Only carefully selected patients may have a beneficial effect of salvage cryoablation in recurrent prostate cancer after radiotherapy

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ABSTRACT

INTRODUCTION: In Denmark, salvage cryoablation of locally recurrent prostate cancer (sCAP) after curatively intended radiation therapy (RT) is the only potentially curable option, and this experimental treatment has only been offered at Aarhus University Hospital. This study presents our experiences with the treatment.

MATERIAL AND METHODS: sCAP procedures were performed from 2006 to 2012. Cases were registered prospectively. Recurrent disease was defined by the Phoenix criterion (prostate-specific antigen (PSA) level > PSA nadir + 2 ng/ml).

RESULTS: A total of 39 sCAP treatments were performed in 37 patients. Four patients had previously been treated with brachytherapy and 33 with external radiation. There were two cases of hemiablations; the remaining cases were total ablations. The median follow-up period was 42 (0-69) months and the age at the time of treatment was 66 (53-78) years. Stratified according to D'Amico et al's 2003 risk definition, five patients had pre-RT intermediate-risk disease, and 31 had high-risk disease. Three cases could not be classified. Biochemical recurrence was found in 27 cases, and the 12-month disease-free survival was 18.2% overall. No patient in the intermediate group had recurrence. In high-risk patients, there were 25 cases of recurrence and the 12-month disease-free survival was 10.7%. There were five (13%) cases of fistula formation and seven (19%) cases of severe post-operative incontinence, all in previous high-risk patients. Information on potency was deficient.

CONCLUSION: In this limited study, sCAP was very infrequently a curable treatment in high-risk patients, and the treatment carried a high risk of severe morbidity. It seems, however, that sCAP could be beneficial to patients, primarily in the intermediate-risk group.

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Cryoablation of the prostate (CAP) remains a controversial issue. However, as a salvage treatment after curatively intended radiation therapy, it is the only potentially curable treatment, as salvage radical prostatectomy is not performed routinely in Denmark. The demand for treatment increases continually as the incidence of prostate cancer has nearly doubled within the past decade in Denmark [1]. Even though radiotherapy of primary prostate cancer has improved with more targeted and higher doses of radiation to the diseased area, failure is still estimated to occur in 10-60% of the cases [2]. Third-generation cryosurgery is a minimally invasive procedure which consists in selective targeting and destruction of pathologic prostate tissue using a freezing technique [3]. We wish to present our experiences with the treatment method after six years.

MATERIAL AND METHODS

Patient selection

In 2006, salvage CAP was introduced in the Department of Urology at Aarhus University Hospital. Treatments were registered prospectively according to the Aarhus Prostate Cancer Database by review of hospital records. With Aarhus being the only authorised CAP centre, patients were referred from all regions of the country. Biopsy-verified local recurrence and a negative metastatic workup were required. The latter was performed at the referring hospital. Post-surgery follow-up was performed at three, six and 12 months. Provided that no recurrent disease or troublesome adverse events had occurred, the patients were referred back to the general practitioner. Prostate-specific antigen (PSA) levels were then tested every sixth months during the following two years, and once a year hereafter. If data were not apparent from the hospital patient system at the deadline for the current follow-up, contact was obtained by phone. Prostate biopsies were not routinely drawn as part of the standard control setting.

Procedures

All the procedures were performed by two surgeons, and SeedNet TM system (GalilMedical, London, UK) was used for all operations. 6-12 cryoneedles were placed in the prostate with ultrasound guidance. During the procedure, a transurethral warming catheter protected the urethra from frost injury. The prostate tissue was cooled down to a temperature below minus 40 °C in two

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TABLE 1

The salvage cryoablation of locally recurrent prostate cancer treatments divided into D'Amico risk group and type of treatment: total number and number of cases with recurrent disease. The values are n (%).

	All	Total ablation	Hemiablation
Total number			
D'Amico:			
Low	–	–	–
Intermediate	5 (13)	4 (11)	1 (50)
High	31 (79)	31 (84)	-
Missing	3 (8)	2 (5)	1 (50)
Sum	39 (100)	37 (95)	2 (5)
Number of cases with recurrent disease			
D'Amico:			
Low	–	–	–
Intermediate	0	0	0
High	25 (81)	25 (81)	0
Missing	2 (67)	1 (50)	1 (100)
Sum	27 (69)	26 (70)	1 (50)

TABLE 2

Demographics of the 39 cases.

