

Original Article

Long-Term Outcomes of 60 Gy Conventional Radiotherapy Combined with Androgen Deprivation for Localized or Locally Advanced Prostate Cancer

Katsuyoshi Hashine¹, Kosaku Numata¹, Koji Azuma¹, Yoshiteru Sumiyoshi¹ and Masaaki Kataoka²

¹Department of Urology and ²Department of Radiology, National Organization Shikoku Cancer Center, Matsuyama, Japan

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Background: Until 1998 in Japan, very few institutions were treating prostate cancer solely with radiotherapy (RT) >70 Gy and most were using ≤65 Gy in combination with hormone therapy. The present study reports the long-term results of RT combined with hormone therapy for localized and locally advanced prostate cancer.

Methods: We investigated 57 patients who were treated by external beam RT plus hormone therapy (median age 79 years, median prostate-specific antigen concentration 15.0 ng/ml) between 1992 and 1998. Patients received 40 Gy of radiation to the pelvis and an additional 20 Gy as a prostatic boost. Hormone therapy was begun on the first day of irradiation and continued thereafter.

Results: The median follow-up was 93.3 months and the 5 and 10 year actual overall survival rates were 67.8 and 32.6%, respectively, with 5 and 10 year cause-specific survival rates of 97.9 and 95.0%, respectively. The expected survival rate was 66.2% at 5 years, and overall survival was above expected survival. Only one patient developed severe proctitis (Grade 3). The 5 year occurrence of Grade 1/2 genitourinary toxicity was 23.2%.

Conclusions: Combined RT and hormone therapy has a good long-term outcome without severe adverse events. The overall survival rate compares well with the expected survival rate.

Key words: prostate cancer – radiotherapy – hormone therapy – long-term outcome

INTRODUCTION

Prostate cancer is a common neoplasm that was the eighth leading cause of cancer death among Japanese men in 2000 (1). Increasingly, prostate cancer is being diagnosed through prostate-specific antigen (PSA) screening and transrectal ultrasound-guided prostate biopsy (2,3), which has resulted in many cases being diagnosed as localized (4,5) and treated by radical prostatectomy or radiotherapy (RT) (6). In the 1990s, RT was not a common treatment for prostate cancer in Japan, and in 2000 only 10.8% of the cases of localized prostate cancer were selected for this treatment (7,8).

Local control of prostate cancer depends on the radiation dose, which has been recommended as >70 Gy (9). However,

there were very few institutions using RT >70 Gy in the early 1990s in Japan (10,11), and in fact, in a randomized controlled study conducted at that time, radiation dose was 60 Gy (12). Therefore, in the early 1990s, prostate cancer was commonly treated by low-dose (60 Gy) RT combined with hormone therapy and thus we treated prostate cancer patients in the same way. In this study, we report the long-term outcome of this combined therapy.

PATIENTS AND METHODS

Between January 1992 and December 1998, 57 men were treated by RT plus hormone therapy. The clinical stage was determined by digital rectal examination using the 1997 TNM classification, and the PSA concentration was measured using the IMx kit (Abbott Laboratories, IL, USA) until 1997, after that we used the ARCHITECT Total PSA kit (Abbott Laboratories). The median age of the patients was 79 years

For reprints and all correspondence: Katsuyoshi Hashine, Department of Urology, National Organization Shikoku Cancer Center, Horinouchi 13, Matsuyama city, Ehime 790-0007, Japan. E-mail: khashine@shikoku-cc.go.jp

(range 58–88) and the median PSA value was 15.0 ng/ml (range 1.4–311.5). Of the 57 patients 20 had well-differentiated, 20 had moderately-differentiated and 17 had poorly-differentiated adenocarcinoma. Instead of Gleason score, 12 patients were 6, 15 patients were 7 and 25 patients were over 7. The median observation period after RT was 93.3 months (range 29.2–159.5). Based on the Seattle group's findings, the risk groups were identified by using pretreatment serum PSA concentration, biopsy Gleason score and clinical stage (13). According to this definition, there were 7 low-risk patients, 11 intermediate-risk patients and 39 high-risk patients. Of five patients who were undefined according to their Gleason score, four were high-risk (three patients had T3 and PSA concentration >10 ng/ml, one patient had T4, PSA concentration 8.5 ng/ml and poorly differentiated) and one was intermediate-risk (T1b, PSA concentration 42.6 ng/ml and moderately differentiated) (Table 1).

