

Cryoiimmunologic Investigations in Patients with Prostatic Carcinoma

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Transurethral cryosurgery was performed with liquid nitrogen in 18 patients with prostatic carcinomas. The clinical course and the effect of cryosurgery on immune competence of patients were observed.

After cryosurgery, pain was relieved in 5 of 6 patients, dysuria was improved in 7 of 12 patients, and the prostatic mass was reduced in 14 of 18 patients. Elevated serum acid phosphatase levels returned to normal in 5 cases.

Changes of serum protein fractions were variable. Serum complement levels were high in advanced cases. Changes of immunoglobulins were variable. Serum anti-prostatic antibody could not be detected by passive hemagglutination test and by indirect immunofluorescent examination. DNCB skin reaction and blastoid transformation of lymphocytes were raised after therapy.

The cellular immune competence may be enhanced by cryosurgery, while the humoral immune competence is scarcely influenced by the therapy.

It has been reported that remission of metastatic lesions occurred after cryosurgery for advanced prostatic carcinoma (Soanes et al.¹⁾). Furthermore, it was suggested that immune competence of the patient with carcinoma may be enhanced after cryosurgery (Ab-lin²⁾). In an attempt to examine the effect of cryosurgery on immune competence, we observed clinical and immunologic responses after treatment in 18 patients with prostatic carcinoma.

MATERIALS AND METHODS

The subjects of this observation were 18 patients with prostatic carcinoma who underwent cryosurgery. As shown in Table 1, the ages of the patients ranged between 63 and

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83 years (the mean 73 years). The stages of those cases were 3 of B, 6 of C and 9 of D. Ten cases had no therapy before cryosurgery.

Transurethral cryosurgery of the prostate was performed with liquid nitrogen. A cryosurgical unit (Torisha CS45-3 type) was used. Freezing was performed under -160°C 1 min, -80°C 2 min, -40°C 3 min, -30°C 4 min and -20°C 5 min. Freezing was repeated 2 or 3 times every 4 weeks.

Before and after freezing, subjective symptoms and objective findings, including examinations of the primary prostatic mass, metastatic lesions and serum acid phosphatase were evaluated periodically.

As a parameter of immune competence of the patient, the following investigations were performed. For humoral immunity, serum protein fractions, complement, and immunoglobulins were determined. The passive hemagglutination test³⁾ and indirect immunofluorescent examination⁴⁾ were performed to detect the anti-prostatic antibody. For cellular immunity, peripheral lymphocytes count, PPD and DNCB skin reaction, rosette formation⁵⁾ and PHA blastoid transformation⁶⁾ of lymphocytes, and macrophage migration inhibition test (MIT)⁷⁾ were carried out.

The observation period of the clinical course was between 10 and 66 weeks after cryosurgery. Hormone therapy was stopped for 10 weeks after cryosurgery and then castration and hormone therapy followed.

Table 1. Clinical responses following cryosurgery.

Case	Age	Stage	Subjective improvement		Objective improvement	
			Pain	Dysuria	Palpation of P.	Acid phos.
1	68	B		+	+	N.
2	78	B			+	-
3	77	B		+	+	+
4	76	C		-	+	N.
5	76	C			+	N.
6	83	C		-	+	N.
7	72	C		+	+	+
8	69	C		+	+	N.
9	71	C		+	+	N.
10	74	D			-	-
11	63	D	+	-	-	-
12	66	D	+	+	+	-
13	73	D	+	-	-	-
14	66	D	+	-	+	transient+
15	72	D			+	transient+
16	82	D			+	-
17	79	D	+	+	-	transient+
18	72	D	-		+	+

+good -poor

N. normal

RESULTS

1. Clinical responses after cryosurgery.

As shown in Table 1, pain was relieved in 5 of 6 patients, and dysuria was improved in 7 of 12 patients. Sizes of prostatic masses were reduced in 14 of 18 patients. No response was found in 4 of 9 cases of stage D. Objective remission of metastatic lesions was not observed in any of the cases.

Responses of total acid phosphatase (TAP) following cryotherapy are shown in Fig. 1. Among 9 cases with elevated TAP, levels of 5 cases returned to normal range except one case whose TAP level increased after 3 weeks. Four cases with high TAP levels showed no significant change.

The response of prostatic acid phosphatase (PAP) was almost parallel with that of TAP as shown in Fig. 2.

2. Influence of cryosurgery on immune competence.

a. Humoral immunity

Responses of serum proteins following cryotherapy are shown in Fig. 3. Alpha-1 globulin increased in 7 of 18 cases and decreased in 7 of 18 cases after therapy. Changes in α_2 , β and γ -globulins were variable.

