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Originals

"Open Perineal Cryosurgery" in Carcinoma of the Prostate – A Possible Curative Alternative

G. Kunit

Urological Department, General Hospital Salzburg, Salzburg, Austria

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Summary. 101 Patients with different stages of carcinoma of the prostate underwent "open perineal cryotherapy" between September 1976 and December 31, 1983. The age of the patients varied between 44 and 80 years. The benefit of this method was a lower rate of complications than in radical prostatectomy with a similar cummulative survival rate in stage B disease. No immunological response was found in this study. Neopterin values – an easily detectable parameter for the T-lymphocyte-macrophage-activity and urinary neopterin excretion immediately after cryosurgery remained in the normal range. In stage D patients no metastases disappeared. Further studies showed no effect on the pituitary gonadal axis after cryotherapy of the prostate.

Key words: Prostate carcinoma, Perineal cryosurgery, Curative alternative, Cryobiology, Cryoimmunology.

Introduction

The various therapeutic options for the treatment of carcinoma of the prostate are presently debated [29]. Radical prostatectomy has been associated with well defined complications: operative mortality is about 1%, total urinary incontinence occurs in 10% and erectile impotence in more than 80% of the cases. The latter effect is stated to decrease to less than 10% by use of the modified technique of Walsh [32] which preserves the cavernous nerve.

Further, stress incontinence, and the formation of a stricture at the anastomosis between the urethra and the urinary bladder are also frequent side effects.

To minimize these complications we have elected to evaluate "open perineal cryotherapy" in a group of patients suffering from carcinoma of the prostate, a method, used by Culp [9], Flocks [11], used by Culp [9], Flocks [11], Loening [15a], Milleman [16], O'Donoghue [17], Requin [19], Rigondet [20–22], Rigotti [23], Sesia [25, 26], Soanes [28] and Tramoyeres [30].

Cryobiology

The principles of cryotherapy and the mechanism which leads to the destruction of the tissue have been published elsewhere [23]. Briefly, to induce ice crystal-formation within cells, it is necessary to lower tissue temperature to −15 °C to −20 °C. Initially, the temperature decreases below the freezing point (the overcooling phase) before crystal formation begins. After the crystalization of the first nucleus, the temperature falls very quickly to the freezing point. Both chemical and morphological changes in the tissue may lead to cell destruction:

- dehydration resulting in increased concentrations of electrolytes
- crystalization and rupture of cell membranes
- denaturation of lipoprotein molecules inside cell membranes
- thermic shock
- intravascular stasis of blood
- disturbances in enzyme metabolism.

Cell destruction is time dependent; during a slow freezing procedure larger crystals will develop with inclusion in the pericellular area so that the cells shrink and become dehydrated; however, few cells may survive. During a rapid freezing process (between −40 °C and −196 °C) the intracellular ice crystals which develop are very small and complete tissue destruction occurs [27]. An additional factor leading to tissue destruction is the slow return to normal temperature. Rapid warming can lead to intracellular melting of the small microcrystals and tissue destruction is jeopardized. After cryotherapy the tissue becomes necrotic and haemorrhagic with leucocyte infiltration. Later, fibroblast formation takes place.

Table 1. Material

Year	Number of patients	Stage B, C, D outside control
1976	9	4
1977	12	2
1978	22	5
1979	13	1
1980	8	3
1981	16	1
1982	14	3
1983	7	0
Total	101	19

age 44–80 yrs, mean age 67.4 yrs

Table 2

Local tumor extent:
- rectal palpation
- cystoscopy

Staging procedures:
- Blood counts, sedimendation rate
- SMA 12 (electrolytes, liver function tests with enzymes)
- i.v.P
- chest-x-ray
- bone scan
- sonography
- lymphography (until 1979)
- computed tomography including liver, retroperitoneal space and small pelvis

Cryoimmunology

Immunological studies after cryosurgery of BPH and of carcinoma of the prostate have been reported by Ablin [1–6], Catalona [8], Eltahir [10] and Milleman [16]. There is a concensus that an increase of α_2-globulin is preceeded by an increase in albumin, gamma-globulin and immunoglobulin A (IgA), immunoglobulin G (IgG) and immunoglobulin M (IgM). The most significant increase has been noted in the concentration of IgG.

