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High-Intensity Focused Ultrasound and Cryotherapy as Salvage Treatment in Local Radio-Recurrent Prostate Cancer

Key Words

High-intensity focused ultrasound · Cryotherapy · Local
 radio-recurrent prostate cancer

Abstract

Background: Salvage high-intensity focused ultrasound (HIFU) and cryotherapy (CRYO) have emerged as interesting alternatives in the treatment of local radio-recurrent prostate cancer. Currently, recommendations concerning the use of CRYO and HIFU in the salvage setting are still evolving. **Aim:** The objective of this review was to analyze the results from studies on CRYO and HIFU as salvage treatment in local radio-recurrent prostate cancer. **Materials and Methods:** A National Center for Biotechnology Information PubMed search (www.pubmed.gov) was conducted from 1993 to 2011 using medical subject headings 'High-Intensity Focused Ultrasound', 'Cryotherapy', 'Local Radio-Recurrent' and 'Prostate Cancer'. **Results:** In the past years, there have been several published series demonstrating promising acceptable morbidity and oncological outcomes in the short term for HIFU and in the intermediate term for CRYO. The introduction of newer-generation devices and technical modifications has facilitated reduction of complications associated with the procedures. As with any salvage treatment, careful patient selection and subsequent follow-up are principal points. **Conclusions:** HIFU and CRYO are promising sal-

vage treatments in patients with local radio-recurrent prostate cancer. The risk of significant complications in the salvage setting is higher compared with primary therapy; therefore, the patients must be informed about the risk of complications and the modality of treatment. However, only further evaluation in formal prospective clinical trials will hopefully confirm their role in clinical practice.

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Introduction

External beam radiotherapy (EBRT) and interstitial brachytherapy are used commonly in the treatment of localized prostate cancer. However, an estimated 20–30% of patients present fail after radiotherapy (RT) treatment. Patients with isolated local recurrence and life expectancy over 5 years may benefit from and be offered some form of local salvage therapy, with curative intent [1]. The management of local radio-recurrent prostate cancer is controversial and there is no consensus regarding the optimal strategy. The decision is often based on biological tumor features, patient age and comorbidities, as well as patient and physician preferences and physician expertise. The vast majority of these patients currently receive androgen-deprivation therapy (ADT), which is non-curative, although it would be appropriate for patients with

a short life expectancy or metastatic disease [2]. Salvage radical prostatectomy (RP) is an established treatment option, which offers the greatest likelihood of secondary control, although it is generally associated with a higher morbidity rate [3]. Minimally invasive therapies such as high-intensity focused ultrasound (HIFU) and cryotherapy (CRYO) have emerged as alternatives showing encouraging results in terms of morbidity rates and cancer control [4]. Currently, HIFU is undergoing FDA trials in the USA and Canada, although it has been approved as a therapeutic option in many European countries. However, the global experience of HIFU as salvage therapy is still limited. Experience with salvage CRYO has been accumulating over the past decade, having benefited from some technological advances. This article reviews the current literature on HIFU and CRYO as whole-gland ablative salvage therapy and evidence for their efficacy and morbidity in localized radio-recurrent prostate cancer.

Definition of Failure

There is no consensus on the definition for biochemical failure after RT. As CRYO and HIFU are both ablative rather than excisional procedures such as RP, comparison of biochemical-free survival rates of the various modalities without taking into account the presence of residual benign prostate-specific antigen (PSA) secreting tissue is not ideal [5]. It is also perhaps unreasonable to compare the definition of PSA failure with that of EBRT which is not a true ablative procedure. Thus there has been a significant variation in the reporting of disease-free survival (DFS) rates with investigators using either the American Society for Therapeutic Radiology and Oncology (ASTRO) definition [6] of three consecutive PSA rises after nadir or the Phoenix definition of nadir + 2 ng/ml [7, 8]. Blana et al. [9], in a recent study with salvage HIFU patients using the Ablatherm system, highlighted the high sensitivity and low specificity of the ASTRO definition versus the low sensitivity and high specificity of the Phoenix criteria. The group proposed the 'Stuttgart' definition of PSA nadir + 1.2 ng/ml, although since a significant proportion of their patients had undergone prior transurethral resection of the prostate. Thus this definition may not be widely applicable to all salvage HIFU patients. Many studies on short-term outcomes following CRYO have high and perhaps misleading DFS. For this reason, many authors use prostate biopsy at 6–12 months following salvage treatment as an indicator for recurrence. However, Shinohara et al. [10] have shown that bi-

opsy failure could be strongly predicted by a PSA nadir >0.5 ng/ml (55%) as compared to PSA nadir <0.4 and <0.1 ng/ml at 10 and 1.5% respectively.