All RT was delivered at 2 Gy per fraction to a total dose of 60 Gy, using a 10 MV linear accelerator. Patients were treated once daily for 5 days each week for 6 weeks. The whole pelvis was irradiated for 4 weeks using a conventional two-field technique, the anterior–posterior field, up to 40 Gy, and during the final 2 weeks the prostate was treated with an additional 20 Gy. At the beginning of the RT, 20 patients underwent surgical castration with or without antiandrogen and 37 underwent

LH–RH agonist with or without antiandrogen, which was discontinued if the PSA concentration was maintained at <0.1 ng/ml between 3 and 5 years after RT.

Cause-specific and overall survival rates were calculated by the Kaplan–Meier method. The starting point of survival time was defined as the date of treatment and the end-point was death from any cause. Expected survival rate was estimated using the survival probability in a general population similar to the subjects with respect to sex, age and calendar period of observation. Sex, age and calendar year specific survival tables prepared by the National Cancer Center using life tables of the Japanese population and Ederer II methods were adopted (14). The relative survival was calculated as the ratio of the overall to the expected survival. The standard error and 95% confidence interval of the relative survival were then calculated. Multivariate analysis used a Cox proportional hazard model to determine the factor which influenced overall survival.

Biochemical relapse was defined according to the consensus definition set by the American Society for Therapeutic Radiology and Oncology (15). In this study, death from prostate cancer was defined as death with clinical failure or symptoms of the disease regardless of PSA concentration at death. Death from other causes was defined as death from other types of cancer or without symptoms of prostate cancer. If the PSA concentration at the time of the death was not determined, the patient's condition at that time was confirmed by a relative and then it was decided whether the case was cancer death or not. Late bladder and rectal adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 scoring scale and the adverse events rate was calculated by the Kaplan–Meier method.

Table 1. Clinical characteristics of the radiation therapy group

Number	57
Age(years)	
Median	79
Range	58–88
T classification	
T1	20 (T1b, 8; T1c, 12)
T2	11 (T2a, 8; T2b, 3)
T3	26 (T3a, 16; T3b, 10)
Histological grade of differentiation	
Well	20
Moderately	20
Poorly	17
Gleason score	
6	12
7	15
8≤	25
Unknown	5
PSA (ng/ml)	
Median	15.0
Range	1.4–311.5
Risk group	
Low	7
Intermediate	11
High	39

RESULTS

All 57 patients underwent irradiation with a schedule dose and none stopped RT (median radiation dose 60 Gy, range 59.6–64); 51 underwent LH–RH agonist/surgical castration with antiandrogen and 6 underwent LH–RH agonist/surgical castration only. Of them, surgical castration was performed in 20 patients (with antiandrogen 18, without antiandrogen 2). The median hormone-treatment period of the 37 patients who underwent LH–RH agonist with or without antiandrogen was 39.5 months (3.0–101.2).

After treatment, the PSA concentration was <0.1 ng/ml in 52 patients. During the follow-up period, there were two prostate cancer deaths and 27 from other causes such as another cancer, cerebrovascular disease, pneumonia, renal insufficiency, traffic accident and senility. The survivors did not have clinical failure, but biochemical relapse was uncertain in six patients because the PSA concentration was not measured for 6 months or more. The 5 and 10 year cause-specific survival rates were 97.9 and 95.0%, respectively, and the 5 and 10 year overall survival rates were 67.8 and 32.6% (Fig. 1). The expected survival rate in all patients was 66.2% at 5 years and 10.0% at 10 years, which resulted in a relative

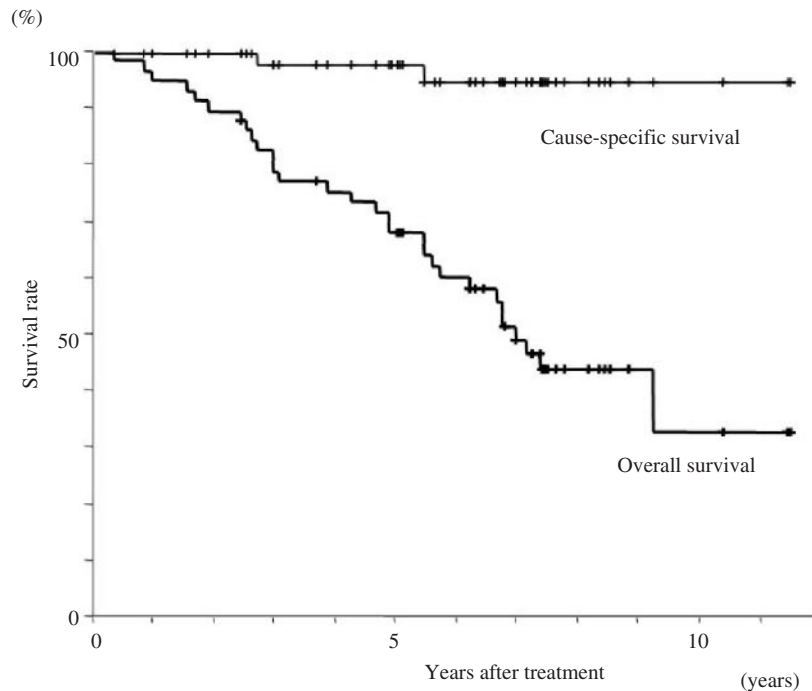


Figure 1. Overall survival and cause-specific curves. The tick marks indicate patients who were still alive at the time of analysis or who were censored.

