Acta Med. Okayama, 2005
Vol. 59, No. 5, pp. 195-199

Acta Medica Okayama
http://www.lib.okayama-u.ac.jp/www/acta/

Original Article

Long-term Clinical Outcomes of 420 Consecutive Prostate Cancer Patients in a Single Institute

Kohei Edamura, Takashi Saika*, Takashi Senoh, Fumihito Koizumi, Daisuke Manabe, Shin Ebara, Haruki Kaku, Teruhiko Yokoyama, Fernando Abarzua, Atsushi Nagai, Yasutomo Nasu, Tomoyasu Tsushima, and Hiromi Kumon

Department of Urology, Okayama University Graduate School of Medicine and Dentistry, Okayama 700-8558, Japan

This study was undertaken to reveal the trends of prostate cancer and the outcome of treatment modalities for each disease stage in patients in a single institute over a 10-year period. From January 1994 through December 2003, 420 consecutive patients with previously untreated and histologically confirmed prostate cancer were analyzed for annual distributions of disease stages and treatment modalities and for long-term clinical progression-free survival, prostate cancer-specific survival, and prostate-specific antigen (PSA) failure-free survival rates for each stage and treatment modality. Annual trends showed that the number of patients, especially those with clinically localized cancer, increased dramatically. The 5-year disease-specific survival rates for patients with clinically localized disease were 100% for all treatment modalities, including hormonal therapy alone. Patients with PSA levels less than 10 ng/ml showed an 81% 5-year PSA failure-free survival rate with radical prostatectomy. Stage C patients treated by surgery or radiation-based therapy with concomitant hormonal therapy obtained 93% and 100% cause-specific survival rates, respectively, and those treated by hormonal therapy alone showed a 79% rate. The number of patients with localized prostate cancer was increasing in this decade. While long-term hormonal therapy alone was highly efficient in controlling localized prostate cancer, radical therapies in conjunction with neo-adjuvant hormonal therapy produced better survival rates in cases of locally advanced disease.

Key words: prostate carcinoma, long-term, cohort, retrospective, outcome

Prostate cancer, the most common male malignancy, was estimated to have an incidence of 220,900 cases in 2003, accounting for approximately a third of new cancer diagnoses in men, and 28,900 prostate cancer deaths were expected, a mortality burden surpassed only by that of lung cancer in the United States [1]. With the advent of widespread prostate specific antigen (PSA) screening, there was a steep increase in prostate cancer diagnoses. The number of patients diagnosed with prostate cancer has also been increasing in Japan [2]. The epidemiology and treatment of prostate cancer have changed dramatically in the last decade, *i.e.*, the PSA-screening era. In an effort to document trends in the management of this disease at our institute, along

Received March 15, 2005; accepted March 24, 2005.
*Corresponding author. Phone: +81-86-235-7287; Fax: +81-86-231-3986
E-mail: saika@cc.okayama-u.ac.jp (T. Saika)

with the oncological outcomes, we analyzed 420 consecutive patients treated in Okayama University Hospital.

Materials and Methods

Four hundred and twenty consecutive patients with previously untreated and histologically confirmed prostate cancer were included in our retrospective analysis of data from January 1994 through December 2003 (Table 1). The mean follow-up was 31 months (range, 1–120 months). Patient age at diagnosis ranged from 40 to 94 years with both the mean and median being 70 years. As a pre-diagnostic screening, serum PSA determination and digital rectal examination (DRE) were used for all patients. Clinical staging before treatment was determined in accordance with the *General Rules for Clinical and Pathological Studies on Prostate Cancer* (3rd edition); unified tumor node metastasis (TNM) [3] was determined by DRE, transrectal ultrasonography (TRUS), magnetic resonance imaging (MRI), computer tomography (CT) and bone scan. Pretreatment pathological diagnosis and tumor grading were made by transrectal biopsy before the initiation of any treatment in all patients. The distribution of Stage is shown in Table 1.