Neopterin, an unconjugated pteridine derived from guanosine-tri-phosphate, is secreted by macrophages. The secretion is induced by Interferon-γ, the product of T-lymphocytes, stimulated by alloantigens and/or chemically or virally modified autoantigens. Neopterin secretion is a specific and easily detectable parameter for the T-lymphocyte-macrophage-system and therefore of the activity of the cellular immune system [7]. We determined basal urinary neopterin values and the urinary neopterin excretion immediately after cryosurgery to evaluate whether activation of the T-lymphocyte-macrophage-system was induced by cryotherapy. Neopterin was measured by HPLC on reversed phase and correlated with creatinine levels [7, 13, 31].

Material and Methods

101 Patients with different stages of carcinoma of the prostate underwent "open perineal cryotherapy" between September 1976 and December 31, 1983 (Table 1). The age of the patients varied between 44 and 80 years (average age 67.4 yrs). In 98 patients the diagnosis was established by perineal or transrectal biopsy; in 3 cases "open perineal cryosurgery" was performed on the basis of positive cytology only. The size of the primary tumor was established by cystoscopy and rectal palpation. Further staging procedures included the determination of electrolytes, liver enzymes, i.v.P., chest-x-ray, bone scan, sonography and lymphography (until 1979). Computed tomography of the abdomen, retroperitoneum and pelvis was performed in all cases after 1979 (Table 2).

The degree of tumor cell differentiation was established using the criteria of Gleason et al. [12]. "Open perineal cryosurgery" was performed as follows:

The prostate was exposed in an extreme dorsosacral (lithotomy) position by the classical, perineal Belt incision. A curved retractor was placed in the bladder. The rectum as well as the posterior leaf of Denonvillier's fascia were dissected from the posterior surface of the prostate. By blunt dissection the seminal vesicles were exposed. The Ch-18-cryoprobe was inserted into the prostate at several locations. For the freezing procedure we used liquid nitrogen (a temperature of $-170\,^{\circ}C$) and a cryotherapy apparatus CE4 made by the Frigitronics Company. The freezing period varied between 2 to 4 min at each location. The positions of the probe were selected to provide overlapping spheres of freezing zones, attempting to affect all of the prostate including the base of the gland and the seminal vesicles, but avoiding the ureters. The probe was easily removed by heating the tip. Finally, a drainage tube was inserted into the wound, the centrum tendineum was reconstructed and the wound was closed in layers. The retractor was replaced by a silastic catheter Ch16, which drained the urinary bladder for 10 days. The wound drain was removed after 8–10 days. Antibiotics were given for 14 days.

The postoperative follow-up is described in Table 1. 19/101 patients refused to participitate in the study after cryotherapy was performed. They are under the care of private urologists and have been excluded from this study.

Three to four months after cryosurgery all patients except 3, classified already as stage D from the beginning, underwent a transurethral resection of the prostate and/or a transrectal biopsy. The statistical evaluation of cummulative survival for all the tumor groups and cummulative survival versus tumor stage was performed as directed by Kaplan-Meier.

Results

The operative procedure was well tolerated by all patients and there were no major perioperative complications. Our clinical findings are encouraging. Three months after cryosurgery carcinoma of the prostate could no longer be diagnosed by rectal examination in 85% of the patients. The prostatic fossa was flat without evidence of prostatic tissue. In 15% of the patients a residual tumor could be

Table 3. Causes of death

1)	12/82 died with a survival time between 7 and 53 months
2)	2 patients with stage B died because of heart infarction and carcinoma of the pancreas. The autopsy showed no evidence of local disease or distant metastases
3)	3 patients with stage C died because of carcinoma of the pancreas, leukemia and bronchopneumonia. The autopsy demonstrated a local extent of prostatic carcinoma and a few regional lymph node metastases
4)	7 patients with stage D died because of severe local and metastatic disease owing to prostatic cancer

