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Analysis of External Radiotherapy for Localized Prostatic Cancer

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ABSTRACT

From 1968 to 1986, 62 patients with Stage C prostatic cancer were treated at Hiroshima University Hospital. Of these, 33 patients were treated by castration plus DES-DP(hormone therapy alone) from 1968 to 1975. Twenty-nine patients were treated by definitive radiotherapy after castration (combined therapy) from 1976 to 1986. Although the expected survivals of both periods were comparable, the survival rate of the combined therapy group was significantly higher than that of hormone therapy-alone group (five-year; 78.3% vs. 46.9% and ten-year; 52.2% vs. 0%, $p<0.05$). Eight of the 29 patients in the combined therapy group died. Four died of prostatic cancer and four of other diseases. Total dose was 6000 cGy or less in the former four, while 19 of the 29 patients (66%) received greater than 6000 cGy. Acute complications during radiation were observed in 18 of the 29 patients (62%). In only one case, however, irradiation was interrupted because of acute complications. Late complications, observed six months or more after the end of irradiation and required admission to the hospital for diagnosis or treatment, were developed in four of the 29 patients (14%). They were contracted bladder, perforation of the rectum, bladder neck contracture and ileus. Patients with ileus and contracted bladder each had history of laparotomy and vesical stone, respectively. As to portals and total dose of these four, anterior-posterior parallel opposing portals only was conducted in all and total dose was less than 6000 cGy in three of them. The results of this study revealed the superiority of the combined therapy over hormone therapy alone for treating Stage C prostatic cancer, and also showed the optimum total dose and portals.

Key words: *Prostatic cancer, Radiotherapy, Hormone therapy*

External radiotherapy was rarely performed for prostatic cancer until recently since prostatic adenocarcinoma is believed to be a so-called radioresistant tumor[21]. Therefore, prostatic cancer was conventionally treated mainly by estrogen therapy, proposed by Huggins et al[13] in 1941. At Hiroshima University Hospital, prostatic cancers were treated by hormone therapy alone, regardless of stage, from 1968 to 1975, using diethylstilbestrol diphosphate (DES-DP), a synthetic estrogen, administered after castration. Since 1976, however, we have conducted definitive external radiotherapy after castration (combined therapy) except for patients with distant metastasis.

In this study, we compare the survival of patients treated by hormone therapy alone with those treated by combined therapy at our hospital to evaluate the usefulness of external radiotherapy after castration for prostatic cancer. We also analyze the cause of death and complications in patients with combined therapy.

MATERIALS AND METHODS

Patients

From 1968 to 1986, 176 patients with histologically - proven adenocarcinoma of the prostate were treated at Hiroshima University Hospital. The clinical stage, according to Whitmore's classification[20], was Stage A or Stage B in 16 patients, Stage C in 66 and Stage D in 94. Of these, Stage C patients were selected as the materials in this study because the tumors were localized at the pelvis and the number of patients with hormone therapy alone and with combined therapy were almost equal. Table 1 shows the clinical characteristics of the Stage C patients in each therapy group except for four patients who were lost from follow-up. The number of patients with hormone therapy alone from 1968 to 1975 was 33 and with combined therapy from 1976 to 1986 was 29. The mean age of the two

Table 1. Characteristics of 62 patients with Stage C prostatic cancer

		Castration + Estrogen	Castration + Radiation
No. of patients		33	29
Mean age		72.8	73.6
Histologic differentiation	WD	1	12
	MD	17	7
	PD	9	9
	UK	6	1

WD = well-differentiated; MD = moderately-differentiated
PD = poorly-differentiated; UK = unknown

groups was nearly equal, being 72.8 and 73.6 years, respectively. The degree of histological differentiation was well in one patient, moderate in seventeen, poor in nine and unknown in six of the hormone therapy - alone group, and was well in 12 patients, moderate in seven, poor in nine and unknown in one in the combined therapy group.

Hormone Therapy

In the hormone therapy - alone group, 500 mg DES-DP was intravenously administered every day starting one week after castration to provide a total dose of 10 g as the initial treatment. Thereafter, daily dose of 300 mg DES-DP was administered orally as long as possible as a maintenance treatment.