Age at time of cryoablation, yrs, median (range)	66 (53-78)
Initial biopsy, Gleason score, n (%)	
< 7	7 (18)
7	13 (33)
> 7	14 (36)
Missing	5 (13)
Clinical stage at diagnosis, n (%)	
< T2b	5 (13)
T2b	6 (15)
> T2b	28 (72)
Missing	0 (0)
PSA level at presentation, n (%)	
< 10 ng/ml	6 (15)
10-20 ng/ml	9 (23)
> 20 ng/ml	22 (56)
Missing	2 (5)
Pre-RT D'Amico risk category, n (%)	
Low	0 (0)
Intermediate	5 (13)
High	31 (79)
Missing	3 (8)
Pre-salvage PSA level, ng/ml, median (range)	4 (0.2-13.6)
Time from RT to recurrent disease, months, median (range)	38 (3-113)
Time from RT to cryoablation, months, median (range)	47 (0-117)
Cases receiving hormonal treatment at the time of cryoablation, n (%)	7 (18)
Type of primary radio therapy, n (%)	
Brachytherapy	4 (10)
EBRT	35 (90)
Follow-up, months, median (range)	42 (0-69)

EBRT = external beam radiation therapy; PSA = prostate-specific antigen; RT = radiation therapy; T2b = tumour stage 2b.

10-minute intervals. The ice ball formed in the targeted tissue was continuously monitored by trans-rectal ultrasound, as was the temperatures in the prostate and near the rectal wall where thermo sensor probes were inserted. Patients were typically discharged from the hospital the next day. The supra-pubic or transurethral catheter was typically removed within two to three weeks.

Statistical analysis

Post-CAP recurrence was defined by the Phoenix criteria PSA level > PSA nadir + 2 ng/ml).

Patients were retrospectively stratified into three groups based on the likelihood of recurrent disease according to the D'Amico et al [4] 2003 risk definition. The outcome was reviewed using Kaplan Meyer curves, and differences in the risk subgroups were determined by use of the log rank-test.

Trial registration: not relevant.

RESULTS

A total of 39 salvage treatments were performed in 37 patients (**Table 1**), and total follow-up was possible in all cases. Recurrence was seen after brachytherapy in four cases and recurrence followed external beam radiation in 33 cases. The median age at the time of treatment was 66 (53-78) years, and the median follow-up period was 42 (0-69) months. The radiation treatments were performed from 1992 to 2008. Demographic data are listed in **Table 2**. There were two cases of hemiablation. Both patients had only positive biopsies from one hemisphere, and hemiablation was performed in an attempt to reduce the side effects. Two patients had had two treatments consisting of total ablation (Table 1).

As most patients were referred from other centres, the information on the duration of radiotherapy and any additional endocrine treatment was deficient. It was, however, found that seven patients were receiving hormonal treatment at the time of referral: five with gonadotropin-releasing hormone analogues and two with antiandrogen treatment. At the latest, these treatments were discontinued at the three-month follow-up after the cryotreatment. The other patients were not routinely given additional endocrine treatment. All patients had new prostate biopsies taken because they experienced a rise in post-radiotherapy PSA levels. All but one had tumour-positive biopsies. This one patient had negative biopsies as well as a negative metastatic workup. As he was a candidate for a kidney transplant, if his prostate cancer could be cured, he was treated in an attempt to achieve a fall in PSA level even though local recurrence had not been verified. The salvage cryosurgery required a negative metastatic workup. As this was usually conducted at the referring hospital, the imaging

use for the workup varied. In 34 cases, the patient had negative bone scans, and this was supplemented with a negative computed tomography (CT) in eight cases, a negative magnetic resonance imaging in five cases, and a negative ultrasound scan in two cases. Two patients had a negative positron emission tomography (PET) CT. One patient only had a negative CT and one only a negative MR. Only one patient had no record of diagnostic imaging. He had experienced recurrence after brachytherapy and his PSA value was only 2.3 ng/ml. His biopsies were tumour-positive in three of six samples. Generally, there were no records of any imaging giving suspicion of metastasis. The median pre-cryo-PSA level was 4 (0.2-13.6) ng/ml. From the pre-radiation information, patients were classified according to the D'Amico et al 2003 risk score classification. In three cases, the information in the patient's medical records was insufficient to classify the patient. Of the remaining 36 cases, five were classified at the primary diagnosis as having an intermediate-risk prostate cancer and 31 cases were classified as high-risk patients (Table 2).

Oncological outcome

At follow-up, five patients (14%) had died from prostate cancer. This occurred 92 (59-201) months after the primary prostate cancer diagnosis and 41 (30-44) months after salvage cryosurgery. One patient (3%) had died from complications to the treatment. Post-operatively, this patient developed a severe case of fistula formation to the rectum and the thigh. The on-going infection eventually induced a sepsis from which he died. There were 27 cases of new, recurrent disease defined in accordance with the Phoenix criteria and the 12-month biochemical recurrence-free survival was 18.2% overall (Table 1, **Figure 1**A). Regarding the D'Amico subgroups, no patient from the intermediate risk group had recurrent disease. In the high-risk group, there were 25 cases of recurrent disease and the 12-month biochemical recurrence-free survival was 10.7% (Table 1, Figure 1B). Of the seven patients receiving hormonal treatment at the time of salvage cryotreatment, five had recurrent disease. The two who did not both had less than seven months of follow-up.