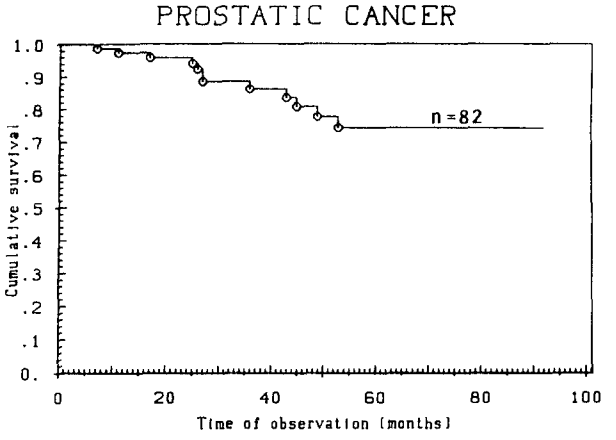

Fig. 1

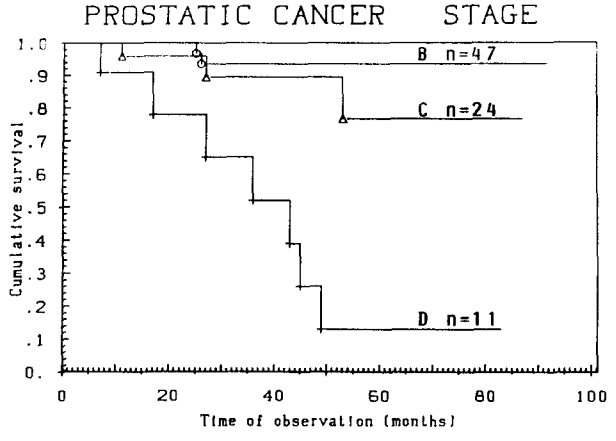

Fig. 2

palpated during rectal examination. Based on postcryosurgical TUR and/or transrectal biopsy and the presurgical staging assessment, the 82 patients remaining in the study were grouped as follows: 47 patients were classified as stage B, 24 as stage C and 11 as stage D. In 27/47 of the patients with stage B disease a pelvic lymphadenectomy was performed immediately prior to cryosurgery. In these cases no positive lymph nodes were found.

Based on histological evaluation of tissue obtained 3–4 months after cryosurgery, either by TUR and/or rectal biopsy, malignant cells were absent in all the stage B subjects, but were present in stage C and D patients.

Twelve patients (2 stage B, 3 stage C and 7 stage D) died between the 7th and 53th postoperative month. The causes of death are summarized in Table 3.

The remaining 70 surviving patients (interval 12 to 99 months) were examined regularly every 3 months. The phosphatases and LDH were found to be normal in all stage B and unchanged in the stage C cases. In some patients with stage C disease a gradual increase of phosphatase concentration was accompanied by a physical deterioration. The patients with stage D and progressive stage C disease were given adjuvant therapy, i.e. external beam radiation, endocrine therapy and/or orchiectomy.

Kaplan-Meier curves were constructed to investigate the cummulative survival rate of all the 82 patients to evaluate the relationship between single tumor stage versus patient survival rate.

The Breslow/Mantel Cox test was added to measure the significance of association. We have found a highly significant association between survival rate and single tumor stage ($p < 0.0001$). The five year crude survival rate including all stages ($n = 82$) was estimated to be 75% (Fig. 1). The five year survival rates according to tumor stage were calculated as follows: stage B ($n = 47$) $> 90\%$, stage C ($n = 24$) 78%, stage D $< 20\%$ ($n = 11$) (Fig. 2).

Contrary to reports by others we did not detect the disappearance of metastases in the stage D patients in our study. Pre- and immediate postoperative urinary neopterin levels in 12 patients who were treated by "open perineal cryosurgery" for stage B disease are shown in Figs. 3 and 4. As can be seen there was a slight increase of neopterin excretion during the postoperative course in 6 patients. Increase in neopterin secretion is often seen after operative intervention and indicates a transient, nonspecific reaction. The neopterin concentrations fell and remained within the normal range as long as the tumors remained dormant indicating a lack of T-lymphocyte-macrophage system activation.

"Open perineal cryotherapy" for carcinoma of the prostate was associated with some complications (Table 4). In our study the perioperative mortality was 0%. A transitory, perineal fistula occured in 3% of the patients; a postoperative epididymitis and a stricture of the urethra developed in 2%. In 1% a bladder stone was found and 38.5% suffered erectile impotence. However, none of the operated patients was incontinent.

Results of basal hormone analyses (LH, FSH, T, E_2 and prolactin) performed in 10 patients classified as group B about 1 year after cryosurgery are tabulated in Fig. 5. The hormonal data show: testosterone values within the normal range, LH and FSH levels varied widely as usually seen in this age group, the E_2 values all in the upper range of normal or slightly elevated – it should be mentioned that no hormonal therapy was performed in this group of patients – while prolactin concentrations were within the normal range except in two cases.

