



Review – Prostate Cancer

Cryosurgery for Prostate Cancer: an Update on Clinical Results of Modern Cryotechnology

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Abstract

Context: Cryosurgery is an evolving treatment for localized prostate cancer in European centers. Modern cryotechnology is associated with a low complication rate, but its definitive role in the spectrum of different treatment modalities remains to be determined.

Objective: The primary objective of this review is to analyze the oncological results and complication rates of modern cryosurgery for prostate cancer. Secondly, the impact of patient selection and the criteria for treatment success are discussed.

Evidence acquisition: A structured literature review was performed by an online Pubmed search for data of primary and salvage cryosurgery of the prostate. Papers with relevant information on clinical outcome and complication rates were selected.

Evidence synthesis: The introduction of gas-based third-generation cryotechnology has significantly decreased side effects with similar oncological results compared to older techniques. The occurrence of severe complications like rectourethral fistulas (<1%) has almost been eradicated, but the rates of erectile dysfunction remain high (90%). With salvage cryosurgery more side effects can be expected with an average incontinence rate of 8% and fistulas up to 3.4%. Nevertheless, this minimal invasive treatment remains an option for radiorecurrent prostate cancer. Focal cryosurgery is considered experimental, but is an interesting new development in cryosurgery. The intermediate-term biochemical disease free survival rates of 60%–90% are comparable to the results of other treatment modalities. However, the current data of cryosurgery in literature are of low-level evidence which should be discussed when counselling patients.

Conclusions: Modern cryosurgery is reliable and results are promising with minimal morbidity. Focal cryosurgery in selected patients aims to reduce side effects, but is currently experimental treatment. Randomized trials comparing the outcomes of the different treatment modalities and long-term follow-up data are needed to define the ultimate role of cryosurgery in the treatment of localized prostate cancer.

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1. Introduction

Cryosurgery for prostate cancer was first applied in 1964 by Gonder et al. using liquid nitrogen [1]. The technique encompassed transurethral freezing of the prostate with the inability to position the cryoneedles precisely and to monitor the extent of freezing. This resulted in severe and frequent complications such as incontinence, urethral sloughing and rectourethral fistulas. Therefore, cryosurgery of the prostate was abandoned until the late 1980s, when Onik et al. [2] refined the technique by using interventional radiologic procedures and transrectal ultrasound (TRUS). The accurate TRUS-guided transperineal placement of cryoprobes with real-time monitoring and control of the freezing process has significantly decreased the number of complications [3,4]. The use of a urethral-warming catheter decreased the sloughing rate of the urethral mucosa and subsequently the risk of obstructive problems [5,6]. Consequently, cryosurgery was recognized by the American Urological Association (AUA) as a therapeutic option for localized prostate cancer in 1996.

Since the use of thermosensors in Denonvilliers' fascia and nearby the neurovascular bundles [7] and the application of gas-based cryosurgery [8], complication rates have further decreased. The introduction of argon gas for freezing and helium gas for thawing, permitted a dramatic reduction in the diameter of the cryoprobes. The ultrathin 17-gauge (1.47 mm) cryoneedles have a very sharp tip, that allows for a direct transperineal placement into the prostate [9]. The cryoneedles are inserted through a brachytherapy-like template and because of the smaller diameter more needles can be placed. This enables a precise contouring of the ice ball, subsequently resulting in a more effective ablation of the gland. The track dilatation and insertion kit, that were needed for older generation cryoprobes (3.5–5.5 mm), are no longer necessary [9–11]. This development has significantly minimized the scrotal swelling and perineal ecchymosis occurring after the procedure [12]. By active instead of passive warming the procedure can be performed much quicker which is advantageous for the patient's recovery. Most patients are discharged from the hospital either the same day or the following day after treatment [13].

These technical improvements have made modern cryosurgery a minimal invasive procedure. Most reports in the literature are from the USA and Canada, but cryosurgery is evolving in European centers [13,14]. Therefore, an update is provided of the latest results of modern cryosurgery as a primary treatment option or as a salvage procedure

for radiorecurrent prostate cancer. We specifically discuss the impact of patient selection and criteria of treatment success on the oncological results. Also, developments such as focal- and nerve-sparing cryosurgery are discussed.