Treatments. Initial treatment was determined for each patient based on cancer stage, age and general health condition. Patients were informed of treatment modalities and gave their consent. Patients treated by surgery underwent radical retropubic prostatectomy (RRP), which was preceded by bilateral pelvic lymph node dissection. Patients treated by radiotherapy underwent 6 months of neo-adjuvant hormonal therapy followed by an average 66 Gy external beam irradiation. The distribution of treatment modalities is shown in Table 2.

Follow-up. Patients were seen every month during the first year of treatment and every 3 months thereafter. Hypersensitive serum PSA levels were determined every 3 months. PSA failure was defined as 3 consecutive elevations of PSA levels. Clinical progression was seen as a local tumor recurrence or distant metastasis as determined by DRE, TRUS biopsy, or a bone scan, which was performed every 6–12 months. We analyzed long-term clinical progression-free survival and prostate cancer-specific survival rates using the Kaplan-Meier method. In addition, we analyzed the PSA failure-free survival rate of patients who could be evaluated. Comparisons of survival curves were performed using the log-rank test. A commercially available statistical package (StatView Version 5) was used to conduct statistical analyses. Values of $P < 0.05$ were considered statistically significant.

Results

The annual trend was for the number of patients with prostate cancer, especially those with clinically localized cancer, to increase dramatically, although the number of patients with advanced disease remained stable (Fig. 1).

Long-term cause-specific survival rates of all 420 patients are displayed according to clinical stage, in

Table 1 Patient characteristics

Follow-up (mo)		
mean		31.4
range		1–120
Age (y.o.)		
median		71
range		40–94
Clinical stage	A: 21	B: 195
	C: 121	D: 83

Table 2 Distribution of treatment modalities and cancer stages

Stage		A	B	C	D
Hormonal therapy	207	8	49	77	73
Open surgery	168	5	136	27	
Radiation therapy	20	4	16		
Watchful waiting	12				
Others	13				

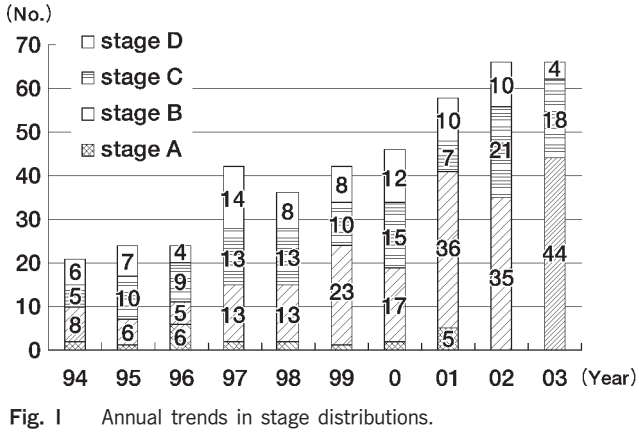

Fig. 1 Annual trends in stage distributions.

Fig. 2. The 5-year cause-specific survival rate for the 216 patients with clinically localized disease was 100%, whereas the survival rates of the 121 patients with stage C and 83 patients with D disease were 87% and 53%, respectively (Fig. 2). The 5-year cumulative PSA failure-free survival rates for patients with clinically localized, stage C, and stage D disease were 71%, 52% and 26%, respectively.

When stratifying by treatment modality, the 5-year cumulative PSA failure-free survival rates for patients with clinically localized disease were 68% for RRP and 53 % for hormonal therapy ($p = 0.38$). However, because of its small number of patients, the radiation group was removed from analysis (Fig. 3). With regard to pre-surgical PSA levels, the failure-free survival rates of patients with a PSA of less than 10 ng/ml were statistically better than those of patients with a PSA of more than 20 ng/ml (Fig. 4).

Among patients with stage C disease, those treated by surgery-based therapy with concomitant neo-adjuvant/adjuvant hormonal therapy, by neo-adjuvant hormonal therapy followed by radiation-based therapy, or by hormonal therapy alone, the 5-year cumulative cause-specific survival rates were 93%, 100%, and 79%, respectively. Statistically significant differences were recognized between surgery/radiation-based therapy and hormonal therapy, although the PSA failure-free survival rates were similar among the 3 groups (Fig. 5).

