

## Biochemical Failure after Carbon Ion Radiotherapy for Prostate Cancer

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**Abstract.** *Background/Aim:* Biochemical failure after radiotherapy for prostate cancer occurs infrequently, but some cases progress to a poor outcome. The aim of this study was to examine prognosis after biochemical failure. *Patients and Methods:* A total of 728 patients were treated with carbon ion radiotherapy, and biochemical failure occurred in 90 (12.4%). Their outcomes were examined according to risk factors, histological findings, and androgen deprivation therapy (ADT). *Results:* Biochemical failure rates were 12%, 6%, and 15% in low-, intermediate- and high-risk patients. Most patients responded favorably to salvage therapy. Some high-risk patients (25%) progressed to poor outcome; half experienced failure after ADT, while the rest during ADT, indicating that ADT had a slight influence. Patients who died from their disease had approximately two years of biochemical failure-free time and three years of survival after failure. Their tumor showed the presence and the increased proportion of histologically high-grade growth patterns. *Conclusion:* Histological growth patterns and short biochemical failure-free time are prognostic factors for poor outcome regardless of ADT.

radiotherapy, which exhibits a strong cytocidal effect, a high linear energy transfer, and limited radiation dose distribution due to spread-out Bragg peak, has been considered to be a suitable strategy for the treatment of localized cancer. The National Institute of Radiological Sciences in Chiba, Japan, constructed the Heavy Ion Medical Accelerator in Chiba (HIMAC), in 1993, and began treatments for localized and locally advanced prostate cancer in 1995. Favorable results for biochemical failure-free, overall, and cause-specific survival rates have been reported (2-4). During treatment with carbon ion radiotherapy, however, some patients experience biochemical failure and progress to a worse outcome. A crucial issue for improving radiotherapy is the determination of progression factors that suggest poor prognosis. Therefore, the present study examined patients experiencing biochemical failure and the potential factors associated with a poor outcome by determining the relationship between cancer characteristics and adjuvant hormone therapy.

### Patients and Methods

*Patients.* Patients with confirmed histological adenocarcinoma and T1-T3N0M0 cancer were enrolled in the study. Between October 1995 and December 2008, 728 consecutive patients were treated with carbon ion radiotherapy. The patients had not received prior treatment for prostate cancer. The clinical records for all of the patients were collected in 2011, and the follow-up period lasted for an average of 83 months (median 87 months and range 16-153 months). When treatment outcome was examined, patients who died of diseases other than prostate cancer were confirmed to have had no elevation of total prostate-specific antigen (PSA; Dainipack, Abbot, Chiba, Japan) before death. Stages were estimated using the TNM classification of UICC 2009 (5). Before radiotherapy, a prostate biopsy with eight or more core samples was performed and the histological examination was conducted by a central pathologist (MH), using the Gleason grading system (6). Concurrently, the histological growth patterns were analyzed in the same specimens with an ocular microgrid (one millimeter squares within ten millimeter). The proportions of the six types of histological growth patterns were calculated according to the WHO-Mostofi grading

Prostate cancer is a common disease in elderly males. In Japan, in 2009 there were 42,517 cases of prostate cancer and 9,527 deaths (1). The proportion of patients with a localized stage of cancer has gradually increased, and treatments for this cancer stage include surgery and radiotherapy with or without hormone therapy. Among these treatment options, carbon ion

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system (7). Risk was classified according to NCCN system (8) with some modifications; T1-T2a, Gleason score  $\leq 6$ , and PSA  $< 20$  ng/ml (low), T2b-T2c or Gleason score 7, or PSA  $\leq 20$  (intermediate), and  $\geq T3a$  or Gleason score  $\geq 8$  or PSA  $> 20$  (high).

Androgen deprivation therapy (ADT) was administered according to the patient's risk classification. The low- and intermediate-risk patients with T1 and T2a tumors were not given ADT. Six months of neoadjuvant and one year or more of adjuvant ADT was given to the intermediate-risk patients with either T2bc or a Gleason score of seven. The high-risk patients were administered six months of neoadjuvant and additional adjuvant ADT for a total of two or more years. The ADT generally consisted of a luteinizing hormone-releasing hormone agonist and a daily dose of 80 mg of bicalutamide. Biochemical failure was determined when PSA levels were higher than baseline by 2 ng/ml (without ADT or after the conclusion of ADT) or had increased in three consecutive measurements (during continuous ADT).