2. Evidence acquisition

The aim of this review is to put the results of third-generation cryosurgery in perspective with older techniques. Therefore, a structured literature review was performed by an electronic Pubmed search from January 1960 until June 2008. Data of primary- and salvage cryosurgery of the prostate with the following search terms: "cryosurgery and prostate cancer" (rendering 426 articles), "cryotherapy of the prostate and prostate cancer" (rendering 83 articles) and "cryoablation and prostate cancer" (rendering 446 articles) were retrieved. We only selected papers with relevant information on clinical outcome and treatment-induced complication rates. As data on overall survival and cancer-specific survival were lacking in most studies, predominantly biochemical disease-free survival (bDFS) rates were included.

We applied the following criteria for identification of articles to be clinically relevant:

- English language.
- Original papers with the elimination of review articles.
- Screening of reports for overlap of patient data by checking the center of treatment, co-authorship and time frame of patient selection.
- Any report of third-generation gas-based cryosurgery.
- A few large series on older techniques with a minimum of 12 months follow-up.

3. Evidence synthesis

3.1. Primary cryosurgery of the prostate

In most studies with intermediate-term follow-up both liquid nitrogen- and gas-based cryosurgery techniques have been used. In general, these show an actuarial biochemical disease-free survival (bDFS) of 60%–90% at 7 years [15,16]. Long-term overall survival data have not been published yet and one report shows a 5-year overall survival of 89% [17]. The bDFS for gas-based third-generation cryosurgery is comparable to the results in previous reports of older techniques [12,14,18]. Table 1 summarizes the results of recently published series, concerning primary cryosurgery of prostate cancer.

3.1.1. Clinical outcome

The PSA value is often used as a surrogate endpoint for treatment success in cryosurgery. The PSA-based definition of biochemical failure in literature varies considerably, complicating the comparison of outcomes. For instance, Long et al. [16] performed a retrospective outcome analysis of a database of 975 patients from five institutions, who underwent cryosurgery as primary treatment for localized or locally advanced prostate cancer. The median follow-up was 24 months. Using a PSA threshold of <0.5 ng/ml and <1.0 ng/ml, the 5-year actuarial bDFS ranged from 36%–61% and 45%–76%, respectively, depending on risk category of the patients. Bahn et al. [15] retrospectively reviewed a series of 590 patients, with a mean follow-up of 5.4 years. This data set of patients was also used by Long et al. [16]. Using a PSA threshold of <0.5 ng/ml, they found a 7-year actuarial bDFS for low-, intermediate- and high-risk patients of 61%, 68% and 61%, respectively. For a PSA threshold of <1.0 ng/ml the respective bDFS rates were 87%, 79% and 71%. However, using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of biochemical failure (three successive increases of PSA level), the bDFS was 92%, 89% and 89%, respectively. The outcome of the largest database for primary cryosurgery [19] shows a 5-year actuarial bDFS of 77% according to the ASTRO criteria, for mainly intermediate to high risk patients. This Cryo On Line Data (COLD) Registry encompasses assembled results from academic and community centers. A significant overlap in patient data exists with previously reported papers (Table 1).

Uniform criteria for treatment success are currently not agreed upon, but the combination of a static threshold with the need for a rising PSA trend with time seems reasonable. For instance, Shinohara et al. [20] evaluating 110 patients after cryosurgery for prostate cancer defined biochemical disease recurrence as a subsequent rise in PSA of >0.2 ng/ml from nadir. Patients with a PSA nadir of <0.1 ng/ml had a 7% biopsy failure rate. Those with nadir values of 0.1 to 0.4 ng/ml had 22% biopsy failures. Patients with a PSA nadir of ≥ 0.5 ng/ml had 60% biopsy failures. Apparently low PSA levels must be achieved after cryosurgery and therefore they suggested a threshold value of $\text{PSA} \leq 0.4$ ng/ml for defining a successful outcome.