Side effects and complications

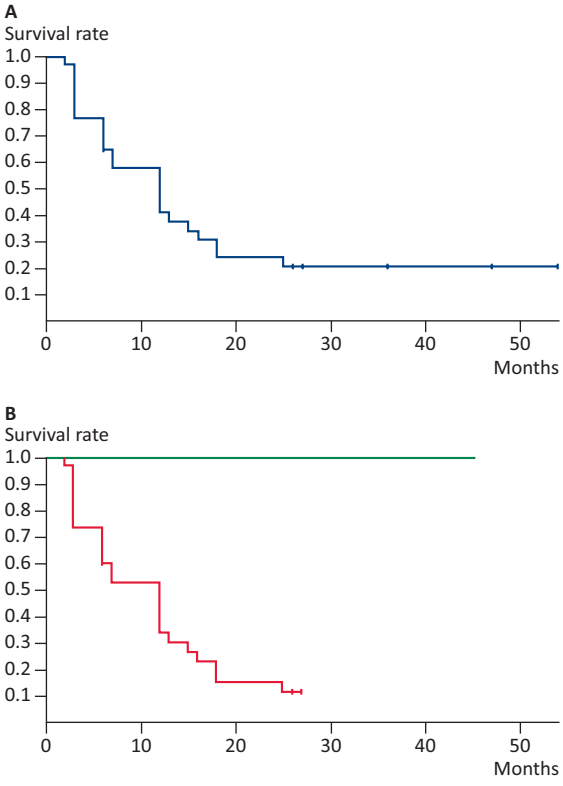
In total, five patients developed fistulas. All fistulas developed from the prostate/urethra to the rectum and one was also connected to the groin. This patient had a severely complicated fistula and was submitted to hospital for months post-operatively due to severe infection. Seven patients were severely incontinent after surgery and three of these later had a continence (Scott) prosthesis implanted. One had a permanent supra-pubic catheter and the remaining three patients did not receive additional treatment. Less severe incontinence was described in a single patient.

Post-operatively, seven patients developed urinary retention. Of these, one patient had a permanent supra-pubic catheter and four had a transurethral resection of the prostate. Two of these patients subsequently became incontinent and one had a continence prosthesis implanted. In all, a total of four patients had Scott prosthesis implanted.

Two patients experienced severe urge, but were not incontinent. One patient had recurrent lower urinary tract infections and was treated with prophylactic antibiotics. Another patient developed wounds in the perineum and was in chronic pain hereafter. Complication data are summarized in **Table 3**.

FIGURE 1

Biochemical recurrence-free survival curves for the salvage cryoablation of locally recurrent prostate cancer cohort using the phoenix criteria of recurrence (prostate-specific antigen level > nadir + 2 ng/ml). **A.** Biochemical recurrence-free survival in months after salvage cryoablation of locally recurrent prostate cancer, overall (blue line). **B.** Biochemical recurrence-free survival after salvage cryoablation of locally recurrent prostate cancer in intermediate (green line) and high (red line) risk group, p = 0.0086.



DISCUSSION

Using the Phoenix criteria, we found very high rates of recurrence after salvage cryosurgery. It needs to be ac-

TABLE 3

Incidence of side-effects and complications, n (%).

Procedure-related deaths	1 (3)
Fistula formation	5 (13)
Incontinence	7 (18)
Scott prosthesis	4 (10)
Urge without incontinence	2 (5)
Urinary retention	7 (18)
TUR-P	4 (10)
Chronic perineal pain	1 (3)

TUR-P = transurethral resection of the prostate.

knowledged, however, that no established definition of failure has been agreed upon. In retrospect, routine post-surgical prostate biopsies would have been ideal to determine recurrence. The definitions of biochemical recurrence vary throughout the literature, which makes biochemical recurrence rates vary according to the definition used. Cells around the urethra survive the CAP treatment and will continuously produce small amounts of PSA [5, 6]. These amounts will vary from patient to patient and no universal acceptance of one criterion has been reached. The most frequently used alternative to the phoenix criteria is the Astro criteria (three consecutive rises in PSA), and use of these criteria suggests higher recurrence rates [7]. Other definitions used are PSA level > 0.4 ng/ml, PSA level > 0.5 ng/ml, and PSA nadir + 0.2 ng/ml [8-10]. The recurrence rates would inevitably have been even higher if any of these definitions had been used in the present study.