Patient Selection

The choice of an adequate salvage therapy is dependent on appropriate patient's evaluation. As with any salvage treatment, it is mandatory to attain histological confirmation of tumor recurrence and exclude metastatic disease with abdominal and pelvic magnetic resonance imaging (MRI) or computerized tomography and ⁹⁹Tc bone scan. In addition, the candidates must also have a sufficiently long life expectancy to justify the use of a potentially morbid treatment rather than a non-curative option such as ADT. A histologic Gleason score <8 as well as PSA <4.0 ng/ml prior to salvage treatment have been shown to be good predictors of 5-year DFS [11].

Positive prostate biopsies are currently the only way to confirm local recurrence but there is significant controversy regarding the role and reliability of biopsy following RT. Histologic analysis is complicated by radiation changes, which may mimic high-grade disease, thereby conceivably leading to an inaccurate Gleason score of false positive results [12]. Within the first 12–24 months following RT, prostate biopsy should be interpreted with caution due to delayed apoptotic cell death [13]. Crook et al. [14] reported that about 30% of positive biopsies obtained at 12 months covert to a negative status by 24–30 months, while about 20% of patients who have a negative posttreatment biopsy will later have a positive repeat biopsy.

Detection of occult local recurrence and distant metastasis in radio-recurrent prostate cancer may be possible with ¹¹C or 18-fluorocholine PET scans [15]. Rinnab et al. [16] reported a sensitivity of 89% with a positive predictive value of 72% for recurrence detection at PSA <2.5 ng/ml.

High-Intensity Focused Ultrasound

HIFU was introduced as a treatment option for prostate cancer in the 1990s. HIFU works by focusing ultrasound waves on a specific target of prostate tissue using a transrectal ultrasound probe, producing thermal and mechanical effects in the prostatic tissue with subsequent coagulative necrosis, generating lesions through a direct dose-related effect.

Table 1. Characteristics of HIFU devices

	Sonoblate 500	Ablatherm™
Patient position	lithotomy	right lateral decubitus
Software	semi-automated	automated
Power	manually adjusted	predetermined settings: primary, salvage, re-HIFU
Temperature range	80–98°C	>85°C
Ablation volume	21–47 mm	29–36 mm
Frequency treatment	4 MHz	3 MHz
Focal point	30–50 mm	45 mm
Treatment algorithm	1	3
Unit	portable	integrate table

Technology

There are currently two commercially available HIFU units in clinical use. The Ablatherm™ device (EDAP-TMS SA, Vaulx-en-Velin, France) is the device more commonly used in Europe and Asia. The Sonoblate 500 (Focus Surgery Inc., Indianapolis, Ind., USA) is in use in Central and South America and is currently undergoing trials in Canada and the USA. It is important to realize that these two devices have specific differences with regard to limitations on patient selection as well as technical differences in intraoperative monitoring. Table 1 shows a comparison of the two available high-intensity focusing ultrasound devices.

Oncological Outcomes

HIFU shows promise as a salvage treatment. Currently there is only limited published literature with respect to the follow-up duration, as would be expected with a new treatment modality. Studies have mean follow-up between 3 and 39 months and DFS rates of between 25 and 54% [17–19] (table 2).

Murat et al. [19] reported 73% DFS at 18.1 months. Similarly, Colombel et al. [20] reported, in control biopsies after salvage HIFU using the Ablatherm™ system, a negative biopsy rate of 80% at 15 months. Published data for CRYO and brachytherapy have reported negative biopsy rates between 77 and 86% respectively [21].