Although cryosurgery is an ablative therapy, detectable levels of PSA are not necessarily associated with persistence of cancer cells, because there is usually preservation of some tissue surrounding the urethra that can be benign and may release PSA. Thus, the definition of treatment

success that is just on the threshold of PSA detection ($\text{PSA} < 0.1$ ng/ml) may be unreasonable to apply for cryosurgery.

In radiotherapy the ASTRO definition is accepted, but because this is a tumour selective therapy targeting dividing over non-dividing cells it is unknown whether it can apply to cryosurgery as well. It is also questionable whether the newer Phoenix or Houston definition may be appropriate for prostate cryosurgery. According to this definition any increase of 2 ng/ml above the nadir value during follow-up is considered to indicate a biochemical recurrence [21]. Because a PSA nadir after prostate cryosurgery is typically achieved, unlike radiation, by 3 months after the procedure, the use of this definition may be reasonable. Lacking uniform criteria for treatment success we propose to define biochemical failure using a PSA threshold of 0.5 ng/ml as well as the Phoenix/Houston definition.

Not only the PSA-based definitions of biochemical failure, but also a stratification of patients into risk groups determines the outcome. Success rates appear to be worse for high risk patients with a $\text{PSA} > 10$ ng/ml and Gleason scores > 7 [15,16]. However, a recent study [18] showed that even in the presence of a $\text{PSA} \geq 10$ ng/ml and Gleason score ≥ 8 , a favourable outcome could be achieved in 80% of patients. The numbers of patients in this study were low and these results should be interpreted cautiously. Besides, the results are probably influenced by concomitant hormonal therapy in 67% of patients. These patients generally have low serum testosterone levels for at least 2 months after cessation of treatment and therefore PSA levels after cryosurgery may be influenced by hormonal therapy.

From the early 1960s, cryosurgery was used as a treatment option for localized prostate cancer, that resulted in survival rates that approximated those of surgery and radiotherapy for all stages of disease [22]. Donnelly et al. [17] stated that the current treatment modalities for low-risk disease as watchful waiting, radical prostatectomy, external beam radiotherapy (EBRT) and brachytherapy achieve excellent local and systemic control. They compared the 5-year bDFS of these modalities to their cryosurgical results of a liquid nitrogen system for intermediate and high-risk patients, using PSA threshold values of <0.5 ng/ml and <1.0 ng/ml. The efficacy of cryosurgery appeared to be superior to both EBRT and three-dimensional conformal RT (3DCRT) for high-risk patients and to EBRT for intermediate-risk patients. Furthermore, the results of their series were comparable to radical prostatectomy as well as brachytherapy for intermediate

Table 1 – Results of primary cryosurgery

Ref. (with actuarial data)	No. patients	Median follow-up in months (range)	Technique	PSA threshold	Low risk	bDFS (%) Intermediate risk	High risk ^a	nADT (%)	Duplication ^b data: y/n (reference)
Long et al. [16] (5-year data)	975	24 (SD ± 16.5)	LN/Ar	<0.5	60	61	36	33	y (15)
Donnelly et al. [17] (5-year data)	76	61 (35–85)	LN	<1.0	76	71	45		
Bahn et al. [15] (7-year data)	590	68 (NA)	LN/Ar	<0.3	60	77	48	34	y (19)
				<1.0	75	89	76		
				<0.5	61	68	61	91	y (16, 19)
				<1.0	87	79	71		
				ASTRO	92	89	89		
Ellis et al. [65] (3-month data)	75	3 (NA)	Ar	<0.4	84 (all risk groups)			NA	n
Han et al. [12] (1-year data)	122	12 (NA)	Ar	<0.4	78	NA	71	37	n
Cytron et al. [66] (NA)	23	11 (mean) (9–18)	Ar	<0.5	78 (all risk groups)			NA	n
Prepelica et al. [18] (6-year data)	65	35 (4–77)	Ar	ASTRO	83 (most high risk)			68	y (19)
Creswell et al. [14] (1-year data)	31	9 (1.5–18)	Ar	<0.5	60	NA	60	NA	n
Polascik et al. [67] (NA)	50	18 (3–43)	Ar	<0.5	90 (all risk groups)			26	n
Jones et al. [19] (5-year data)	1198	24 (SD ± 26)	LN/Ar	ASTRO	85	73	75	NA	y (15, 17, 18)
				Phoenix	91	79	62		
Hubosky et al. [68] (2-year data)	89	11 (1–32)	Ar	<0.4	74	70	60	35	n
				ASTRO	94 (all risk groups)				
Cohen et al. [62] (10-year data)	204	12.6 (9.7–15.0)	LN	ASTRO	56 (all risk groups)			0	n
				Phoenix	81	74	46		
Chin et al. [23] (4-year data)	33	19 (NA)	Ar	ASTRO	13 (all risk groups)			100	n
				Houston	36 (all risk groups)				