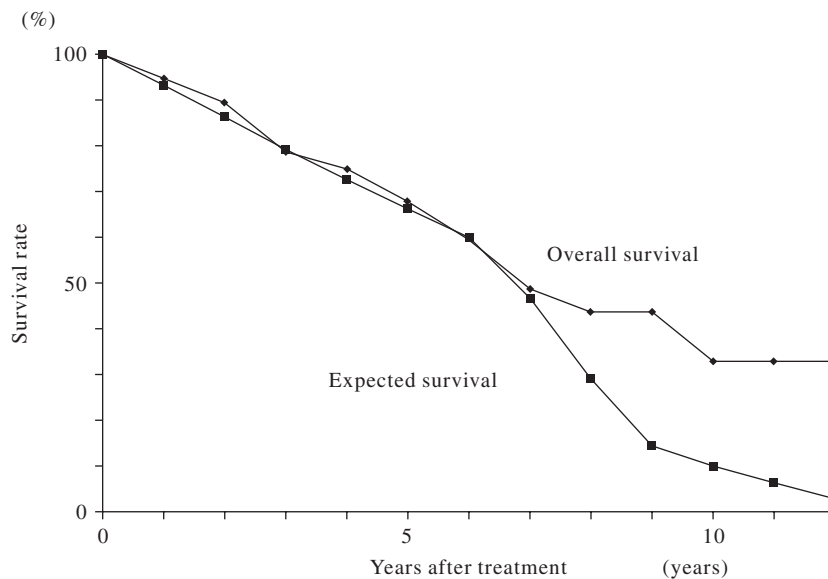


Figure 2. Overall survival and expected survival curves.

survival rate of $102.4 \pm 9.5\%$ at 5 years (Fig. 2). Multivariate analysis did not reveal significant factors influencing overall survival, such as age, duration of hormone therapy or risk group.

During the follow-up period, only one patient developed Grade 3 proctitis, a Grade 1/2 genitourinary adverse event was seen in 13 patients, and the 5 and 10 year appearance rates were 23.2 and 36.0%, respectively (Fig. 3). There were no other severe adverse events (Grade 3/4/5).

DISCUSSION

RT has now become one of the important treatments for localized or locally advanced prostate cancer. However, in the first half of the 1990s, RT was not performed commonly and the radiation dose was low in Japan (10,11). Akakura *et al.* (12) reported a randomized trial comparing prostatectomy and external beam RT (EBRT) for clinical B2 and C disease between 1989 and 1993. In that study, almost all patients in the RT arm were treated by irradiation of 60 Gy. On the basis

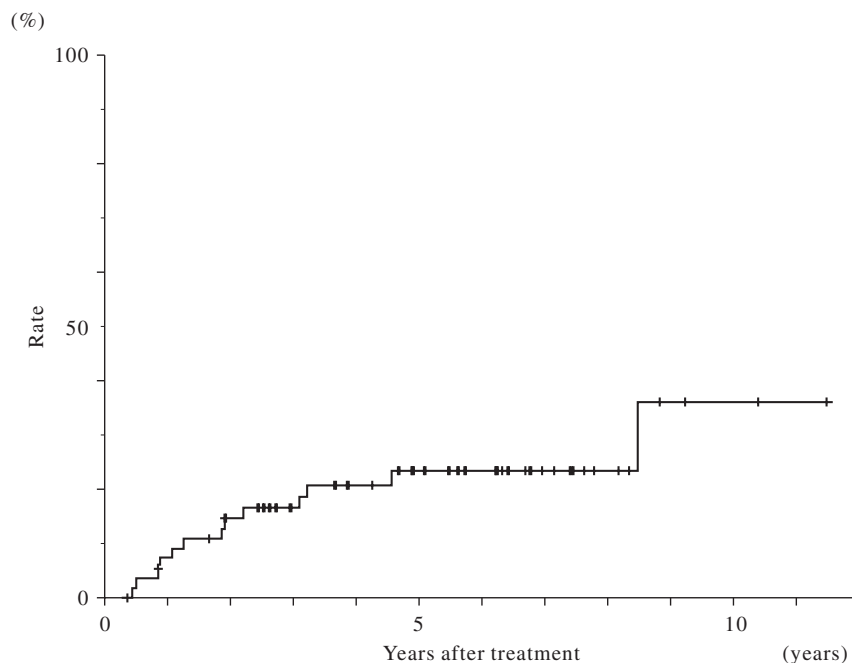


Figure 3. Actual incidence of Grade 1/2 genitourinary adverse events.

of that study, we started to treat prostate cancer using low-dose RT (60 Gy) with a two-field technique, in combination with hormone therapy from 1992.