Radiotherapy

In the combined therapy group, all patients were treated with 8 MEV or 10 MEV linear accelerator from one week after castration with a daily dose of 180 cGy or 200 cGy, five times per week. Table 2 shows total dose and portal for 29 patients. Nineteen patients (66%) received a tumor dose greater than 6000cGy. The remaining ten patients received a tumor dose less than 6000cGy. In the latter group were patients over 80 years old and those treated in the initial period when we conducted radiotherapy for prostatic cancer with a curative intent. Concerning portals, anterior-posterior parallel opposing portals (A-P) only for the whole pelvis which extended from the L4-L5 interspace to lower borders of the ischial tuberosities were used in all patients by 1981. Since 1982, a tumor dose of 4,500 cGy has been delivered to the whole pelvis through A-P. Thereafter, the portal was reduced to the prostatic region to deliver an additional 2000 cGy using A-P or 360 degree rotation technique in principle.

Statistical Methods

The actuarial survival rate for prostatic cancer patients was calculated in accordance with Kaplan and Meier method[15]. Obtained data were tested for statistical significance by means of the generalized Wilcoxon test[8]. Survival was calculated from the date of initiation of treatment until the date of last follow-up.

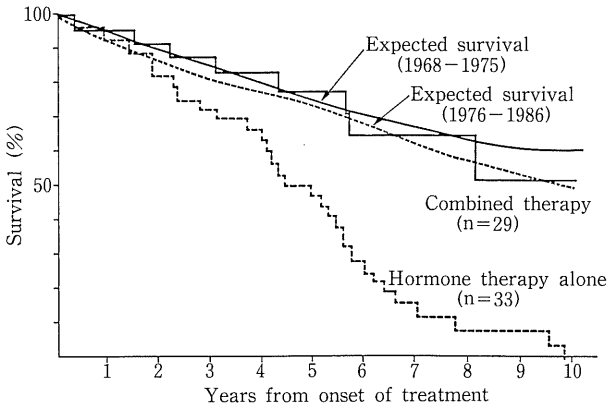

Fig. 1. Comparison of survival curves

RESULTS

Survival

Fig. 1 shows the actuarial survival rates for the two groups with different therapies and the expected survival rates for the specific age distributions of each group in both periods. The expected survival rates in both periods were comparable. The five- and ten-year actuarial survival rates for the hormone therapy-alone group were 46.9% and 0%, respectively, while those for the combined therapy group were 78.3% and 52.2%, respectively. There are significant differences in the survival rates between the two groups ($p < 0.05$). Furthermore, the

Table 2. Dose and portals

Dose (cGy)	WP(A-P)	PR(A-P)	WP(A-P) +PR(A-P)	WP(A-P) +PR (rotation)	WP(A-P) +PR(box)	total
<5000	3	0	0	0	0	3
5000-5999	1	4	2	0	0	7
6000-6499	0	2	4	1	1	8
6500-6999	0	0	0	8	1	9
≧7000	0	0	2	0	0	2
total	4	6	8	9	2	29

WP = whole pelvis; PR = prostatic region
A-P = anterior-posterior parallel opposed portals
rotation = 360 degree rotation; box = four field

Table 3. Features of 4 patients died of prostatic cancer

Age	Survival time	Histologic differentiation	Dose (cGy)	Portal
80	4m.	PD	5040	WP(A-P)
75	18m.	PD	5800	WP(A-P) +PR(A-P)
79	51m.	PD	6000	PR(A-P)
73	67m.	WD	5000	PR(A-P)

PD=poorly-differentiated; WD=well-differentiated WP=whole pelvis; PR=prostatic region
A-P=anterior-posterior parallel opposed portals

survival curve for the combined therapy group was almost the same as that expected for a group of males without cancer.

Cause of Death

Eight of the 29 patients (28%) died in the combined therapy group. Of the eight, four died of prostatic cancer and the other four of other diseases. In the latter four, cause of death was senility, heart disease, cerebral hemorrhage and unknown, respectively. The survival time of the four patients who died of prostatic cancer ranged from four months to sixty-seven months(Table 3). Both two patients who died within two years from onset of treatment had histologically poorly-differentiated adenocarcinoma. Clinically, each of them had a localized palpable mass in the abdomen. Only one patient died of well-differentiated adenocarcinoma. In this patient, bone metastasis occurred twenty-six months from onset of treatment. Nevertheless, he survived for five years and seven months. The total dose was 6000cGy or less in all four patients.