Responses of serum complement and immunoglobulins following cryotherapy are shown in Fig. 4. Serum complement levels before therapy were high in 4 of 9 advanced cases. Changes of levels of complements and immunoglobulins after therapy were variable. The serum anti-prostatic antibody could not be detected by passive hemagglutination test

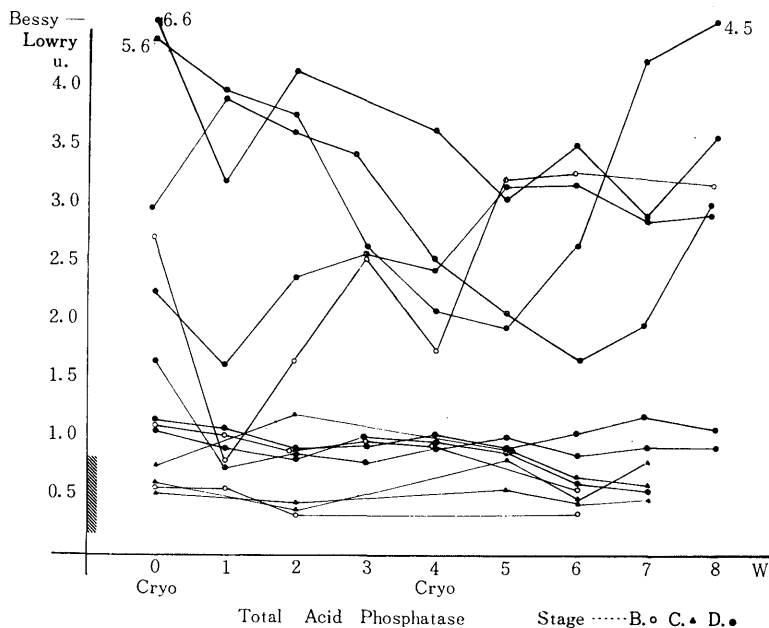


Figure 1. Responses of total acid phosphatase following cryosurgery.

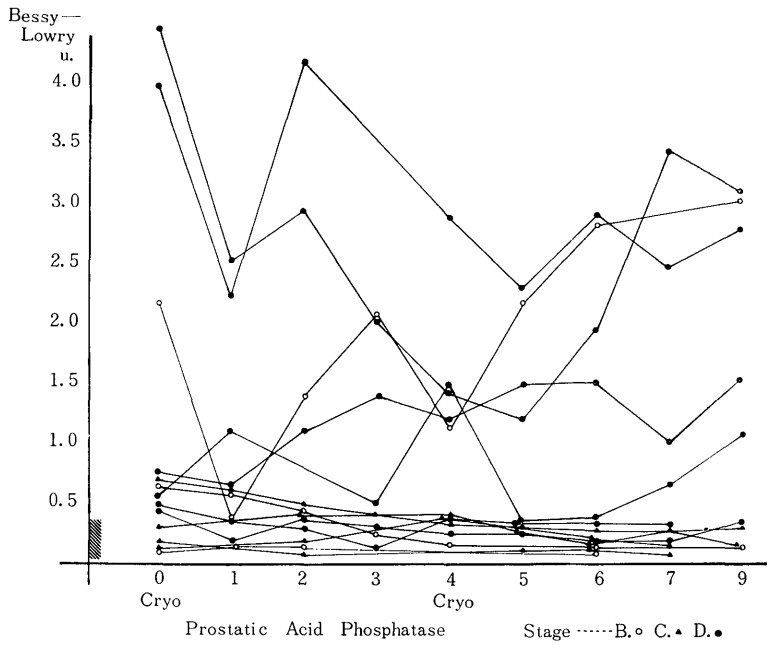


Figure 2. Responses of prostatic acid phosphatase following cryosurgery.