The patients underwent a digital rectal examination and PSA determination every three to six months. When abnormal findings were suspected, imaging examinations including a bone scan and magnetic resonance imaging were performed along with frequent PSA assays. After biochemical failure, conventional hormone therapy followed by other salvage therapy, was used according to the EAU Guidelines (9). The endpoints of the study were the overall and cause-specific survival rates.

**Carbon ion radiotherapy.** To establish the radiation modality, the following four protocols were adapted sequentially (2): Protocol 9402 (35 patients) with a dose escalation of 54.0-72.0 Gy equivalent (GyE); Protocol 9703 (61 patients) with a dose escalation of 60.0-66.0 GyE; Protocol 9904-1,2 (466 patients) with a fixed dose of 66.0 GyE; and Protocol 9904-3 (166 patients) with a fixed dose of 57.6 GyE. The radiation fractions were 20 in five weeks with, the exception of Protocol 9904-3 which included 16 fractions in four weeks.

The technique of carbon ion radiotherapy has been previously reported (2). Briefly, the head and feet of the patient were positioned in a customized cradle and the pelvis was immobilized with a thermoplastic sheet. The bladder was filled with 100 ml of sterilized water in the anterior direction during a computed tomographic (CT) planning session and during each treatment session from the anterior direction. The clinical target volume was designed for the prostate and seminal vesicle after referring to a 5-mm thick CT scan. The initial planning target volume was created by adding 10 mm anterior and lateral margins, and a 5 mm posterior margin which was positioned on the anterior wall of the rectum to limit the dose received by the rectum to less than 50 GyE. Radiation was performed with one anterior port and a set of lateral ports, which were alternated at each session once a day.

**Statistical analysis.** The survival rate was calculated using the Kaplan Meier method. The statistical differences were determined by the unpaired two-group *t*-test, and a *p*-value of  $\leq 0.05$  was considered significant. All calculations were performed using the SPSS statistical computer program (IBM Japan Ltd, Tokyo, Japan).

## Results

**Biochemical failure.** Among 728 patients treated, 90 patients (12.4%) experienced biochemical failure. The profiles of the patients who experienced biochemical failure are shown in

Table I. With regard to ADT, the patients were classified into three groups: no ADT until failure (No-ADT), failure some time after the conclusion of ADT (After-ADT), and failure during continuous ADT (During-ADT). Although the addition of ADT was scheduled by the protocol, a minority of patients did not complete the ADT because of comorbidities or adverse effects. The biochemical failure-free times were longer in the intermediate-risk group than in the other groups; this result is partly because of the influence of ADT.

The fraction of patients who died of prostate cancer was the highest in the high-risk group (16/63, 25%, Table I); the low- and intermediate-risk patients rarely died of prostate cancer. To examine the poor outcome in the high-risk cases, the patients were divided into ADT groups and their respective characteristics were compared (Table II). During-ADT patients exhibited a shorter time between radiation and biochemical failure (biochemical failure-free time), compared with the No-ADT and After-ADT patients. Sixteen patients died of prostate cancer after biochemical failure, and these included eight of the During-ADT patients (8/23, 35%), seven of the After-ADT patients (7/36, 19%), and one of the No-ADT patients. This suggests that the mode of ADT appears to have a slight influence on the treatment outcome in some high-risk patients.

Among the patients in the high-risk group, the disease characteristics of the patients who died of prostate cancer were compared with those of the 47 patients, including alive cases and those who died of non-prostate cancer (Table III). The initial PSA values of those who died of prostate cancer and of the other patients had a similar distribution. The stage and Gleason score had similar patterns in the two groups. However, a comparison of the histological growth patterns in tumors between those who died of prostate cancer and the other patients yields significant differences (Figure 1). The proportion of tumor with large and/or small simple glands and micro-glands, which are the low-grade growth patterns, was much lower in the patients who died of prostate cancer than in the other patients ( $p=0.01$ ). Various high-grade growth patterns, such as medullary/solid and columns-and-cords/trabecular patterns, were predominantly found in the patients who died of prostate cancer.

