Outcome of Patients with Localized Prostate Cancer Treated by Radiotherapy After Confirming the Absence of Lymph Node Invasion

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Received November 27, 2009; accepted February 23, 2010

Objective: Management of lymph nodes in radiotherapy for prostate cancer is an issue for curative intent. To find the influence of lymph nodes, patients with T1–T3 prostate cancer and surgically confirmed negative nodes were treated with radiotherapy.

Methods: After lymphadenectomy, 118 patients received photon beam radiotherapy with 66 Gy to the prostate. No adjuvant treatment was performed until biochemical failure. After failure, hormone therapy was administered. Follow-up period was 57 months (mean).

Results: Biochemical failure occurred in 47 patients. Few failures were observed in patients with low (24%) and intermediate risks (14%). In contrast, 64% of high-risk patients experienced failure, 97% of whom showed until 36 months. Most patients with failure responded well to hormone therapy. After 15 months (mean), a second biochemical failure occurred in 21% of patients who had the first failure, most of them were high risk. Factors involving failure were high initial and nadir prostate-specific antigen, advanced stage, short prostate-specific antigen-doubling time and duration between radiation and first failure. Failure showed an insufficient reduction in prostate-specific antigen after radiotherapy. Factor for second failure was prostate-specific antigen-doubling time at first failure.

Conclusions: Half of high-risk patients experienced biochemical failure, indicating one of the causes involves factors other than lymph nodes. Low-, intermediate- and the other half of high-risk patients did not need to take immediate hormone therapy after radiotherapy. After failure, delayed hormone therapy was effective. Prostate-specific antigen parameters were predictive factors for further outcome.

Key words: prostate cancer – radiotherapy – biochemical failure – high risk – PSA-doubling time

INTRODUCTION

Localized prostate cancer has been treated with various methods, and the results were improved gradually. Of these technologies, surgical and radiological treatments play a leading part in the field (1). An important issue in radiotherapy is conjecture of the status of regional lymph nodes. There are many guidelines for the estimation of possible invasion in the lymph nodes, where they are estimated from the stage, prostate-specific antigen (PSA) and histological findings from biopsy (2,3). The predictive score obtained by assuming these guidelines, however, may be indefinite (4,5). On the basis of the uncertainty for predicting invasion, whole pelvic radiotherapy has been discussed to improve PSA-free survival (6). In order to exclude the influence of regional lymph nodes on whether invasion may be present,
extirpation of them before radiotherapy seems to be advisable. The present study was undertaken first to perform the lymphadenectomy in patients with localized prostate cancer. Thereafter, the patients with N0 received radiotherapy alone.

PATIENTS AND METHODS

PATIENTS

Between January 1999 and January 2006, pelvic lymphadenectomy was performed in 168 patients with T1–T3 prostate cancer who selected rather non-aggressive treatment at Asahi General Hospital. For lymphadenectomy, the obturator, external and internal iliac lymph nodes were removed via an abdominal incision or laparoscopic surgery. Of these cases, 144 cases (86%) showed negative findings. Stage was defined with UICC TNM classification (6th edn, 2002). Risk was classified into low (T1bc and T2a, <10 ng/ml of PSA and ≤6 of Gleason score), intermediate (T2b,c or 10–20 ng/ml of PSA or 7 of Gleason score) or high (> T3 or >20 ng/ml of PSA or >8 of Gleason score) according to NCCN criteria (7). After radiotherapy, no adjuvant hormone therapy was administered until biochemical failure. PSA was determined every 3 or 6 months, and when elevation occurred, duration of determination was shortened. Biochemical failure was judged with Phoenix criteria (elevated 2 ng/ml of PSA or more from baseline, or clinical relapse) (8). Some patients with biochemical failure experienced second failure, which was judged with increase in PSA from baseline. Prostate biopsy was carried out with 8–12 cores via a perineal route. Gleason score was determined according to ISUP (9).

Records of all patients were collected in June 2009 (follow-up, mean 57 months, median 52 months and range 9–119 months). After biochemical failure, most patients received hormone therapy with luteinizing hormone–releasing hormone agonist and 80 mg of bicalutamide daily until the hormone therapy failed. Evaluation for hormone therapy was determined from response to the therapy: decrease of ≥50% from baseline in the PSA (partial response, PR), increase of ≥25% from baseline in the PSA (progressive disease, PD) or change between PR and PD (no change, NC).