^a d'Amico risk stratification (1992 American Joint Committee on Cancer): low risk = PSA < 10 ng/ml and Gleason biopsy ≤ 6 and clinical stage T1c–T2a; intermediate risk = PSA 10–20 ng/ml or Gleason biopsy 7 or clinical stage T2b; high risk = PSA > 20 ng/ml or Gleason biopsy ≥ 8 or clinical stage ≥ T2c; nADT, neoadjuvant androgen deprivation therapy.

^b Duplication of reporting some patient data likely: yes or no (reference); NA, not available; SD, standard deviation; LN, liquid nitrogen; Ar, argon gas; bDFS, biochemical disease free survival; ASTRO = three successive rises in PSA; Houston/Phoenix = PSA 2 ng/ml above nadir.

and high-risk patients and to 3DCRT for intermediate-risk patients. Also the incontinence rates in this series compared favourably with the complications of the other treatment modalities. Although these results are encouraging, the patient numbers are small making valuable comparison difficult and possibly inappropriate. Other studies confirm that the 5-year to 7-year bDFS and positive biopsy rates after cryosurgery are comparable to matching outcomes reported after EBRT, 3DCRT and brachytherapy with similar morbidity rates [15,16].

Despite the relative deficiency in patient numbers and trial design, in a randomized trial comparing third-generation cryosurgery with EBRT for locally advanced prostate cancer it was concluded that the results of cryosurgery were less favourable compared to those of EBRT and cryosurgery was considered suboptimal primary treatment in these

patients [23]. Although the bDFS at 4 years was clearly in favour of EBRT (13% and 47%, respectively), the disease-specific and overall survival were identical. However, a major advantage of cryosurgery over radiation therapy is that it can be repeated for residual disease without increasing the side effects.

3.1.2. Complication rates

The current technology of primary cryosurgery has minimal severe side effects (Table 2). In the COLD Registry database [19] the incontinence rate necessitating the use of pads was 2.9%. Rectal fistulas occurred in 0.4% and impotence in 91%. Very early series of first-generation cryosurgery reported high rates of rectourethral fistulas which have been virtually eliminated by third-generation cryosurgery [14]. The morbidity that was reported in second-

Table 2 – Complications (%) after primary cryosurgery

Ref.	No. patients	Technique	Fistula	Slough	Retention	Incontinence	Impotence	UTI	Perineal pain
Long et al. [16]	975	LN/Ar	0.4	NA	10	7.5	93	NA	NA
Donnelly et al. [17]	76	LN	NA	3.9	NA	1.3	100 (53: >3 yr)	NA	NA
Bahn et al. [15]	590	LN/Ar	0.004	NA	5.5	4.3	95	NA	NA
Ellis et al. [65]	75	Ar	0	6.7	6.7	5.4	82	NA	NA
Han et al. [12]	122	Ar	0	4.9	NA	3	87	NA	6
Prepelica et al. [18]	65	Ar	0	NA	3.1	3.1	NA	NA	3.1
Jones et al. [19]	1198	LN/Ar	0.4	NA	NA	2.9	91	NA	NA
Hubosky et al. [68]	89	Ar	1	2	4	2	NA	1	6