Independent predictors for risk of disease progression have been analyzed in different series. Patients who had received hormonal therapy prior to salvage HIFU were 2.8 times more at risk of disease progression compared to patients who did not. The presalvage PSA level is most important and has been identified as an independent predictive factor for progression. In contrast, the presalvage

Table 2. Salvage HIFU in local radio-recurrent prostate cancer

Reference (first author)	Patients	DFS	Year
Mallick [17]	50	54% (1 year)	2006
Gelet [18]	106	40% (40 months)	2006
Murat [19]	167	25–53% (3 years)	2009

Gleason score and percentage of positive biopsies are not significantly linked to treatment failure and disease progression [22].

Morbidity

As expected, morbidity rates of salvage HIFU are higher compared to primary HIFU treatment. However, they compare favorably to salvage RP in terms of urinary incontinence rates [17–19]. Since the risk of rectourethral fistula following RT increases due to poor tissue viability and poor periprosthetic blood supply precluding effective tissue repair, this complication has been reported to be from 3 to 12.5% of patients [19]. Evidence related to other patient-relevant outcomes is limited to adverse events of the urinary tract such as bladder neck contracture or urethral stricture at 10–20%, urinary tract infection from 1 to 6%, and prolonged urinary retention at 6% [17–19].

Failure following Salvage HIFU

Postprocedural prostate biopsy is performed routinely by some surgeons and only if clinically indicated by others. PSA nadir is generally reached between 6 and 12 months, and is generally regarded as the ideal time for

biopsy [22]. Uchida et al. [23] showed that patients with a PSA nadir <0.2 ng/ml had a low rate of cancer detection on post-HIFU biopsy of only 11%, as compared to 54 and 52% if the PSA nadir was 0.21–1.00 or >1 ng/ml respectively. This has led to some investigators suggesting that routine biopsy may not be required in patients with a PSA nadir <0.2 ng/ml. However, further studies are required to validate this assertion, especially given the relatively low morbidity of repeat HIFU treatment in these patients. Preliminary results suggest that dynamic contrast-enhanced MRI may provide accurate detection of local recurrence following HIFU, with a sensitivity and specificity of 0.98 and 0.81 respectively [24]. This may be promising as a postoperative monitoring modality.

HIFU is a procedure that is theoretically repeatable and reproducible despite previous HIFU treatment [25]. Clinical experience with repeat HIFU, however, has been limited, with a small percentage of cases from several reported HIFU series. One needs to be cautioned about incremental risks of complications such as fistula formation and incontinence if repeat HIFU is contemplated.

Cryotherapy

CRYO now is a well-established treatment option in the salvage setting with approval by the FDA attained as early as 1999 for primary therapy. Contemporary CRYO is performed transperineally with transurethral ultrasound guidance of probes and real-time monitoring of the procedure. Recent advances in third-generation technology have resulted in less morbidity whilst maintaining efficacy.

Different mechanisms of cell death have been implicated in the efficacy of CRYO [26]. A key mechanism is the induction of ice crystals within the prostate cancer cells which results in physical disruption of the cells. Crystallization and cellular death begin when the temperature falls below 0°C within the prostate cells. However, adequate tissue destruction and resultant coagulative necrosis requires significantly lower temperatures of at least -40°C . Ideally, once temperatures reach -40°C , the cells would break down to allow maximal destruction of the cellular matrix, resulting in cellular death. Intracellular changes such as protein denaturation damages and electrolyte and osmotic changes are also part of the cytotoxic process. At the extracellular level, thromboses of the microvasculature and tissue matrix destruction also contribute to destruction of the prostate gland.

Technology

Whilst first-generation CRYO had little in the way of safeguards against collateral damage other than the vigilance of the operating surgeon, modern CRYO units have numerous safety features to reduce the complications associated with the procedure. Ice-ball formation is monitored real-time with transurethral ultrasound including three-dimensional views employed at some centers [27]. The use of thermocouples in areas of interest allows us to protect areas such as the external urinary sphincter and rectal wall to reduce the risk of incontinence and fistula formation respectively by careful monitoring against excessive freezing. Active warming is now performed on the urethra via closed systems that irrigate warm fluid allowing the mucosa to stay warm throughout the procedure, thus reducing the risk of urethral sloughing. Various maneuvers, including prerectal placement of protective balloons and injection of special fluids into the perineum, have been used to protect the rectum. Improved computerized systems allow more reliable treatment planning, more predictable treatment patterns, improved visual monitoring [27–29] and, at least in theory, a lower risk of cryo-damage to important structures whilst ensuring adequate freezing of malignant tissue.