PSA KINETICS

PSA was determined as total PSA using AxSYM PSA Dainapack (Abbot, Tokyo, Japan). PSA-doubling time (PSA-DT) and velocity were calculated by linear regression. A slope was obtained by the least-square test with values of ln PSA (PSA-DT) or those of PSA (velocity) from three or more points. PSA-DT was obtained from ln 2/slope (10). Velocity was determined as a difference per year (11).

RADIATION

Conformal radiation with a photon beam at 10 MV was used with a multileaf collimator (leaves 10 mm at isocenter).

The clinical target volume was the whole prostate and the planning target volume was created by adding 10 mm anteroposterior and lateral margins. A conventional fractionation of 2 Gy/fraction was administered five times per week for 66 Gy of total radiation dose.

STATISTICAL ANALYSIS

Overall survival was calculated with the Kaplan–Meier method. Statistical difference was determined by the unpaired two-group t-test. Odds ratio was calculated by the logistic regression analysis. Values of $P \leq 0.05$ were considered to be significant. All calculations were used with the StatView program.

RESULTS

BIOCHEMICAL FAILURE

Of 144 patients with negative node, 118 cases received radiation after confirming no distal metastatic disease using bone scan and abdominal echogram (Table 1). The other 26 cases were treated surgery or hormonal therapy as chosen by the patients. Of 118 patients who received radiation, 47 patients experienced biochemical failure (47 of 118, 40%). Until 36 months after radiation, 42 patients showed biochemical failure, in which high-risk patients were 34 (81%). Occurrence of biochemical failure gradually decreased in number and there was no failure in the remaining patients after 55 months of the latest failure. Duration of biochemical failure was mean of 21 months (median 17 months and range 4–55 months). Rate of failure was 24% in low-risk, 14% in intermediate-risk and 64% in high-risk patients.

The profiles of patients with biochemical failure and failure-free patients were compared (Table 2). Patients with biochemical failure showed the initial, 12 months later and nadir PSA values higher than those in failure-free patients and had a short duration between radiation and nadir. Influences on biochemical failure were the initial PSA values, stage and duration between radiation and nadir (Table 3). Since PSA-DT is a parameter for tumor growth, patients with failure were divided by PSA-DT. A positive relation between duration until nadir and PSA-DT was confirmed (Table 4).

Of 47 patients with biochemical failure, four cases did not receive an additional hormone therapy because of a slow rise in PSA. The other 43 patients received hormone therapy after failure, and responded well as PR, except for one patient who showed NC temporarily then showed a rapidly rising PSA and died of prostate cancer 46 months after the start of radiation.

SECOND BIOCHEMICAL FAILURE AND OUTCOME

Among 47 patients with first failure, 10 cases showed a second increase in PSA (21%). Risks of these 10 patients
were 1 of low (1 of 8, 13%) and 9 of high (9 of 35, 26%). Duration between hormone treatment and the second failure was mean of 15 months (median 14 months and range 3–28 months). Factors estimated at first failure were compared between patients with second failure and those without second failure (Table 5). Patients with second failure showed shorter PSA-DT, shorter duration between radiation and first failure. These patients were treated with second-line hormone therapy and/or chemotherapy. Except for one dead patient, the other nine patients included seven showing favorable responses and two revealing slowly progressive disease. These nine patients were alive in June 2009.

Biochemical failure-free survival rate was 52% (61 of 118) at 3 years after radiation. Overall survival rate at 5 years was 87% (Fig. 1). There was only one patient due to prostate cancer-specific death. Eight patients died of other causes except for prostate cancer. There was no complication due to lymphadenectomy. Concerning the toxicity after radiation according to scoring of Radiation Therapy Oncology Group, 34% and 5% of early and late Grade 1–2 morbidity, respectively, showed in the genitourinary system, with 25% and 5% of early and late Grade 1–2 morbidity, respectively, in the rectum. No toxicity was developed for Grade 3 or higher.

**DISCUSSION**

Survival of patients with prostate cancer after radical treatment is influenced by the status of the regional lymph nodes. The number and findings of invasive nodes correlate with subsequent outcome (12,13). As a curative treatment with radiotherapy, aggressive radiation which includes the pelvic lymph nodes is controversial (14,15). In this discussion, the adverse effects caused by radiation to the outside of the prostate may be a serious consideration. Alternatively, lymphadenectomy before radiation may be proposed. The result from lymphadenectomy may help to determine the strategy of further treatment (16). Moreover, this procedure serves to make a contribution to the relationship between stage and status of lymph nodes.

Surgical lymphadenectomy causes slight, if any, complications such as intraoperative injury and postoperative events (17). The most common complications are lymphocysts or lymphoceles after radical prostatectomy, but the present series performed lymphadenectomy alone, so such adverse effect may be less likely to occur.