UTI, urinary tract infection; NA, not available; LN, liquid nitrogen; Ar, argon gas.

generation series of liquid nitrogen-based systems was mainly due to the use of older ultrasound equipment with less controllable freezing of the gland. This resulted in complications like urethral slough and retention in 10–23% and incontinence in 8–15% [24–26]. The temporal restriction by the US Food and Drug Administration on the type of urethral warming catheter that was used in 1994 was another important factor increasing the rates of slough [5,16]. Once the warming catheter was reintroduced to practice, the sloughing level decreased to the 4% that was seen just before 1994 [5]. As some studies have shown that 66% and 45% of prostate cancers is located within 5 mm and 1 mm from the urethra respectively, the increased risk of residual periurethral tumour due to sublethal periurethral temperatures caused by the use of a warming catheter should be taken into consideration [27]. The only adverse event that affects most patients (80–90%) nowadays is erectile dysfunction. Some reports suggest a recovery of sexual function, because the neurons for erectile function are not killed but injured and axonal regeneration after freeze injury may lead to functional recovery [28]. Despite this phenomenon cryosurgery should not be offered to patients who are willing to keep their potency. There are few published data on the effect of primary cryosurgery on quality of life. One study showed that the quality of life will generally return to the level before treatment by one year after cryosurgery [29].

3.2. Nerve-sparing and focal cryosurgery

The application of nerve-sparing cryosurgery can improve the functional outcome after treatment with better potency rates. It is known, from incidental autopsy studies that up to 20–30% of prostate cancers are solitary and unilateral [30]. The use of saturation prostate biopsies (up to 24 cores) could delineate monofocal compared to multifocal prostate cancer. In a recent report radical prostatectomy specimens from patients with clinically

localized prostate cancer were analyzed [31]. Completely unilateral cancers were identified in 18% of patients and the majority of these tumours (72%) were low volume. In this study it was suggested that only a select group of men would be amenable to focal cryosurgery targeting one lobe. The feasibility of nerve-sparing cryosurgery by active warming of the neurovascular bundle (NVB) was evaluated in a canine model [32]. In this model NVB preservation was possible but not consistently reproducible. In some cases NVB preservation with active warming may result in incomplete peripheral prostate tissue ablation. The authors conclude that these results have significant clinical meaning when attempting nerve-sparing cryosurgery. Because of the possible compromising effect on oncological outcome, nerve-sparing focal therapy should be considered experimental. In a preliminary study 9 patients were treated with focal, unilateral nerve-sparing cryosurgery [33]. After a mean follow-up of 36 months, all patients had a stable PSA and negative biopsies. Seven patients remained potent. The authors have appreciated the problem of multifocality in many prostate cancers and advised the patients to undergo repeated biopsies at a stable PSA level. Lambert et al. [34] reported the safety and efficacy of focal cryosurgery to preserve genitourinary function in men with localized, unifocal disease. With a median follow-up of 28 months, 84% were without biochemical failure and 68% remained potent. No patient had worsened LUTS, incontinence, rectal pain, perineal discomfort or fistula formation. Based on a 3-year observation period, focal cryosurgery of the prostate appeared to be associated with minimal morbidity and a promising efficacy.

Modern imaging techniques like 3-T endorectal coil MR imaging, dynamic contrast enhanced MRI and 3D MR spectroscopy have emerged with promising features in prostate cancer delineation [35,36]. Although these modalities are not widely available yet, an improvement in the detection of tumour volume and local extension as well as precise image-guided prostate biopsies is possible.

Further, the results of focal therapy can be monitored with these techniques. Other innovations like real-time “cellular” imaging [37] and computer planned positioning of the probes will improve efficacy and safety of the treatment.

