A Randomized Trial Comparing Radical Prostatectomy Plus Endocrine Therapy versus External Beam Radiotherapy Plus Endocrine Therapy for Locally Advanced Prostate Cancer: Results at Median Follow-up of 102 Months

Koichiro Akakura1, Hiroyoshi Suzuki1, Tomohiko Ichikawa1, Hiroyuki Fujimoto2, Osamu Maeda3, Michiyuki Usami3, Daisaku Hirano4, Yukie Takimoto4, Toshiyuki Kamoto5, Osamu Ogawa5, Yoshiteru Sumiyoshi6, Jun Shimazaki1*, Tadao Kakizoe2* and the Japanese Study Group for Locally Advanced Prostate Cancer†

1Department of Urology, School of Medicine, Chiba University, Chiba, 2Urology Division, National Cancer Center Hospital, Tokyo, 3Department of Urology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, 4Department of Urology, Nihon University School of Medicine, Tokyo, 5Department of Urology, Faculty of Medicine, Kyoto University, Kyoto and 6Shikoku Cancer Center, Matsuyama, Japan

Received May 6, 2006; accepted August 14, 2006; published online November 2, 2006

Background: To investigate the optimal treatment of locally advanced prostate cancer, a prospective randomized trial was conducted to compare radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy.

Methods: One hundred patients with T2b-3N0M0 prostate cancer were enrolled and 95 were evaluated. Of 95 cases, 46 underwent radical prostatectomy with pelvic lymph node dissection and 49 were treated with external beam radiation by linear accelerator with 40–50 Gy to the whole pelvis and 20-Gy boost to the prostatic area. For all patients, endocrine therapy was initiated 8 weeks before surgery or radiotherapy and continued thereafter. The long-term outcome and morbidity were examined.

Results: Median follow-up period was 102 months. At 10 years overall survival rates in the surgery group were better than the radiation group (76.2% versus 71.1% for biochemical progression-free rates; \( P = 0.25 \), 83.5% versus 66.1% for clinical progression-free rates; \( P = 0.14 \), 85.7% versus 77.1% for cause-specific survival rates; \( P = 0.06 \), and 67.9% versus 60.9% for overall survival rates; \( P = 0.30 \)), although none of them reached statistical significance. Erectile dysfunction was recognized in almost all patients as a result of continuous endocrine therapy. Incontinence requiring more than one pad per day was observed more frequently in the surgery group than the radiation group (\( P < 0.01 \)).

Conclusions: For the treatment of patients with locally advanced prostate cancer, when combined with endocrine therapy, either radical prostatectomy or external beam radiotherapy demonstrated favorable long-term outcomes. The radiation dose of 60–70 Gy might not be enough for the local treatment of locally advanced prostate cancer.

Key words: prostate cancer – locally advanced – randomized trial – radical prostatectomy – external beam radiotherapy

INTRODUCTION

For the treatment of non-metastatic prostate cancer, definitive therapies such as radical prostatectomy or radiation therapy have been widely applied (1–4). Retrospective studies reported that the long-term outcomes of patients with localized and low-risk prostate cancer were equally favorable.
with radical prostatectomy or external beam radiation therapy (5,6). For locally advanced high risk-diseases, however, satisfactory results could not be achieved with such monotherapeutic modalities (7,8). Therefore, combination with endocrine therapy has been proposed to improve the outcomes (9,10). To investigate the optimal treatment of locally advanced prostate cancer, a prospective randomized trial was conducted to compare radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy (11,12). Here we report the long-term results of the trial at median follow-up of 102 months.

PATIENTS AND METHODS

A prospective randomized trial was conducted to compare radical prostatectomy versus external beam radiotherapy with a common endocrine therapy in both modalities for locally advanced prostate cancer. The design of the trial and the patient characteristics were described previously (11,12). Briefly, patients with histologically confirmed adenocarcinoma of the prostate, T2b-3N0M0 according to UICC 1987 classification (13), 75 years old or younger, and performance status of 0 or 1, were eligible. No evidence of lymph node metastasis was confirmed with CT scan in patients of the radiation group. Informed consent was obtained from all patients. Between 1989 and 1993, 100 patients were enrolled from six institutions in Japan. Five patients were excluded before randomization. After 8 weeks of neoadjuvant endocrine therapy by daily 300 mg of diethylstilbestrol, 95 patients were randomly assigned into surgery or radiation therapy. Randomization was based on stratification with institution, clinical stage and histological grade. For the surgery group, radical prostatectomy with pelvic lymph node dissection was performed. For the radiation group, irradiation by linear accelerator with a 40–50 Gy beam to the whole pelvis followed by a 20 Gy boost to the prostatic area for 6–7 weeks fractionated five times per week was carried out. Adjuvant endocrine therapy with orchietomy or LHRH agonist with or without antiandrogen, alternatively reduced dose of estrogen, was continued until progression was evident. After the onset of progression, the choice of treatment was made according to each physician’s opinion. Initial level of serum total-prostate specific antigen (t-PSA) was assayed with either Markit-F (three institutions) or Eiken (two institutions) kit. The two assay systems were known to have good correlation and show almost the same value (14).