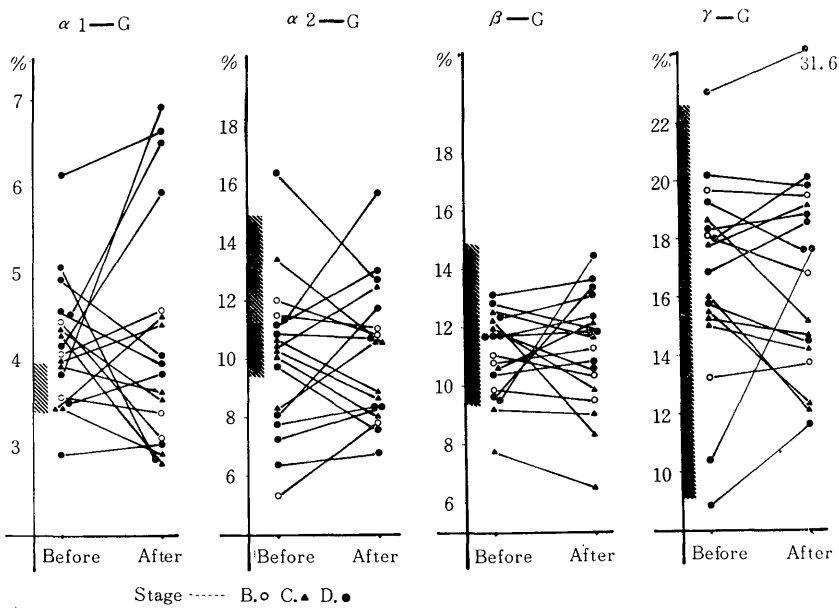


Figure 3. Responses of serum protein fractions following cryosurgery.

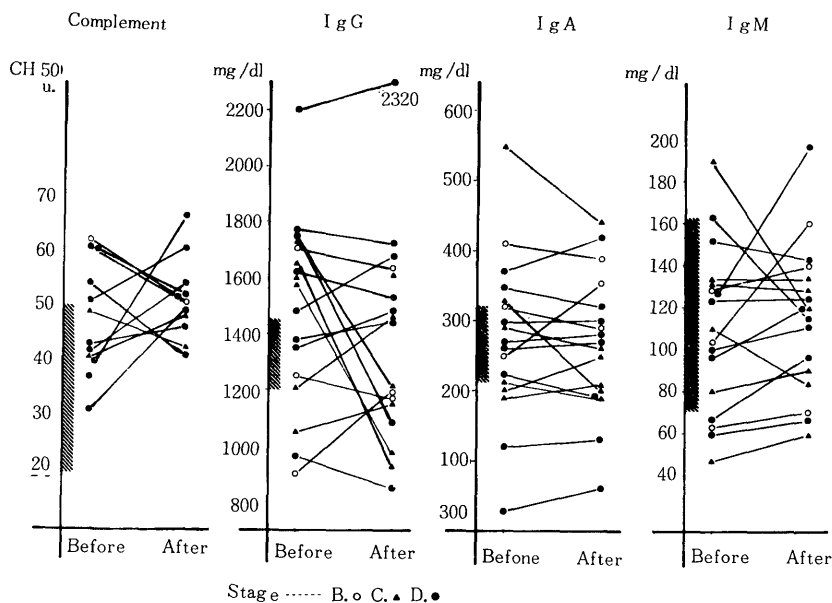


Figure 4. Responses of serum complement and immunoglobulins following cryosurgery.

and by indirect immunofluorescent examination.

b. Cellular immunity

Changes of peripheral lymphocytes counts and DNCB skin reaction following cryotherapy are shown in Fig. 5. Changes of peripheral lymphocytes counts were not significant. DNCB skin reactions before therapy were positive in 11 cases (3 of stage B and C, 5 of stage D) and negative in 7 cases (3 of stage C and 4 of stage D). After therapy, reactions were raised in 9 of 18 cases. Among them, the reactions were changed to positive in 6 negative cases. The effects of cryotherapy on PPD skin reactions were variable.

Influences of cryotherapy on blastoid transformation, rosette formation test of lymphocytes, and macrophage migration inhibition test are shown in Fig. 6. The blastoid transformation rates before therapy were low in all 18 cases. However, blastoid transformation rates were increased in 11 of 15 cases after therapy. The rosette formation rates before therapy were high in 4 cases and low in 2 cases (stage C and D). The rates were slightly increased in 4 of 15 cases after therapy.

The result of MIT was indicated as the ratio (%) of macrophage migration area to the control area without antigen. The ratio below 80% was regarded as positive and above 80% as negative. Before therapy, MIT were positive in 5 cases (1 of stage B, 2 of stage C and D) and were negative in 12 cases (2 of stage B, 4 of stage C and 6 of stage D). After therapy, MIT changed to positive in 2 of 5 negative cases and changed to negative in 5 of 12 positive cases.