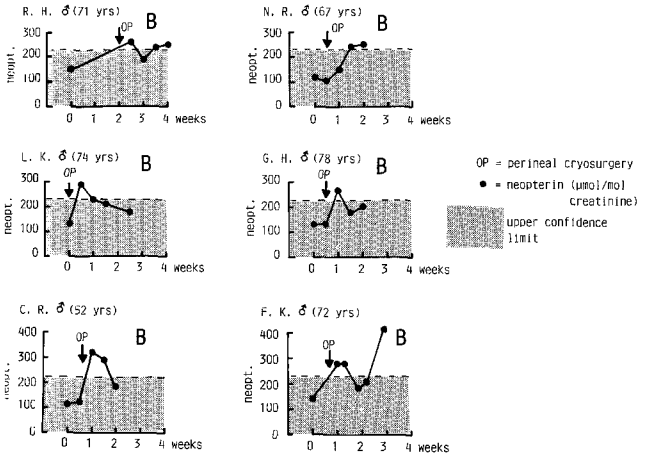

Fig. 3

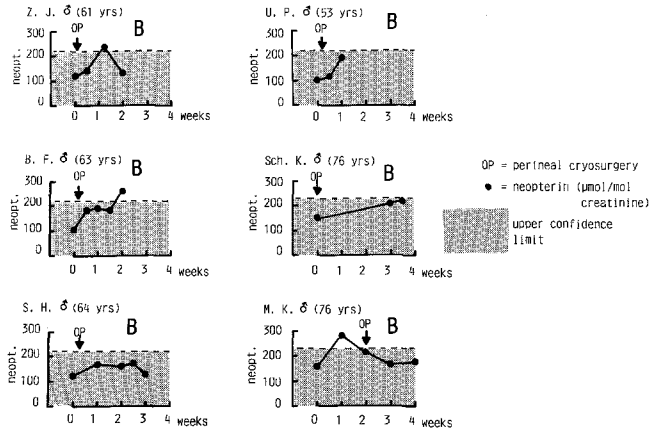

Fig. 4

Table 4. Rate of complications

Perioperative mortality	0,0%
Perineal fistula	3,0%
Postoperative epididymitis	2,0%
Stricture of the urethra	2,0%
Bladder stone	1,0%
Erectile impotence	38,5%
Incontinence	0,0%

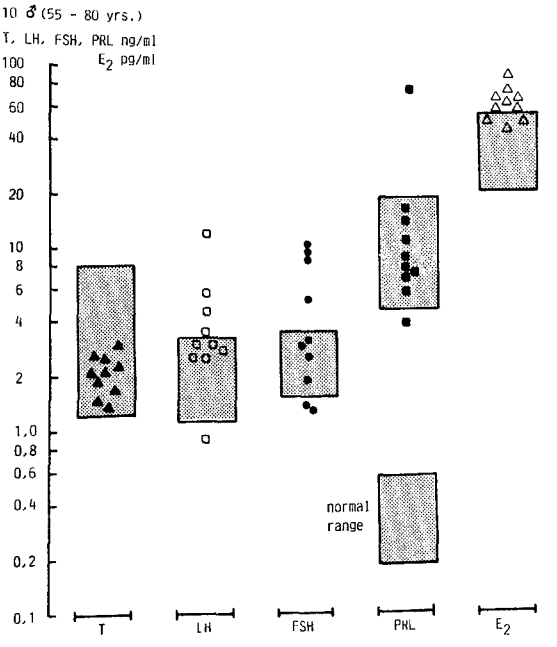

Fig. 5

Discussion

The principal aims in the treatment of prostatic cancer are to eradicate the primary lesion, to control the local spread of the disease, to prevent the onset of metastases and, if possible, to relieve the symptoms caused by the tumor.

We have seen no acute perioperative complications and the procedure was well tolerated. The percentage of postoperative complications was lower than occurs with other methods of curative therapy which usually guarantee excellent life-quality. Our estimated 5-year cummulative survival rates (Kaplan-Meier method) related to tumor stage may be comparable to other forms of curative treatment comparable to other forms of curative treatment [15a]. To provide a more accurate estimate of this method it will need a longer follow-up and a larger number of patients. 10 year follow-up is recommended. In our series 26 patients have survived beyond five years and show no evidence of local tumor spread or of metastatic disease.

Culp and others [9, 10] reported that following cryosurgery metastatic lesions regressed, or disappeared in some cases. There has arisen considerable speculation concerning the mechanism by which these changes might occur. The most popular explanation was related to immunologic suppression by the release of cellular antigens from destroyed prostatic tissue. We did not find any regression and/or disappearance of metastases after cryosurgery in our study. Neopterin measurements did not indicate an activation of the T-lymphocyte-macrophage system which suggested an absence of immunological suppression.

Measurements of hormone concentrations indicated that the function of the pituitary-gonadal axis was not affected by cryotherapy. The impotence rate of more than 30% seen in this study can be explained by partial, or total damage, to the cavernous nerve during the operation. Alternatively, erectile impotence might have been caused by psychological factors, stimulated by concern for the course of the disease.

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Dr. G. Kunit
Department of Urology
General Hospital Salzburg
A-5020 Salzburg
Austria