Clinical records of the patients until the end of March 1997 were investigated and analyzed (12). Re-evaluation was performed at the end of July 2003. Three consecutive increases in serum PSA within reliable range were regarded as biochemical progression (15). Clinical progression was defined as local regrowth and/or appearance of distant metastasis. The survival rates were calculated by the Kaplan–Meier method and compared with the log-rank test. Statistical difference was examined by Student’s t test and the chi-square test. Values of P less than 0.05 were considered statistically significant.

RESULTS

Of the 95 evaluable patients, 46 and 49 patients were assigned into the surgery and radiation groups, respectively (Table 1). Between the two groups, there was no statistically significant imbalance of patients and disease characteristics, including age, performance status, clinical stage, histological grade and serum PSA level before treatment (Table 2). Median follow-up period was 102 months with a range of 6–178 months.

For the biochemical and clinical progression-free rates, no significant difference was observed between the surgery and radiation groups (Fig. 1A and B). The surgery group tended to show better cause-specific survival rate than the radiation group (P = 0.06), although the difference was not statistically significant (Fig. 2A). There was no significant difference in the overall survival rates between both groups (Fig. 2B). At 10 years, the survival rates in the surgery and radiation groups were 76.2% versus 71.1% for biochemical progression-free rates, 83.5% versus 66.1% for clinical progression-free rates, 85.7% versus 77.1% for cause-specific

Table 1. Number of patients from each institution

<table>
<thead>
<tr>
<th>Institution</th>
<th>Surgery</th>
<th>Radiation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiba University</td>
<td>12</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>National Cancer Center</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Center for Adult Diseases, Osaka</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Nihon University</td>
<td>7</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Kyoto University</td>
<td>6</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Shikoku Cancer Center</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>49</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 2. Patients’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>Surgery (n = 46)</th>
<th>Radiation (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.1 ± 7.0</td>
<td>68.7 ± 6.6</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>C</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Poorly</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19.9 ± 22.7</td>
<td>21.6 ± 30.5</td>
</tr>
<tr>
<td>Range</td>
<td>1.7–140</td>
<td>1.5–150</td>
</tr>
</tbody>
</table>

SD, standard deviation; PSA, prostate specific antigen.
survival rates, and 67.9% versus 60.9% for overall survival rates, respectively.

Early and late morbidities were investigated during the time course (Fig. 3). Erectile dysfunction was seen in almost all patients owing to continuous endocrine therapy. Incontinence requiring more than one pad per day was observed more frequently in the surgery group than the radiation group \((P < 0.01)\). Although micturition pain and pain on defecation were frequently seen in the radiation group for early morbidities, incidences of other morbidities were not remarkably different between the two groups.

**DISCUSSION**

To evaluate the efficacy of distinct therapeutic modalities, several endpoints have been utilized for comparison. In the present study, biochemical and clinical progression-free rates as well as cause-specific and overall survival rates were compared between the surgery and radiation groups. Because the significance of the absolute value of serum PSA must be different following radical prostatectomy and radiation therapy \((15)\), it would be difficult to define biochemical progression based on the common definition in the patients who had received surgery or radiation. In the present study, however, all the patients had been treated with endocrine therapy and thus three consecutive increases in serum PSA were considered as biochemical progression. Cause of death would be sometimes difficult to determine and overall survival might be less affected by the choice of treatment because intercurrent deaths are frequently observed in such an aged population of the patients. In the present study, however, all prognostic estimates including biochemical and clinical progression-free rates as well as cause-specific and overall survival rates demonstrated similar results. The previous report based on analysis of this trial at median follow-up of 58.5 months showed that radical prostatectomy combined with endocrine therapy might contribute to the survival benefit compared with radiation plus endocrine therapy \((5\text{-year cause-specific survival rates: } 96.6\% \text{ versus } 84.6\%, P = 0.024)\) \((12)\). On the contrary, the present analysis revealed no statistically significant difference in survivals between the two groups, probably owing to extended follow-up period. Long-term outcomes in locally advanced high-risk patients may be dependent on sensitivity to endocrine therapy rather than local therapy.