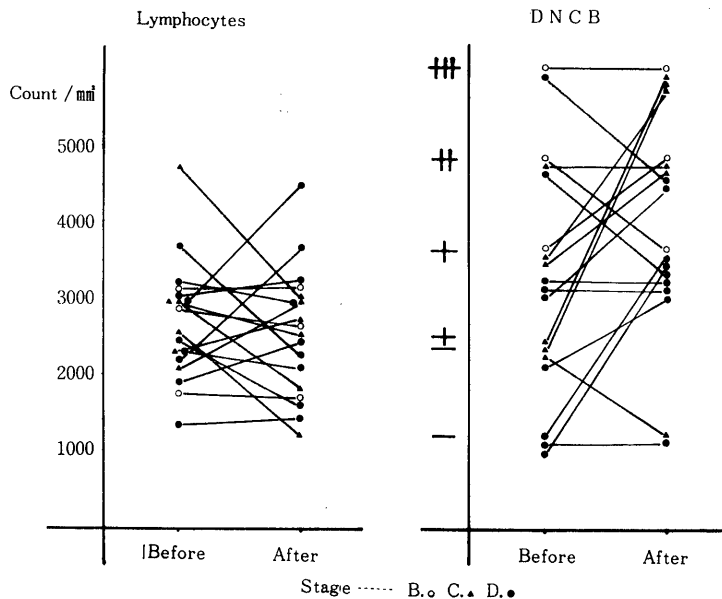


Figure 5. Responses of peripheral lymphocytes counts and DNCB skin reactions following cryosurgery.

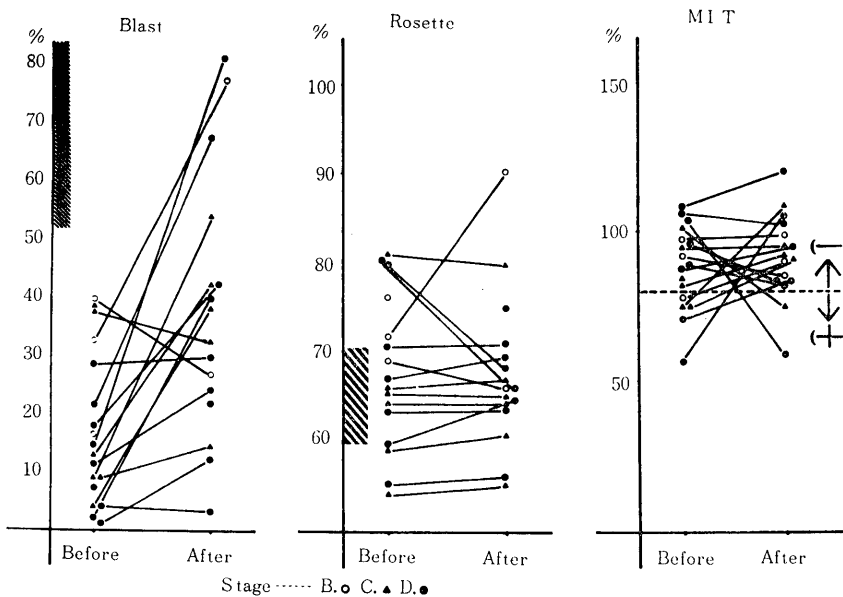


Figure 6. Responses of blastoid transformations, rosette formations of lymphocytes and macrophage migration inhibition tests following cryosurgery.

DISCUSSION

As mentioned above, we performed cryotherapies for 18 patients with prostatic carcinomas, and observed the clinical course after treatment and the effect of cryosurgery on immune competence of patients.

It is reasonable to conclude that the primary prostatic mass was remarkably reduced and consequently dysuria was improved by cryosurgery. On the other hand, pain was relieved in many cases and elevated serum TAP levels returned to normal in 5 cases. Therefore, it is suggested that cryosurgery effects not only the local prostatic lesion but also the general condition of the patient. It may be summarized that the effect of cryosurgery on subjective symptoms and objective findings of the prostatic carcinomas is as good as that of usual hormone therapy, but the duration of response is not as long. Therefore, it is recommended that castration and hormone therapy follow cryosurgery.

In regard to the immune response of frozen rabbit prostate, it was reported that the anti-prostatic antibody was developed in serum after freezing (Yantorno, et al.⁷⁾, Jagodzinski, et al.⁸⁾ and Zappi, et al.⁹⁾). We also confirmed the same results in the freezing experiments of the rabbit kidney and prostate (Kanetake¹⁰⁾, Shindo, et al.¹¹⁾). However, we could not detect the circulating anti-prostatic antibody by the passive hemagglutination test and by the indirect immunofluorescent examination during our clinical experiences. Furthermore, changes of serum protein fractions, complements and immunoglobulins were not significant. Therefore, it is considered that cryosurgery may have little influence on humoral competence of the patient.

On the contrary, the cellular immune responses, DNCB skin reactions, and blastoid transformations of lymphocytes increased after cryosurgery. Therefore, it is suggested that cellular immune competence of the patient may be enhanced after cryosurgery.

Ablin²⁾ reported that α_2 -globulin decreased and blastoid transformation increased after cryosurgery. He suggested that α_2 -globulin may act as a blocking factor in the blastoid transformation of lymphocytes. However according to our clinical experiences with cryosurgery, α_2 -globulins decreased in 6 cases and increased in 6 cases. Changes of α_2 -globulins after therapy did not correlate with results of blastoid transformation tests.

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