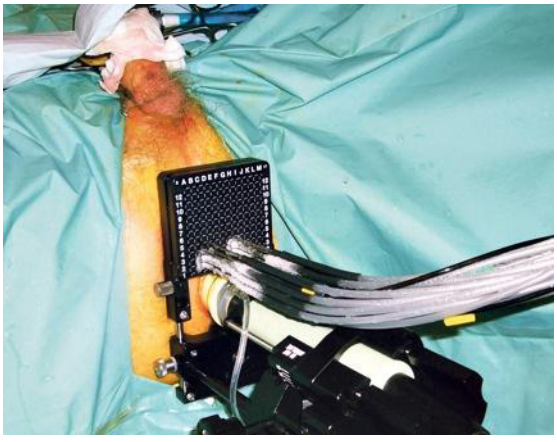
As mentioned above, recurrence rates in the literature differ widely as the definition of recurrence differs (recurrence rates of 35%-66%) [10-12]. However, a study of 132 patients by Spiess et al, where recurrence was defined by the Phoenix criteria, found a biochemical disease-free survival after one year of 87.8% [13]. This share is much higher than what we found in the present study. Since the treatment method was not introduced at the department until 2006, the high rates of recurrence could be due to a learning curve. This risk was, however, minimised . As one of the CAP physicians had considerable experience from another hospital, the first ten CAP procedures were performed in collaboration between him and the trainee. Also, the percentage of recurrence between the surgeons was found to be similar.

Patient selection is essential for a successful outcome after salvage treatment. Recommendations vary, but patients should, of course, have a negative metastatic workup. In our study, there was no standardised use of pre-cryodiagnostic imaging. This will, of course, increase the risk of recurrence. In the literature, a high PSA level, Gleason score and clinical stage at the time of diagnosis, as well as initial risk-group stratification have been found to predict a higher risk of recurrence. In a study by Spiess et al, it was established that a high PSA level at diagnosis was the strongest predictor [11]. In the present study, 56% of the patients had PSA levels above 20 ng/ml and 31% of the patients had PSA levels above 40 ng/ml at the time of the prostate cancer diagnosis. Another recent study by Spiess et al found that pre-salvage PSA level is a strong predictor of recurrence and that patients optimally should be treated before their PSA level reached 5 ng/ml [14]. In our cohort, this was obtained only in 19 (49%) cases. Regarding the D'Amico classification in this study, four patients were classified as belonging to the intermediate-risk group prior to the original radiation therapy and none of these patients had recurrent disease (Table 1). Even though this intermediate group is very small, this indicates that the preoperative risk group is a predictor for recurrence (p = 0.009) (Figure 1B).

At the time of treatment, seven patients were receiving androgen-deprivation therapy (ADT). Five had biochemical recurrence, and the other two had only short follow-up. It is well-known that ADT during and after radiation therapy improves disease-free and overall survival [15], and it is now standard treatment. Theoretically, the additive effect of combining the two treatments, which would inhibit repopulation during treatment, could perhaps be transferred to the cryoablation treatment. To our knowledge there are, however, no randomized trials on the subject and no tendency towards this outcome could be detected in our limited population.

It is well-known that side effects after salvage are more common than after primary CAP, as previously irradiated tissue is more fragile [16]. In our cohort, five patients (13%) developed fistulas, and post-surgery incontinence levels were also high with seven (19%) pa-

Needles positioned in the prostate during cryoablation procedure for local recurrent prostate cancer.



tients complaining about severe incontinence. In a new review of the present literature on the subject, Finley et al found severe incontinence rates to range from 3% to 64% depending on the definition used [17]. It is thus well-known that incontinence is likely after salvage CAP. In the same study, fistula rates were found to range from 1% to 6%. These rates are, however, somewhat lower than those found in our study. The reason for our high incidence of fistulas is unknown, but it was probably part of a learning curve as all cases were seen in the treatments performed during the first year.

Besides the obvious limitation due to the small number of CAP cases, another major limitation in this study was the retrospective setup. Regarding side-effects and complications, not all complaints are necessarily recorded in a consultation where the natural focus is the oncological outcome. This is also the reason why erectile dysfunction is not listed as a side effect; the material from the medical records was simply insufficient to make relevant observations. Also in the matter of lower urinary tract symptoms and chronic pain, the incidence rates are probably even higher than those listed in Table 3 as these are not considered to be as severe as fistula formation and incontinence.

CONCLUSION

At our department, salvage cryoablation of the prostate was only infrequently a curable treatment, and as it also had a high potential for severe morbidity, the treatment has been questionable and is no longer an option in Denmark. In this rather limited material it nevertheless seemed that the salvage procedure could be beneficial to carefully selected patients, primarily in the intermediate-risk group. If only these patients were offered the treatment, the total number of treatments at the department would be far too low to offer sufficient routine in the use of the method.

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