---

**Figure 1.** Biochemical (A) and clinical (B) progression-free rates between surgery group (closed triangle) and radiation group (open triangle); \(P = 0.25 \text{ (A), } P = 0.14 \text{ (B).}\)

**Figure 2.** Cause-specific (A) and overall (B) survival rates between surgery group (closed triangle) and radiation group (open triangle); \(P = 0.06 \text{ (A), } P = 0.30 \text{ (B).}\)
There has been accumulated evidence that radical prostatectomy, external beam radiotherapy and brachytherapy demonstrate favorable efficacy as curative therapeutic modality of prostate cancer, although it seems controversial which is superior to the others (5,6). To our knowledge, the present study is the only randomized trial to compare surgery with radiation for the management of non-metastatic locally advanced prostate cancer, except for the old trial by Paulson et al. (16). For localized low-risk diseases, either of radical prostatectomy, external beam radiotherapy or brachytherapy has been reported to be equally effective for the long-term prognosis (5,6). On the contrary, for locally advanced high-risk prostate cancer, the results have been unsatisfactory with any single treatment and there must be limitation of efficacy achieved with monotherapy. The long-term survivals with external beam radiotherapy were shown to be improved when combined with neoadjuvant and/or adjuvant endocrine therapy (17,18). However, survival benefit could not be demonstrated for radical prostatectomy with neoadjuvant endocrine therapy (19,20). It was reported that adjuvant endocrine therapy was effective to improve long-term survival for prostate cancer patients who had undergone radical prostatectomy and proved to have lymph node metastasis (21). In the present trial, radical prostatectomy was compared to external beam radiotherapy as a definitive local therapy, with a common endocrine therapy in both modalities.

When the cancer extends to the bilateral lobes (T2b), accuracy of clinical diagnosis was reported to be low (0–36%) and the prognosis became poorer than that of unilateral lesions (T2a) (22). T2b cancer was therefore treated in a similar fashion to locally advanced T3 disease in the present study. Micrometastasis in regional lymph nodes has frequently been observed in locally advanced prostate cancer. The results of definitive radiation therapy became better for patients who were surgically staged as negative for lymph node metastasis (23). Thus, in the present study, 13 patients (28%) with positive lymph node micrometastasis in 46 surgery group patients were not excluded because of justification of comparison of the two groups.

The rate of incontinence seems to be relatively high in this group operated before 1993, possibly because of difficulty of surgery and/or tumor invasion to the apex in the locally advanced disease. Recently, surgical technique has improved to reduce the incidence of incontinence. To obtain the satisfactory results with definitive external beam radiotherapy, sufficient dose of irradiation should be delivered to the prostate gland without significant morbidity of surrounding normal tissues (24). In fact, a randomized trial showed that higher dose of irradiation of 78 Gy demonstrated better biochemical failure-free rate than conventional dose of 70 Gy (62% versus 43% at 6 years in those with a pretreatment PSA of greater than 10 ng/ml) (25). Recent advancement of radiation technology, such as conformal radiotherapy, intensity modulated radiotherapy and heavy particle radiotherapy, made it possible to irradiate greater dose to the prostate without severe complication (26–28). In this context, the applied dose of irradiation in the present study might be smaller than the optimal dose. If more dose of irradiation had been applied safely, the outcomes of the radiation in the present trial would have become better.

It was reported that the patients with localized and locally advanced prostate cancer could be well controlled with endocrine therapy alone (29,30). Thus, the use of definitive local therapy is yet to be justified for the management of locally advanced prostate cancer. However, the patients who had been treated with endocrine therapy alone tended to develop local progression and symptoms during the long-term observation period (31). Therefore, the patient with locally advanced prostate cancer without distant metastasis could be considered for the definitive treatment such as radical prostatectomy and radiation therapy, unless his life expectancy would be short.

In conclusion, for the treatment of patients with locally advanced prostate cancer, when combined with endocrine therapy, either radical prostatectomy or external beam radiotherapy demonstrated favorable long-term outcomes. The radiation dose of 60–70 Gy might not be enough for the local...
treatment of locally advanced prostate cancer. Technical improvement of surgery and radiation would expect better outcomes in the aspect of both efficacy and morbidity for the treatment of locally advanced prostate cancer.

Acknowledgments


References


Appendix: List of Investigators

Chiba University: S. Isaka, S. Akimoto, H. Ito
National Cancer Center: K. Tobisu
Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka: T. Kotate
Nihon University: T. Hachiya, K. Okada
Kyoto University: Y. Arii, O. Yoshida
Tokyo University: Y. Ohashi