In patients with stage D disease, the 5-year cumulative PSA failure-free and cause-specific survival rates were 26% and 53%, respectively. Most patients with stage D disease were treated by endocrine-based therapy.

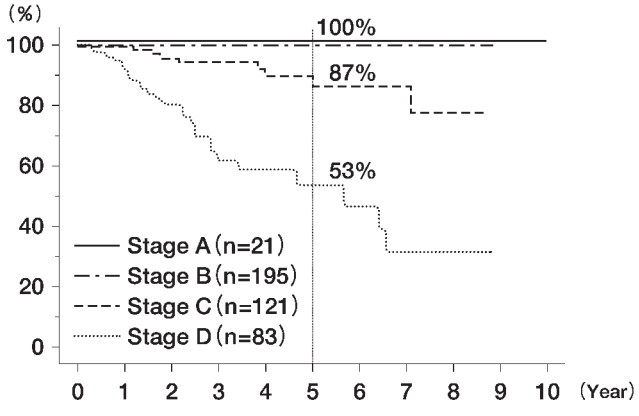

Fig. 2 Cause-specific survival according to cancer stage.

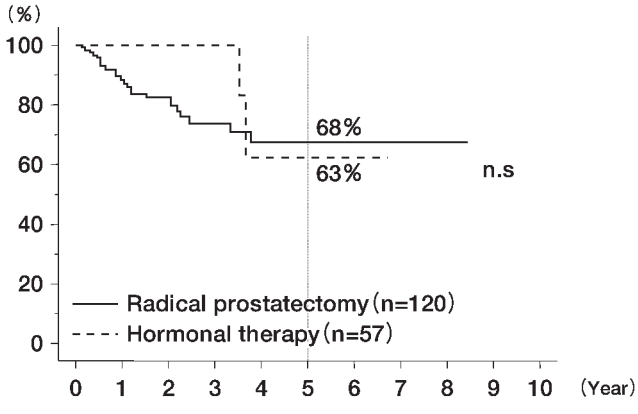

Fig. 3 5-year cumulative PSA failure-free survival rates for patients with clinically localized disease according to treatment.

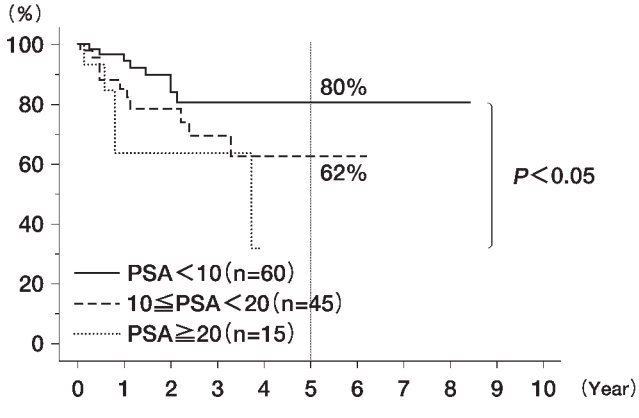

Fig. 4 PSA failure-free survival rates after radical prostatectomy according to pre-surgical PSA values.

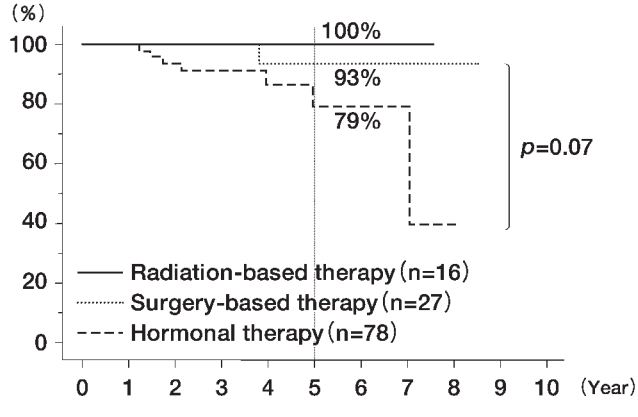

Fig. 5 5-year cumulative cause-specific survival rates according to treatment modality in patients with Stage C disease.