Oncological Outcomes

As mentioned previously, there is no standardized definition of failure following salvage CRYO. Most physicians recommend repeat prostate biopsy at 6 months to check for viable tumor tissue. Salvage CRYO can be repeated if viable prostate cancer tissue is found. However, as with repeat salvage HIFU, there is always concern of increased risk of fistula formation and incontinence. Published data in terms of DFS have achieved ranges from 11 to 73% at 5 years [30, 31]. Data from our institution have shown a DFS rate at 10 years of between 39 and 64% with presalvage PSA <5 ng/ml and presalvage Gleason score ≤ 7 being the best predictor of disease-free recurrence at 10 years [32]. Recently, Philippou et al. [33] have reported a DFS rate at 2 years of 58% with a median PSA nadir of 0.20 ng/ml. A summary of available studies is included in table 3.

The PSA level at the time of salvage CRYO has been reported to be an important prediction factor for disease progression [32]. In a post-RT setting, Ng et al. [11] from our center reported a 5-year biochemical recurrence-free survival of 56 versus 1% for presalvage CRYO PSA <4 and >10 ng/ml respectively. Similarly, Izawa et al. [34] reported that patients with PSA <10 ng/ml presented DFS 57 versus 23% for PSA >10 ng/ml at 5 years respectively.

Table 3. Salvage CRYO series in local radio-recurrent prostate cancer

Reference (first author)	Patients	DFS (years)	Year
Benoit [41]	87	58% (5)	2000
Chin [36] ¹	125	34% (5)	2001
Ghafar [30]	38	74% (2)	2001
Izawa [34]	131	23–57% (5)	2002
Bahn [42]	59	59% (7)	2003
Donnelly [43]	46	44% (2)	2005
Ng [11] ¹	187	37% (8)	2007
Ismail [31]	100	11–73% (5)	2007
Pisters [35]	279	59% (5)	2009
Williams [32] ¹	168	39–64% (10)	2011
Philippou [33]	19	58% (2)	2012

¹ Data which are from the same center with respective updated results.

Pisters et al. [35] reported on a case-control comparative study comparing salvage CRYO with salvage RP, performed at separate institutions respectively. Unfortunately as with all case-control comparisons there was a degree of bias in the selection of patients. However, Pisters et al. showed that salvage RP was associated with an increased DFS rate using definitions of failure of PSA nadir <0.4 ng/ml and two rises above PSA nadir. This underscores that the gold standard remains complete surgical removal of recurrent prostate cancer for patients capable of undergoing a more invasive surgical procedure. However, CRYO still maintains a strong fallback option for patients with relative contraindications to salvage RP or preference for a minimally invasive approach.

Morbidity

Side effects of salvage CRYO are more prevalent and serious compared with those reported in the primary setting. With improvements in CRYO devices and techniques, the incidence of complications has decreased with time. Urinary incontinence rates ranging from 10.5 to 36% [21, 33] in comparison to incontinence rates of 41% reported in salvage RP, whilst the fistula rates were from 2.6 to 5.3% [22, 33], have been reported with CRYO in comparison with rectal injury rates from 2 to 15% with salvage RP. The risk of complications seems to be higher in the presence of prior transurethral surgery. Prior transurethral resection of the prostate increases the risk of incontinence with salvage CRYO, reported in 6.7% [36]. Langenhuijsen et al. [37] have reported urethral

stricture ranges from 0 to 5% and sexual function recovery in only 14% of patients submitted to salvage CRYO with a modified technique. One of the more common and problematic complications of CRYO is perineal pain. This has been reported to occur in up to 8% in patients series [37].