The time between radiation and biochemical failure was shorter for the patients who died of prostate cancer, compared with that for the remaining patients ( $p=0.0001$ ). Patients who died of prostate cancer survived  $37.1 \pm 23.2$  months after biochemical failure. This suggests disease progression in a state of castration-resistant prostate cancer (CRPC), which might have led to the poor outcome.

**Outcome.** After biochemical failure, the No-ADT and After-ADT patients received ADT for 2-3 years or more. The During-ADT and After-ADT patients, when resistant to

Table I. Patients with biochemical failure by risk group.

	Low	Intermediate	High	<i>p</i> -Value
No. patients	15 (12%) <sup>#</sup>	12 (6%)	63 (15%)	
Age (year)*	66.0±5.7 (59-79)	65.5±5.7 (53-73)	67.2± 6.9 (51-87)	
PSA (ng/ml)	9.8±4.1 (5-17)	11.2±5.3 (4-19)	48.8±42.0(4-191)	L.I vs. H<0.0001
Stage**				
T1,T2a	15	8	7	
T2bc		4	10	
T3			46	
Gleason score				
≤6	15	8	1	
7		4	20	
≥8			42	
ADT				
No-ADT	15	2	4	
After ADT		9	36	
During ADT		1	23	
Biochemical failure-free time (months)	38.9±20.1 (9-88)	53.7±39.9 (5-133)	38.7±27.0 (4-125)	
Outcome				
Alive	14	9	40	
Death of prostate cancer		1	16	
Other	1	2	7	

\*Mean±SD (range). \*\*Number of patients. <sup>#</sup>Number in parentheses is the ratio of biochemical failure in respective groups. Total number of patients: Low: 126 (17%), Intermediate: 187 (26%), High: 415 (57%). ADT: Androgen deprivation therapy, see text.

Table II. Characteristics of high-risk patients with biochemical failure.

	No-ADT(4)**	After-ADT (36)	During-ADT (23)	<i>p</i> -Value
Age (year)*	70.8±3.4 (66-74)	67.1±7.0 (51-87)	66.8±7.2 (52-79)	
PSA (ng/ml)	22.3±10.6 (7-32)	49.1±37.9 (5-174)	52.6±50.2 (4-191)	N vs. A,D ≤0.01
Stage**				
T1,T2a	4	3		
T2bc		7	2	
T3		26	21	
Gleason score				
≤6		1		
7	2	14	4	
≥8	2	21	19	
Duration of ADT (months) <sup>#</sup>		23.1±16.3 (2-60)	30.4±19.8 (7-83)	
Duration between radiation-failure (months)	48.9±24.5 (18-70)	46.2±29.2 (4-125)	26.7±20.0 (4-80)	A vs. D 0.003
Outcome				
Alive	2	26	12	
Death of prostate cancer	1	7	8	
Other	1	3	3	

\*Mean±SD (range). \*\*Number of cases. <sup>#</sup>Sum of the durations of neoadjuvant and adjuvant androgen deprivation therapy.

ADT, sequentially received alternative antiandrogens, estramustine with/without etoposide, dexamethasone, and chemotherapy.

The overall and cause-specific survival rates were classified according to the corresponding risk group and are shown in Figure 2A and B. At five and eight years after radiotherapy

respectively, the cause-specific survival rates were 100 and 100% in the low-, 100 and 86% in the intermediate-, and 83 and 73% in the high-risk groups. The patients in the low- and intermediate-risk groups had a favorable prognosis, and the prostate cancer in these patients was well-controlled by additional ADT, when biochemical failure occurred. The high-

Table III. Factors leading to worse outcome in high-risk patients.

	Other (47)*	Died of prostate cancer (16)	p-Value
Age (years)**	67.2±6.7	67.3±7.8	
Stage#			
≥T2/T3	13/34	4/12	
Gleason score			
≤7/≥8	16/31	5/11	
Histological growth pattern(%)			
Low grade†	25.2±15.4	11.8±15.4	0.01
Medullary/solid	3.2±6.1	7.5±7.9	0.08
Pretreatment PSA (ng/ml)	46.3±42.7	56.1±41.2	
Androgen deprivation (months)	29.2±19.6	16.9±6.6	0.0007
Mode, Androgen deprivation			
After ADT/During ADT	33/14	7/9	
Biochemical failure-free time (months)	44.3±27.9	20.5±16.1	0.0001

\*High-risk patients except death of prostate cancer. \*\*Mean±SD.  
#Number of patients. †Proportion of low grade (large, intermediate, or small simple glands+microglands), see legend of Figure 1.

risk group exhibited an unfavorable prognosis. In each group, many of the patients were elderly at the start of treatment, therefore, some patients died of other causes, which is shown by the overall survival rate.