Discussion

This study represents the current status and comparable outcomes of therapies for patients with prostate cancer in a single institute over ten-year period, within the PSA-screening era.

In Japan, the age-adjusted mortality rates due to prostate cancer have gradually and steadily increased [2]. The incidence of the disease also has increased, especially since the 1990's. In this study, similar trends were observed. Several factors are involved in the increases in incidence and mortality rates; first, the population of older men has increased; second, PSA testing is widely available in clinical practice; third, PSA screening has resulted in stage migration from late to early stage, a fact observable in our current study as well as in reports nationwide [2].

Based on these trends, the number of surgical treatments has dramatically increased. In addition, since 2004 brachy therapy for localized prostate cancer has become another available modality in Japan. Although not described in this study, brachy therapy is expected to be an important part of treatment for localized prostate cancer.

For clinically localized disease, current results suggest that hormonal therapy may be associated with a good prognosis, although our surgical treatment series resulted in 5-year cumulative PSA failure-free survival rates comparable to those in recent reports [4, 5]. Cause-specific survival of patients with clinically localized cancer was, however, 100% irrespective of the therapy chosen. The present data show that long-term and continuous hormonal treatment is highly efficient in controlling localized prostate cancer and may even cure the disease, based on the similarity between the 5-year cumulative PSA failure-free survival rate of this group and that of the radical surgery group. Hormonal therapy is being used with increasing frequency as the primary monotherapy in patients with localized disease, but to date there has been no randomized prospective trial examining the survival benefit. The present data show that long-term hormonal therapy alone is highly efficient in controlling localized prostate cancer. Labrie *et al*. [6] reported in their relatively small but long-term follow-up series that combined androgen blockade (CAB) showed the possibility of long-term control of localized prostate cancer. When CAB was continued, a much higher rate of success was achieved, with an approximately 90% cure rate at treatment durations ranging from 6.5 to 11.7 years. Our current results are consistent with these findings, and our data suggest that hormonal therapy may be a possible modality for stage B prostate cancer. Risk factors such as natural history, co-morbidity, life expectancy, and improvement of QOL for stage B patients when selecting treatment modalities such as radical prostatectomy, hormonal therapy or radiation therapy should be examined-in a larger controlled study.

For stage C disease, radical therapies such as radiation or surgery should be considered in conjunction with hormonal therapy. We obtained significantly better survival rates in patients who underwent surgery or radiation in conjunction with neo-adjuvant hormonal therapy than in those who received hormonal therapy alone. Several studies have investigated the utility of hormonal therapy in patients with locally advanced disease. Several prospective randomized trials have recently demonstrated that a significant prolongation of life was observed in patients with localized prostate cancer treated by surgery or radiation in conjunction with hormonal therapy [7–13]. At the 5-year follow-up, these studies showed improved cancer-specific survival rates ranging between 37% and 81%. In comparison, our current results of surgery or radiation used in conjunction with hormonal therapy are so significant that multidisciplinary therapy should be considered for stage C disease.

For stage D disease, the incidence of advanced cancer has decreased in the past decade. Survival rates for patients with stage D prostate cancer were consistent or slightly superior to those of prior reports (15% to 81% of patients alive at 2 years) [14].

In summary, this uncontrolled single-institute study revealed the following. 1) There was an obvious trend toward an increasing number of patients with prostate cancer, especially with localized cancer diagnosed by PSA examination. 2) Patients with a PSA of less than 10 ng/ml showed good PSA failure-free survival rates after radical prostatectomy. 3) Long-term hormonal therapy alone, as well as with surgery, was highly efficient in controlling localized prostate cancer. 4) Radical therapies, such as radiation or surgery in conjunction with neo-adjuvant hormonal therapy, produced-better survival rates in patients with locally advanced disease.

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