3.3. Salvage cryosurgery of the prostate

In the EAU guidelines 2007 it is stated that achieving a PSA nadir after radiotherapy of less than 0.5 ng/ml seems to be associated with a favourable outcome. The interval before reaching the nadir PSA may take up to 3 years or more. A PSA rising more than 2 ng/ml above the nadir PSA is the current definition of biochemical failure after radiotherapy. Also, the PSA doubling time following radiotherapy appears to aid in predicting the time to prostate cancer-specific death. Local recurrence rates after curative radiotherapy, confirmed by prostate biopsy, vary between 25% and 30% [38–41] and even a percentage of over 90% has been reported [42]. Recently, Touma et al. [43] reviewed the published data of salvage therapies following radiation failure. The authors state that the final success rate of curative radiotherapy depends on the modality being used, like conventional radiotherapy, 3DCRT or intensity modulated conformal radiotherapy (IMRT). It has been proven that dose escalation is an independent predictive factor of outcome. Also, local failure was found to be a strong predictor of distant metastasis. Others have suggested that recurrent prostate cancers are biologically more aggressive, either because of cytological evolution, perhaps induced by radiation or due to the progression of an innately aggressive tumour already resistant to radiation [44]. Therefore, in a patient with low risk of systemic disease (pre-treatment tumour stage, negative restaging imaging and greater than 12 months’ PSA doubling time) and a life expectancy of more than 10 years salvage cryosurgery may be applied when PSA reaches 2 ng/ml above nadir after an interval from radiotherapy of at least 18 months.

Because of the relatively high rates of local disease recurrence after radiotherapy and its implications for outcome, salvage treatment options with curative intent have been applied since 1985 when the first series of salvage radical prostatectomy was published [45]. Five-year bDFS rates after salvage radical prostatectomy have been reported varying from 55% to 69% [43].

3.3.1. Clinical outcome

Biochemical failure rates of salvage cryosurgery also depend on the PSA threshold being used. Again, like for primary cryosurgery, there is no clear definition

Table 3 – Results of salvage cryosurgery

Ref. (with actuarial data)	No. patients	Median follow-up in months (range)	Technique	PSA threshold	Low risk	bDFS (%) Intermediate risk	High risk ^a	nADT (%)	Duplication ^b data: y/n (reference)
de la Taille et al. [54] (1-year data)	43	22 (mean) (1–54)	LN/Ar	<0.1	66 (all risk groups)	NA	34	100	y (57)
Chin et al. [48] (5-year data)	118	19 (3–54)	Ar	<0.5	NA	NA	NA	60	y (58)
Ghafar et al. [57] (2-year data)	38	21 (mean) (3–37)	Ar	Nadir + 0.3	74 (all risk groups)	NA	NA	100	y (54)
Han et al. [11] (1-year data)	18	12 (NA)	Ar	<0.4	77 (all risk groups)	NA	NA	NA	n
Bahn et al. [69] (7-year data)	59	82 (NA)	Ar	<0.5	59 (all risk groups)	NA	NA	NA	y (47)
Creswell et al. [14] (1-year data)	20	9 (1.5–18)	Ar	<0.5	67 (all risk groups)	NA	NA	NA	n
Ismail et al. [13] (5-year data)	100	33 (mean) (12–79)	Ar	<0.5	73	45	11	46	n
Ng et al. [58] (8-year data)	187	39 (mean) (NA)	Ar	ASTRO	59 (all risk groups)	NA	14	71	y (48)
Pisters et al. [47] (5-year data)	279	22 (SD ± 25)	LN/Ar	ASTRO	59 (all risk groups)	NA	NA	NA	y (69)
				Phoenix	55 (all risk groups)				

^a d’Amico risk stratification (1992 American Joint Committee on Cancer): low risk = PSA < 10 ng/ml and Gleason biopsy ≤ 6 and clinical stage T1c–T2a; intermediate risk = PSA 10–20 ng/ml or Gleason biopsy 7 or clinical stage T2b; high risk = PSA > 20 ng/ml or Gleason biopsy ≥ 8 or clinical stage ≥ T2c; nADT, neoadjuvant androgen deprivation therapy.