In the present study, the cancer-specific survival was good despite the low radiation dose and the overall survival was above the expected survival. Of the 57 patients, 50 were classified as intermediate or high-risk, who showed a good response to the treatment. However, there are some problems in this study. First, some patients did not have information about their PSA level at the time of death. Because death with prostate cancer was defined as the presence of clinical failure or symptom of disease, these cases could not be categorized as death from the disease. Only two patients were formally identified as dying from prostate cancer, but the cause of death might have been wrong and cancer death patients might be included among death from other causes.

Second, the age of the patients in this study was high: median age was 79 years old. Because often patients under 75 years chose radical prostatectomy and watchful waiting did not spread very much in the first half of the 1990s, most of the patients older than 75 years old opted for RT, which made the average age higher. However, it should be noted that there was no significant difference in overall survival rate between patients younger than 79 years and those older than 79 years, and overall survival rate of patients older than 79 years was above expected survival rate (data not shown). Furthermore, the age did not become an important factor about overall survival by multivariate analysis.

Finally, there is possibility that patients might die before disease progression and this outcome might mainly be caused by hormone therapy rather than RT because of their high age. However, low-risk patients were only seven patients and

median survival time was 86.3 months in all patients and 81.0 months in the patients older than 79 years. To examine this combination therapy, moreover, the overall survival rate was compared with the expected survival rate instead of cause-specific survival rate and was above it. It may be considered that this outcome was effect of RT as well hormone therapy, although it was not possible to prove the benefit of RT.

Admitting these problems, it is nevertheless significant that not only the treatment outcome was good but also the overall survival rate exceeded the expected survival rate without severe adverse events other than one case of Grade 3 proctitis. On the basis of these results, we further developed RT where radiation dose has now been escalated up to 72 Gy, gradually using four-field technique. Moreover, we employ combination hormone therapy only for locally advanced prostate cancer.

RT was performed as monotherapy for localized prostate cancer, and RT combined with hormone therapy was usually performed for locally advanced prostate cancer. But, for localized prostate cancer, D'Amico *et al.* (16) reported that the addition of 6 months of hormone therapy to 70 Gy RT conferred an overall survival benefit. Moreover, improved outcomes have been reported with new techniques of safely escalating the RT dose to the prostate, for example, three-dimensional conformal radiation therapy (17,18).

However, for locally advanced prostate cancer the benefits of adjunctive hormone treatment with RT have been reported. Bolla *et al.* (19) studied 415 men with poor risk clinical stage T1–4, N0 disease who were randomly assigned to EBRT alone or with LH–RH agonist for 3 years starting on the first day of EBRT. After a median follow-up of 66 months, combined hormone ablation plus EBRT was associated with a significant improvement in both 5 year disease-free survival (74 versus

40%) and overall survival (78 versus 62%). Moreover, the benefit for adjuvant androgen suppression has been reported in a prospective randomized trial, the Radiation Therapy Oncology Group (RTOG) trial 85-31 (20), and in the RTOG trial 92-02 (21). Based upon these findings, adjuvant hormone therapy is currently considered standard to EBRT for locally advanced prostate cancer.

In the near future, technical progress in RT may enable monotherapy for locally advanced prostate cancer, but for now adjunct hormone therapy is necessary (19–21). However, the side effects of hormonal therapy, including hot flushes, weight gain, diminished libido and potency, and gynecomastia must be discussed with the patient before the start of treatment. More recently, the problem of increased risk of bone fracture with hormone therapy has been identified (22,23). The extent of these side effects is, in large part, dependent upon the duration of hormone therapy, but the appropriate treatment period for androgen ablation has not yet been decided. Yamanaka *et al.* (24) are conducting a randomized controlled trial of RT combined with hormone therapy in which adjuvant hormone therapy is randomly selected to long-term or intermittent and their results should indicate the appropriate duration. At present in Japan >80% of patients with prostate cancer are treated by RT combined with hormone therapy (7,10). Although this combined therapy is safe and its usefulness has been proved, in future the appropriate RT mode should be selected so that unnecessary hormone therapy is avoided.

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