Biochemical failure occurred in more than 50% of patients with high risk at 5 years after radiotherapy (18). For extended radiotherapy including pelvic area, biochemical failure in patients with high risk was 43% at 5 years (19). Patients receiving radical prostatectomy whose regional lymph nodes had been removed showed elevation of PSA a few years later. It was reported that the obturator, external and internal iliac nodes may be insufficient for the removal of all suspicious nodes (20,21). The limitation of lymph node management for curative treatment remains to be resolved.

The similar biochemical-failure rate was noticed after radiation to patients with N0 in the present study. Together with the reports, it suggests that patients with high risk already have the small foci in the distant places. As most biochemical failure in high-risk patients occurred by 36 months, their tumors may be rapidly growing with an increase in 2 ng/ml or more of PSA in this term. Although late recurrence cannot be ruled out, incidence of biochemical failure slowly diminished thereafter.

A plausible cause of biochemical failure may be an insufficient dose of radiation to the prostate. It has been claimed that a radiation dose of <70 Gy is insufficient for cure of prostate cancer (22,23). It is recommended that >72 Gy of radiation is administered to the prostate of patients with high risk. Although no cancerous mass in the prostate was found in the present study, an insufficient dose of radiation cannot be ruled out.

**Table 1. Patients’ characteristics**

| Age (years) |  |
|------------|---|
| ≤60        | 4 |
| 61–70      | 7 |
| 71–80      | 102 |
| ≥81        | 5 |

| Initial PSA (ng/ml) |  |
|---------------------|---|
| <10                 | 60 |
| 10.1–20             | 25 |
| 20.1–30             | 10 |
| 30.1–40             | 5 |
| 40.1–50             | 3 |
| 50.1–60             | 4 |
| ≥60.1               | 11 |

| Stage   |  |
|---------|---|
| T1b     | 3 |
| T1c     | 45 |
| T2a     | 18 |
| T2b     | 4 |
| T2c     | 5 |
| T3a     | 33 |
| T3b     | 10 |

| Gleason score |  |
|---------------|---|
| ≤6            | 56 |
| 7             | 37 |
| ≥8            | 25 |

PSA, prostate-specific antigen.
The risk for recurrence after radiotherapy was pointed out with initial PSA, Gleason score and stage, which are well-known risk factors, and risk classification is used from these factors (24). Patients judged to be high risk might have progress in unfavorable courses. Duration of time between radiotherapy and biochemical failure influences the outcome (25). Among these factors, the level of PSA is crucial since patients with >30 ng/ml of PSA showed 20% of PSA-free rate at 5 years and this rate was independent of other factors (26). After radiotherapy, insufficient decrease in PSA to reach a low nadir and a rising pattern of PSA are also considered as factors for recurrence (27). Patients showed biochemical failure in short duration from radiation have rapidly growing tumors as estimated from short PSA-DT.

Additional hormone therapy is recommended along with radiotherapy for patients especially with high risk. Radiation combined with hormone therapy decreased the biochemical failure and improved clinical progression-free and cancer-specific survival (28). According to literatures, duration of hormone therapy varies between 4 months and 5 years, or up

### Table 2. Patient characteristics, PSA and duration to nadir in patients with or without biochemical failure

|                      | Failure (47)                  | Failure-free (71)          | P value |
|----------------------|------------------------------|----------------------------|---------|
| Age (years)          | 74, 75 (54–83)               | 75, 75 (61–82)             | ns      |
| No lymph node        | 9.3, 8, (–21)                | 9.1, 8, (2–28)             | ns      |
| Risk                 |                              |                            |         |
| Low                  | 8                            | 26                         |         |
| Intermediate         | 4                            | 25                         |         |
| High                 | 35                           | 20                         |         |
| Initial PSA (ng/ml)  | 43.0, 23.4 (4.1–290)         | 11.6, 7.5 (3.1–79.8)       | 0.0009  |
| 12 months PSA (ng/ml)
| a                      | 3.1, 1.9 (0.1–14.5)          | 1.2, 0.8 (0.3–4.8)         | 0.019   |
| Nadir PSA (ng/ml)    | 4.3, 1.9 (0.2–51.9)          | 0.8, 0.5 (0.01–5.5)        | 0.004   |
| Radiation–nadir (months)| 14.3, 12 (2–45)             | 27.5, 26 (1–69)            | <0.0001 |

Data are shown as mean and median (range), except ‘risk’ (number of cases).

aPSA 12 months after radiation.

