 year and 67% bDFS at 3 years, whereas higher PSA nadirs were associated with progressively worsening outcomes (Levy et al. 2010a). In this study, it was also determined that Gleason scores of the recurrent cancer correlated with the outcome. The same group found that disease burden (the ratio of positive cores to prostate volume) is of prognostic value following salvage cryoablation (Levy et al. 2010b). Another study showed that preradiation PSA, Gleason score, as well as presalvage PSA level and postsalvage PSA nadir were associated with biochemical disease-free survival (Williams et al. 2011). The authors showed that patients with presalvage Gleason score of ≤6 had a 54% bDFS at 10 years, underlining the importance of disease characteristics in defining cancer control outcomes.

Spiess and colleagues (2010) developed a nomogram that quantifies the risk of biochemical failure after salvage cryotherapy based on initial PSA level, Gleason score, and clinical stage. This tool may be useful to generate realistic expectations with regards to the probability of biochemical failure in candidates for salvage

cryoablation. However, this nomogram's performance is not optimal, and it requires external validation.

16.9 Future Directions: Focal Therapy

Technological advances, specifically those that brought cryotherapy to be recognized as an option in the treatment of prostate cancer, have enabled physicians to rethink treatment schemes and potentially move away from whole-gland treatments towards a targeted, partial ablation of the gland (Polascik and Mouraviev 2009; Polascik et al. 2009). The concept of focal therapy relies on a selective, targeted destruction of known cancer while sparing the uninvolved tissue, thereby potentially reducing morbidity and improving quality of life. The concept of focal therapy for prostate cancer has gained interest and popularity, especially in the era of growing evidence that overdiagnosis and overtreatment of prostate cancer is becoming a pressing public concern (Welch and Black 2010).

Advances in imaging of the prostate, namely, magnetic resonance and novel ultrasound techniques, are permitting the physician to visualize PCa foci within the prostate and characterize those with a guided, targeted biopsy. The same imaging technology can then potentially be used, in appropriate candidates to guide the targeted ablation of these lesions while leaving intact the remainder of the prostate.

Early results of focal therapy are promising, albeit based on a small number of single-institution, small-sized studies. Biochemical disease-free survival reported in the literature ranges between 84% and 96% at 2–5 years while potency is preserved in the vast majority (72–89%) of patients (Ellis et al. 2007b; Bahn et al. 2006; Lambert et al. 2007; Onik et al. 2008, 2007). There remains a lack of consensus on the appropriate candidates and selection methods for focal therapy, as well as tools to be used in postablation follow-up. Despite the hurdles, the focal therapy approach is being investigated intensively and followed with great interest. Randomized trials are under way to set stage for the introduction of this intriguing therapeutic option.

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