The overall and cause-specific survival rates were classified by ADT and are shown in Figure 3A and B. At five and eight years after radiotherapy respectively, the cause-specific survival rates were 100 and 100% in the No-ADT, 98 and 85% in the After-ADT, and 58 and 48% in the During-ADT groups. Some patients in the After-ADT and During-ADT groups responded to the salvage treatment to a certain extent and experienced stable disease, while other patients progressed to a poor outcome.

Five patients experienced local relapse (0.7%), and these were not patients who died of prostate cancer. The incidences of acute and late morbidities in the bladder or urethra were both 3% of G3 at maximum, and those in the rectum were below G3 (2-4).

## Discussion

External beam radiation therapy (EBRT) has been used over the last 15 years. Recently, improved techniques, such as three-dimensional conformal radiotherapy and intensity-modulated radiation therapy (IMRT), have been developed. The aim of radiotherapy with various technical procedures is to deliver curative treatment to local tumor fields. Dose escalation is performed to reinforce the cytotoxic effects, and when compared with the standard 68-70 Gy, a dose of more than 78-84 Gy demonstrated an excellent benefit against cancer tissues (10-12). Carbon ion radiation with 66 GyE to the prostate,

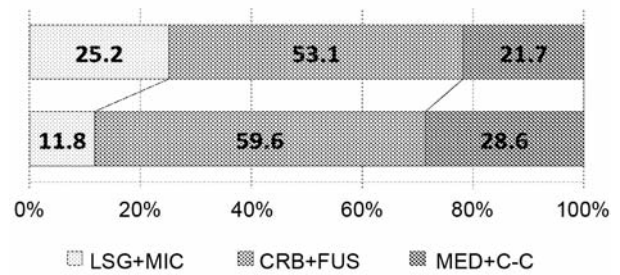


Figure 1. Histological growth pattern analysis of high-risk patients who experienced biochemical failure. Upper: Patients except prostate cancer-specific death, lower: patients who died of prostate cancer. LSG: Large, intermediate, or small simple glands with well-formed glandular lumina; MIC: micro-glands, less differentiated simple glands formed by several small cuboidal tumor cells with abortive inconspicuous luminal formation; CRB: cribriform, smoothly outlined glandular structures forming a gland-in-gland-like pattern with multiple glandular lumina without supporting stroma; FUS: fused glands, small or micro-glands closely packed and fused into irregularly outlined sheets, nests, or cords, or so-called clear-celled, hypernephroid-fused glandular pattern; MED: medullary/solid, tumor cells growing in solid nests or sheets without forming glandular lumens; C-C: columns-and-cords/trabecular, tumor cells arranged in a single, double or diffuse array without forming glandular structures. LSG+MIC,  $p=0.01$  between patient groups.

demonstrated comparable radiation effects with a dose-escalation effect by EBRT as few local relapses were observed.

From a clinical standpoint, the hypofractionation of the radiation number is an important issue because it allows for shortened radiation times with more powerful radiation effects (13,14). Based on an escalated dose protocol, standard fractionation requires seven weeks. With hypofractionation, however, IMRT at a dose of 70 Gy was given in 2.5 Gy fractions within five weeks and yielded excellent biochemical failure-free survival rates at five years, which demonstrated an increased benefit without serious morbidity (15). Carbon ion radiotherapy was performed for five weeks and generated more cytotoxic results compared with the effects derived from an escalated dose of EBRT. Recently, Protocol 9904-3, in which 57.6 GyE are given over four weeks of radiation, has been initiated and to date, results similar to those using previous protocols have been observed. As carbon ion radiotherapy has demonstrated favorable local effects compared with those of both dose escalation and hypofractionation by EBRT, carbon ion radiotherapy may be confirmed to treat localized and locally advanced prostate cancer.