Of the 33 patients with hormone therapy alone, sixteen died of prostatic cancer, 5 of other diseases and 12 of unknown causes.

Complications

Radiation-induced acute complications were observed in 18 of the 29 patients (62%) during radiation therapy, including diarrhea in 14 patients, anal pain in seven, dermatitis in six, miction pain in five and leukocytopenia in one (Table 4). However, these acute adverse effects were usually reduced by symptomatic treatment and irradiation had to be interrupted in only one case because of these acute complications.

Late complications, observed six months or more after the end of irradiation and required admission to the hospital for diagnosis or treatment, were developed in four of the 29 patients (14%). As shown in Table 5, they were contracted bladder, perforation of the rectum, bladder neck contracture and ileus. The time of development of these complications ranged from fifteen months to fifty-two months. The patients with ileus and contracted bladder each had history of laparotomy and vesical stone, respectively. The patient who died of perforation of the rectum had a big mass which was palpable on examination of the abdomen. Although the perforation was suspected to be caused by direct infiltration of cancer to the rectum, this patient was included in cases with complications since retention of cancer was unclear in the operation for perforation. Concerning portals and total dose, A-P only was conducted in all four of these patients. The total dose was less than 6000cGy in three of them (5800, 5800, 4200cGy).

Table 4. Acute complications

Complications	No.	(%)
Diarrhea	14	(48.3)
Anal pain	7	(24.1)
Dermatitis	6	(20.7)
Miction pain	5	(17.2)
Leukocytopenia	1	(3.4)

Table 5. Late complications (4 patients)

Complications	Age	Time after radiation	Salvage		Dose (cGy)	Portal
Contracted bladder	58	15m.	surgery	alive	5800	WP(A-P)
Rectal perforation	75	18m.	surgery	dead	5800	WP(A-P) +PR(A-P)
Ileus	71	48m.	conserv.	alive	4200	WP(A-P)
Bladder neck contracture	67	52m.	conserv.	alive	6400	WP(A-P) +PR(A-P)

WP=whole pelvis; PR=prostatic region
A-P=anterior-posterior parallel opposed portals

DISCUSSION

External beam radiotherapy for prostatic cancer has been reported since the 1930's[21]. However it has been valued only as a palliative method for advanced cases[14,21]. Since the estrogen therapy proposed by Huggins and Stevens[13] yielded good results, hormone therapy has long served as the principal method of treating prostatic cancer. On the other hand, definitive radiotherapy for localized prostatic cancer had been tried using high-energy megavoltage apparatus, Co-60 and linear accelerator, with favorable results by Bagshaw[2], del Regato[6] and others[3,9] in the 1960's. In 1973, the clinical trial published by the Veterans Administration Co-operative Urological Research Group (VACURG)[5] revealed that the use of Diethylstilbestrol (DES) increased some risk of cardiovascular morbidity and DES-treated Stage A and B patients had distinctly worse survival rates. It was also clarified that in Stage C the mortality of patients treated with DES was similar to that with placebo, partly because of the excessive cardiovascular deaths. Therefore, a review of the methods of treating prostatic cancer was required.

In accordance with the history of treatment for prostatic cancer described above, we performed hormone therapy alone, in which DES-DP was administered after castration, until 1975 at Hiroshima University Hospital. Thereafter, we have conducted radiotherapy mainly on the basis of the clinical trial results by VACURG and reports of favorable results of definitive radiotherapy.

In this study, we compared the survival rate between the group with hormone therapy alone and that with radiotherapy after castration. Though historical control was used, the expected survivals of both periods were comparable and the survival rate of the combined therapy group was significantly higher than that of the hormone therapy-alone group(5-year; 46.9% vs. 78.3% and 10-year; 0% vs. 52.2%, $p<0.05$). Moreover, the survival curve of the combined therapy group was similar to the expected survival curve for Japanese males with a similar age distribution without cancer. These results indicate that radiotherapy combined with castration is superior to hormone therapy alone for treating Stage C prostatic cancer.