Failure following Salvage Cryotherapy

A PSA nadir of >1 ng/ml post-CRYO usually portends inevitable disease-free recurrence as does a presalvage PSA >10 ng/ml [32]. Thus patients with a PSA >10 ng/ml are poor candidates for salvage and any patient who does not attain a nadir <1 ng/ml, regardless of presalvage PSA, should be considered for early alternative therapy such as androgen deprivation. Although CRYO can be repeated for biopsy-proven local recurrence of prostate cancer following salvage CRYO, biochemical recurrence without biopsy-proven recurrence strongly suggests metastatic recurrence and thus repeat CRYO is not appropriate without (a) repeat histological confirmation of local disease persistence and (b) repeat metastatic work-up. As with repeat salvage HIFU, one can anticipate with repeat salvage CRYO a higher risk of fistula formation and urinary incontinence [11].

Follow-Up after Salvage Therapy

The available published literature is variable regarding a standardized follow-up protocol and the use of definitions following salvage therapy. The principal key of follow-up in radio-recurrent prostate cancer is based on periodic serum PSA measurements and surveillance for possible local or distant recurrence. Policies on posttreatment prostatic biopsy have been variable, with some authors adhering to strict biopsy routines and others using a more ad-hoc approach. Current evidence supports the practice of routine PSA levels in addition to a posttreatment biopsy performed 6–12 months postoperatively [38].

Focal Salvage Therapy

This review has dealt only with whole-gland salvage HIFU and CRYO ablation. Recent reports have highlighted that although prostate cancer is a multifocal disease, frequently an 'index lesion' is the only significant cancer lesion [39, 40]. Although current experience has been mainly limited to whole-gland ablation, focal salvage

therapy is now conducted at some centers. Proper patient selection remains a challenge. Ongoing advances in prostate functional imaging modalities as well as molecular oncology should improve accurate cancer localization as well as tumor grading and risk stratification. Focal salvage therapy with selective lesion-directed ablation instead of whole-gland ablation would merit clinical trials.

Discussion

Whole-gland CRYO and HIFU have emerged as alternatives for the treatment of local radio-recurrent prostate cancer in patients with relative contraindications to salvage RP. Currently, there is no consensus on the use of these modalities in the salvage setting, as there is a lack of long-term follow-up and a paucity of evidence concerning improved quality of life and improved cancer-specific survival.

In fact, the current evaluation of oncological outcomes following salvage HIFU or CRYO remains a challenge for the urologist. A variety of definitions of PSA relapse in a heterogeneous population have been used. As yet, none of these definitions have been validated against clinical progression or survival and therefore, it is not possible to give firm recommendation on the definition of failure. In this context, an acceptable definition of disease control is required. We believe that one definition based on a predictive model can be a potential solution in clinical practice. Firstly, one needs to create a model that includes biological and histopathological variables according to the patient's risk stratification and the use of ADT and/or RT in order to estimate the risk of treatment failure. Secondly, new imaging modalities such as multiparametric MRI

with image-guided biopsies performed systematically during follow-up to discriminate between local and systemic failure, reducing the significance of false negative results, will be relevant. Thirdly, an accurate interpretation of prostatic biopsies by an expert uropathologist is required due to difficulties in the identification of residual malignant tissue and the differentiation of histologic effects produced by ADT, EBRT, CRYO or HIFU.

In terms of morbidity, HIFU and CRYO have been considered as alternative options in the salvage setting to patients with comorbidities rendering them suboptimal for surgery. Although both are considered minimally invasive modalities, the risk of significant complications in the salvage setting is higher compared with primary therapy and the nature of the complications is inherent to the procedure. Thus, the patients must be informed about the risk of complications and modality of treatment. Ongoing technologic advancement and technical improvements will further reduce procedure-related complications and increase clinical applicability and patient acceptance.

Conclusion

HIFU and CRYO are promising salvage treatment alternatives in patients who have localized failure after RT. A careful selection of patients for mini-invasive treatment is mandatory due the risk of significant complications inherent to salvage treatment. The patients must therefore be informed about the risk of complications and the modality of treatment. However, only further evaluation in formal prospective clinical trials will hopefully confirm their role in clinical practice.

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