Low-risk patients are candidates for radiotherapy alone, and there are many reports that demonstrate biochemical failure-free survival rates of approximately 85% or more with EBRT (16). Other types of radiotherapy, such as low-dose or high-dose rate brachytherapy, also reported similar results (17, 18). Monotherapy with carbon ion resulted in an improved outcome compared with standard EBRT (4).



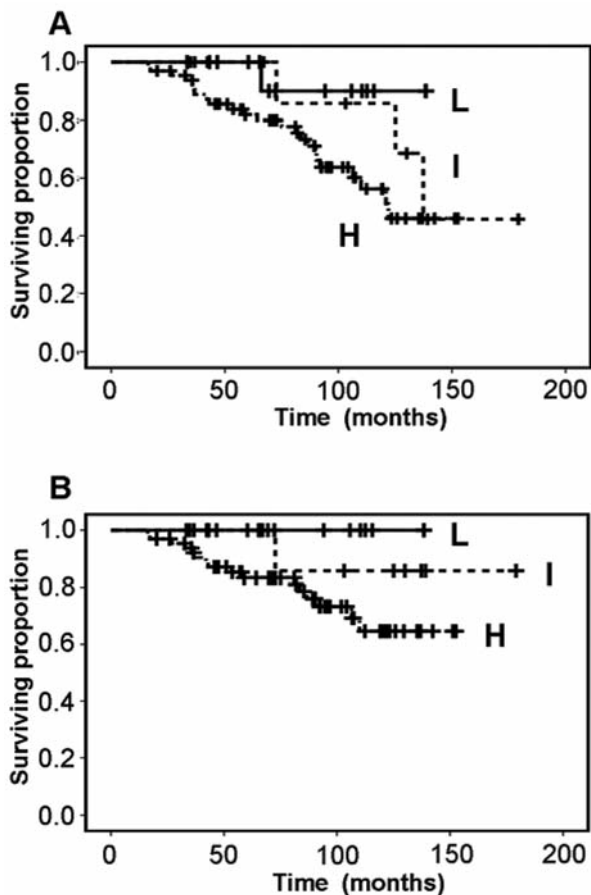


Figure 2. Overall survival rate (A) and cause-specific survival rate (B) of patients who experienced biochemical failure after carbon ion radiotherapy. The patients were classified into the following risk groups: L (low), I (intermediate), and H (high).

For intermediate-risk patients, there is debate concerning whether radiotherapy alone is suitable or if the addition of ADT is necessary. Radiation with dose escalation (68-78 Gy) or hypofractionation (66 Gy/22 fractions) provided an advantage to intermediate-risk patients (19, 20). However, the addition of ADT may be expected to result in a more favorable outcome. Previously, we showed favorable results among the intermediate-risk patients with longer than one year of ADT compared with those without ADT or with less than one year of ADT (3, 4). Salvage therapy resulted in tumor control after biochemical failure, which was the same effect observed in the low-risk patients.

Conventional radiotherapy with a dose of 66 Gy alone has an approximately 30% biochemical failure-free rate at five years, therefore, monotherapy with radiation is insufficient for treating high-risk prostate cancer (21). For this patient group, radiotherapy regimens tend to incorporate high-dose