^b Duplication of reporting some patient data likely: yes or no (reference); NA, not available; SD, standard deviation; LN, liquid nitrogen; Ar, argon gas; bDFS, biochemical disease free survival; ASTRO = three successive rises in PSA; Houston/Phoenix = PSA 2 ng/ml above nadir.

of failure. In an older series of salvage cryosurgery Pisters et al. [4] reported on 150 patients comparing a single and a double freeze-thaw cycle for local recurrence after radiotherapy. The mean follow-up was 13.5 months and the PSA threshold was <0.1 ng/ml. Six months after a double freeze-thaw cycle, a higher negative biopsy rate was found of 93% compared to 71% after a single freeze-thaw cycle. The biochemical response rate after a double freeze was favourable with a bDFS of 56%. Data from Allegheny General Hospital, Pittsburgh, USA, with different cryosurgery techniques being used, demonstrate a 10-year bDFS of 57%. The PSA nadir level was <0.4 ng/ml and failure was defined as two consecutive rises in PSA level of 50% or more [46]. Data from the largest database on salvage cryosurgery (COLD Registry) [47], in which 14 physicians participated and 277 patients were treated with either liquid nitrogen or gas-based technology, the five-year actuarial bDFS was 59% according to the ASTRO definition of biochemical failure. Again, the results of this database are assembled from many centers which leads to overlap of reporting. The results of the latest series of third-generation salvage cryosurgery are comparable to or even better than the previous techniques (Table 3). Several authors have defined predisposing factors for a worse outcome of salvage cryosurgery, including high PSA > 10 ng/ml and high Gleason score > 8 [48–50]. Also, patients with clinical stage T3 or T4 disease have an unfavourable outcome [48,49]. Complete ablation of the prostate is usually not attained in salvage cryosurgery, subsequently resulting in the release of PSA. In two series of salvage cryosurgery viable benign prostate tissue was identified in a substantial number of prostates, even though the biopsies after cryosurgery were negative for cancer [51,52]. This suggests incomplete ablation of the prostate was performed, but recurrence rates after salvage cryosurgery were not associated with this presence of benign prostate tissue [52].

3.3.2. Complication rates

Salvage radical prostatectomy is technically more challenging than primary prostatectomy. Significant complications will occur because of tissue plane obliteration, fibrosis and radiation-induced vasculitis. The average rates of rectal injury, anastomotic stricture and urinary incontinence are 6.6%, 18% and 45%, respectively [43]. Therefore, cryosurgery has emerged as a feasible minimal invasive treatment, although the complication rates are higher than those of primary cryosurgery (Table 4). This is especially true for incontinence rates and pelvic pain [53,54]. Initial salvage cryosurgery series reported incontinence rates of 73% or higher [4,55]. With third-generation techniques a significant decrease in serious side effects, such as incontinence and rectourethral fistulas, was found [46,56,57]. Currently, the average incontinence rate is 8% (range 3%–13%), depending on the definition of incontinence. Mostly, incontinence is defined as the daily use of one or more pads [54]. In the COLD Registry database [47] a rectourethral fistula rate of 1.2% and incontinence rate of 3.8% was reported. The incidence of other complications, like urethral sloughing and strictures vary from 10%–15% to as low as 0%–5%, with the application of a urethral warming catheter and the newer cryotechnology [48,54,57]. Less frequently reported complications, but nevertheless bothersome are lower urinary tract symptoms (LUTS), occurring in up to 16% of patients [13,57,58]. The rates of impotence after salvage cryosurgery are high but many patients already have significant erectile dysfunction as a consequence of the foregoing radiotherapy. Perrotte et al. [59] found that quality of life was adversely affected especially by perineal pain, not so much by incontinence or impotence. They showed that treatment without an effective urethral warming catheter was highly associated with incontinence, perineal pain and slough. They concluded that salvage cryosurgery does not seem