There has been controversy as to the radiation technique, treatment volume and dose of radiation. Bagshaw[1] reported that low stage, low grade prostatic cancers (clinical stage A and B, with histologic grades of either 1 or 2) have a less than 5% chance of lymph node involvement, so that the treatment volume may be restricted to the prostate and immediate periprostatic region. Also, he reported that the incidence of lymphadenopathy was 59% in patients with extracapsular extension (Stage C) and the treatment volume must be enlarged to include appropriate regional lymph nodes. The RTOG (Radiation Therapy Oncology Group) performed a randomized clinical trial (RTOG 75-06) involving 523 patients and presented a clear conclusion on treatment volume for Stage C[19]. That is, whole pelvic irradiation is favorable regardless of pelvic lymph node involvement, and elective periaortic irradiation shows no apparent benefit for Stage C.

As to total dose, Perez et al[18] reported pelvic recurrence in 38% of their patients receiving 5500 to 6000 cGy, 20% of those receiving 6500 cGy and 12% of those receiving 7000 cGy or more in Stage C. Hanks[10] reported that in T3 cases, corresponding to patients in Stage C, local recurrence was observed four years after treatment in 37% of those receiving 5999 cGy or less, 21% of those receiving 6000-6499 cGy and 11% of those receiving 6500-6999 cGy. He stated that the local control rate rose with the radiation dose. And Harisiadis et al[12] reported the five-year survival rate of patients with Stage C tumor and a dose of more than 6500 cGy was 75.6%, whereas, it was 53.0% for patients with the same stage tumor and a dose equal to or less than 6500 cGy. However, Lipsett et al[16] reported 24% local failures in patients who received less than 5900 cGy, but only 7% recurrences between 6000 and 6900 cGy and 11% with doses over 7000 cGy. Neglia et al[17] reported no difference in local control for Stage C patients when less than 6750 cGy was given as compared to doses greater than 6750 cGy. Duttenhaver et al[7] reported no difference in local control when comparing a group of patients who received 6000-6800 cGy to a group boosted with protons to 7000-7650 cGy. In this study, 19 of 29 patients (66%) received greater than 6000 cGy, while four patients who died of prostatic cancer received less than 6000 cGy (6000, 5800, 5040, 5000 cGy). This result suggests insufficient dose may be the main cause of our failures. Since 1982, we have delivered 4500 cGy to the whole pelvis and subsequently 2000 cGy to the prostatic region (except in patients with unfavorable general status) to a total dose of 6500 cGy. Coupled with our results and other reports, 6500 cGy is thought to be the optimum dose for Stage C.

Complications due to treatment are the most critical point in treatment for prostatic cancer, since most of patients are aged and the natural history is long[4]. The mean age of the patients with radiotherapy was 73.6 years in this study. However, irradiation was interrupted in only one case because of acute complications during radiation. This finding suggests that even aged patients can sufficiently tolerate definitive radiotherapy, including whole pelvic irradiation. Late complications due to irradiation were found in four of the 29 patients (14%) in this study. A national survey in the U.S.[2] has revealed that major complications which required admission to the hospital for diagnosis or treatment were found in 4.2% of the subjects, and that surgery was required because of complications in 2 percent. The survey also showed that major com-

plications were significantly more frequent when the total dose exceeded 7000 cGy. Neglia et al[17] reported no complications with doses of 6500 cGy and fields smaller than 10 × 12 cm in contrast to approximately 10% with larger volumes. With 7000 cGy they also reported 9.8% complications with small fields and 11.1% with larger fields. Of the four patients with complications in this study, the total dose was less than 6000 cGy in three, but A-P only was administered in all. However, two of four had a history of laparotomy and vesical stone, so we believe these are factors predisposed to induce ileus and contracted bladder, respectively. It is thought, therefore, that not only A-P but either four-field(A-P and lateral parallel opposing) box technique or perineal field technique[6] must be selected in patients having such predisposing factors since there is the possibility that complications can develop in such patients even at a dose level less than 6000 cGy.

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