### Table 3. Logistic regression analysis for biochemical failure

|                      | Odds ratio | 95% CI          |
|----------------------|------------|-----------------|
| Initial PSA (ng/ml)  | 1.054      | 1.019–1.090     |
| Stage                |            |                 |
| T2b                  | 5.25       | 1.325–20.803    |
| T3                   | 6.927      | 1.837–26.121    |
| Gleason              |            |                 |
| 7b                   | 0.462      | 0.128–1.666     |
| ≥8                   | 0.739      | 0.160–3.416     |
| Nadir PSA (ng/ml)    | 1.477      | 0.977–2.233     |
| Radiation–nadir (months)| 0.95   | 0.908–0.993     |

aReference: stage T1.
bReference: Gleason ≤6.

### Table 4. Factors influenced biochemical failure divided by PSA-DT

|                      | PSA-DT≤8.3 (24) | PSA-DT > 8.3 (23) | P value |
|----------------------|-----------------|-------------------|---------|
| Initial PSA (ng/ml)  | 51.3, 25 (4.1–290) | 33.9, 18 (6–245) | 0.322   |
| Nadir PSA (ng/ml)    | 3.4, 2.0 (0.2–11.2) | 5.2, 1.7 (0.4–51.9) | 0.47    |
| Radiation–nadir (months)| 10.3, 9 (2–21) | 18.5, 18 (5–45) | 0.001   |
| Radiation–failure (months)| 18.5, 17 (4–36) | 14.3, 13 (8–55) | 0.06    |

Data are shown as mean and median (range).
Median of PSA-doubling time (DT) (8.3 months).

### Table 5. Factors influencing second biochemical failure

|                      | Second failure (10) | No second failure (37) | P value |
|----------------------|---------------------|------------------------|---------|
| Initial PSA (ng/ml)  | 26.8, 15.8 (4.1–82.7) | 47.4, 25.2 (5.7–290) | 0.148   |
| Nadir PSA (ng/ml)    | 4.6, 3.3 (0.2–11.2) | 4.2, 1.4 (0.3–51.9) | 0.83    |
| Failure PSA (ng/ml)  | 10.6, 2.0 (2.6–31.9) | 6.8, 4.0 (1–56.8) | 0.29    |
| Radiation–failure (months)| 14.3, 14 (4–28) | 31.7, 27 (5–55) | <0.0001 |
| PSA-DT (months)      | 4.8, 6 (0.9–11.2)  | 10.6, 9.6 (2.5–30.8) | 0.0002  |
| Velocity (ng/ml/year)| 25.1, 11.5 (2.7–96.5) | 6.0, 3.2 (0.4–31.9) | 0.09    |

Data are shown as mean, median and range. All data are quoted from the first biochemical failure.

The risk for recurrence after radiotherapy was pointed out with initial PSA, Gleason score and stage, which are well-known risk factors, and risk classification is used from these factors (24). Patients judged to be high risk might have...
but it might be advisable to make treatment plans adaptable hormone therapy with radiotherapy is an issue under debate, the presence of residual cancer foci. The treatment period of chemical failure seems to be long, and this might be due to condition in patients. Duration of hormone therapy after bio-
in general, and this may be attributable to a hormone-naïve present study, the response to hormone therapy was favorable to appearance of progression (29). The adverse effects of hormone therapy have been indicated recently (30). In the present study, the response to hormone therapy was favorable in general, and this may be attributable to a hormone-naïve condition in patients. Duration of hormone therapy after biochemical failure seems to be long, and this might be due to the presence of residual cancer foci. The treatment period of hormone therapy with radiotherapy is an issue under debate, but it might be advisable to make treatment plans adaptable to the individual situations of patients.

CONCLUSION
Patients with T1–T3 prostate cancer who were surgically confirmed to be N0 were treated with radiotherapy. Few biochemical failures were observed in patients with low and intermediate risks. Patients with high risk, however, showed biochemical failure in 64%, in whom 97% of failure occurred by 3 years after radiation. Initial and nadir PSA, and duration between radiation and nadir were the factors for biochemical failure. Some patients with first failure, mostly high risk, showed the second failure, and PSA-DT was the factor for second failure, suggesting that patients with second failure had rapidly growing hormone-independent tumors. Most patients after the biochemical failure responded well to hormone therapy, showing favorable results by delayed hormone therapy. It is emphasized that half of patients with high risk can be treated with radiation and lymphadenectomy alone.

Acknowledgements
This work was approved by the Ethical Committee of the Asahi General Hospital.

Conflict of interest statement
None declared.

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