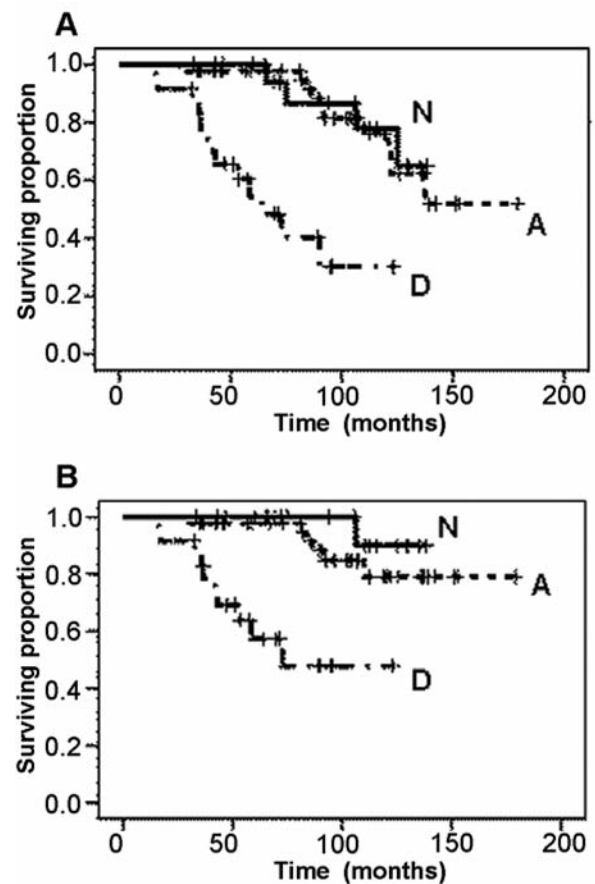


Figure 3. Overall survival rate (A) and cause-specific survival rate (B) of patients who experienced biochemical failure after carbon ion radiotherapy. The patients were stratified into the following three androgen deprivation treatment (ADT) groups: N (No-ADT), A (After-ADT; failure some time after the conclusion of ADT), D (During-ADT; failure during continuous ADT).

radiation and hypofractionation with a certain amount of ADT. A review of seven randomized clinical trials demonstrated that high-dose radiotherapy resulted in a significant reduction in biochemical failure, however, there was no difference in the mortality rate compared with conventional dose radiotherapy (22). A radiation dose of 86.4 Gy with six months of ADT improved the biochemical failure-free and distant metastasis-free survival rates of high-risk patients (12). Hypofractionated radiotherapy (62 Gy/20 fractions/five weeks) with nine months of ADT resulted in a 79% of biochemical failure-free rate with a toxicity equivalent to that of conventional radiation (23). Pelvic nodal radiotherapy has been claimed for the management of high-risk patients, but this method has not been commonly used because of the increased morbidity in neighboring organs (24, 25). From these results, one could say that the use of additional ADT may be advisable, but the

duration of ADT is controversial, that is from three months to three years or more. Meta-analyses determined that longer treatment times significantly improve the biochemical failure-free, cause-specific, and overall survival rates (26). The addition of ADT for three years was applied to radiotherapy for locally advanced cancer and resulted in significant improvement in all of the parameters of progression-free survival (27). Therefore, radiotherapy with ADT is considered a preferred therapy for high-risk patients when compared with surgery (28). Together with these results, management trends for high-risk patients point to a combination of forced radiotherapy with a certain term of ADT. Accordingly, we have treated patients with neoadjuvant and adjuvant ADT for more than a total of two years and found favorable results (4).

Although patients at different risk levels have been administered carbon ion radiotherapy to treat localized prostate cancer with a favorable outcome, a certain number of patients experience biochemical failure. Most patients have their disease controlled with salvage treatments after failure, but some patients, mostly high-risk patients, gain only a slight benefit from ADT, followingly enter a state of CRPC, and then die of prostate cancer. One of the predominant risk factors for disease progression is the presence and increased occupancy of histologically high-grade growth patterns in the tumors. Out of the patients with tumor of Gleason score seven, those with a 4+3 tumor had a worse outcome than those with a 3+4 tumor (29). There are many reports that the presence of tumors with a Gleason pattern of five is associated with a poor outcome (30-32). A Gleason pattern of five is considered almost similar to patterns of medullary/solid and columns-and-cords/trabecular types. The subsequent disease course may be influenced not only by the presence but also by increased occupancy of high-grade growth patterns in the tumors. From this situation, the biochemical failure-free time shortens and the disease progresses rapidly to a worse outcome (33). ADT affects the subsequent outcome in high-risk patients, but the effect may be limited to highly malignant cancer tissues.

Patients with bone metastases have an approximately two-year survival after relapse from the first hormone therapy (34). In the present study, the survival after resistance to ADT was three years, which suggests that a course of CRPC progresses rather straight a way. It may be necessary to select those high-risk patients who are more likely to experience disease progression and who might require additional treatments, since their tumor progression continues despite the administration of ADT. Although new chemotherapeutic drugs, such as docetaxel are available, treatment for CRPC remains problematic.

## Conflicts of Interest

None declared.

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