Table 4 – Complications (%) after salvage cryosurgery

Ref.	No. patients	Technique	Fistula	Slough	Retention	Incontinence	Impotence	UTI	Perineal pain
de la Taille et al. [54]	43	LN/Ar	0	0	4	9	NA	9	26
Chin et al. [48]	118	Ar	3.3	5.1	8.5	6.7	NA	NA	NA
Ghafar et al. [57]	38	Ar	0	0	0	7.9	NA	2.6	39.5
Han et al. [11]	18	Ar	0	11	0	11	86	NA	5.6
Bahn et al. [69]	59	Ar	3.4	NA	NA	8	NA	NA	NA
Ismail et al. [13]	100	Ar	1	2	2	13	86	NA	4
Ng et al. [58]	187	Ar	2	NA	21	3	NA	10	14
Pisters et al. [47]	279	LN/Ar	1.2	3.2	NA	4.4	NA	NA	NA

UTI, urinary tract infection; NA, not available; LN, liquid nitrogen; Ar, argon gas.

to have any advantage compared to salvage prostatectomy in terms of morbidity and quality of life. Another study, in which quality of life was prospectively evaluated two years after salvage cryosurgery, showed that QOL returned to preoperative levels in all domains by 24 months after treatment, with the exception of urinary- and sexual functioning [60]. The overall QOL score was high and the satisfaction rates competed with the alternative of radical prostatectomy or androgen deprivation therapy. A single institution study, comparing quality of life between primary and salvage cryosurgery showed better physical and social functioning of the primary cryosurgery patients [61]. Overall QOL scores were high and the symptom scale pain scores were low for both treatment groups.

3.4. Evaluation

Despite the encouraging results urologists should be cautious when counselling patients about the outcomes of cryosurgery for a number of reasons. First of all, in many study protocols different cryosurgery systems have been used making comparison of outcome difficult. Because a uniform definition of treatment success is lacking, the end-points vary considerably. Usually varying definitions of biochemical recurrence are used as surrogate endpoints. Concomitant androgen deprivation therapy has an influence on short-term treatment results and must be taken into consideration (Tables 1 and 3). Most studies report the results of retrospective, single-institute case series and only one peer-reviewed publication of a randomized trial comparing cryosurgery with radiotherapy is available. Moreover, long-term follow-up data on disease-specific and overall survival are not available yet. Only one report of long-term bDFS with a median follow-up of 12.55 years has been published with a 10-year negative biopsy rate of 77% [62]. Furthermore, it should be realized that many studies are from only a few leading centers of excellence in the USA and Canada with considerable overlap in reporting of patient data (Tables 1 and 3). This typically leads to publication bias of positive studies and the results should be interpreted with caution. According to a recent Cochrane analysis, it must be concluded that results of cryosurgery are of low-level evidence [63]. Cryosurgery is a technically demanding procedure and the learning curve to reach an acceptable expertise level has been 200 cases in earlier days [64]. Since then, new computer planning programs and guidance systems have greatly facilitated the

procedure, but cryosurgery should be done only after adequate training.

4. Conclusions

There are increasing numbers of European centers applying cryosurgery for prostate cancer. The long learning curve has declined with new computer planning programs and guidance systems which greatly facilitate the procedure. Modern cryotechnology is therefore highly reliable and results are promising. The introduction of gas-based third-generation cryosurgery has decreased the complication rates significantly with similar clinical outcome when compared to older techniques. Salvage cryosurgery has more adverse effects, but remains an option for radiorecurrent prostate cancer patients. Stratifying patients into risk groups is an important aid for the urologist to select patients for cryosurgery. Further, a specific definition of treatment success is urgently needed. New developments like focal- and nerve-sparing cryosurgery for unifocal prostate cancer aim at further reducing the side effects but are still considered experimental. In counselling patients it is important to discuss the possible therapeutic gain of cryosurgery, the associated side effects and the impact on quality of life. The current data are derived from studies of low-level evidence and this should be taken into consideration when making treatment decisions. Although biochemical disease free survival rates seem to be comparable to those of other treatment modalities, randomized trials with long-term follow-up are needed to define the role of cryosurgery in the treatment of localized prostate cancer.

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Study concept and design: Langenhuijsen, Vergunst.

Acquisition of data: Langenhuijsen, Broers, Vergunst.

Analysis and interpretation of data: Langenhuijsen.

Drafting of the manuscript: Langenhuijsen.

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