Erectile Function Following External Beam Radiotherapy for Clinically Organ-confined or Locally Advanced Prostate Cancer

Shin-ichi Hisasue1, Ryuichi Kato1, Atsushi Takahashi1, Naoya Masumori1, Naoki Itoh1, Noriomi Miyao1, Keiji Takatsuka2, Masahiro Yanase3, Atsushi Oouchi3, Masato Hareyama4 and Taiji Tsukamoto4

1Department of Urology, Sapporo Medical University, Sapporo, 2Department of Urology, Muroran City General Hospital, Muroran, Hokkaido, 3Department of Urology, Sunagawa City Medical Center, Sunagawa, Hokkaido and 4Department of Radiology, Sapporo Medical University, Sapporo, Japan

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Background: External beam radiotherapy (XRT) has been a standard treatment for clinically localized prostate cancer. However, preservation of erectile function following XRT is controversial. In this study, the influence of XRT on erectile function of patients with clinically organ-confined or locally advanced prostate cancer was retrospectively evaluated.

Methods: The study included 34 of 84 patients with organ-confined or locally advanced prostate cancer who underwent XRT between 1995 and 2002. Erectile function following radiotherapy was assessed by a simple mailed questionnaire that was constructed for the study. To determine the predictive factors for erectile dysfunction following radiotherapy, data were analyzed by multivariate analysis with the Cox proportional hazards model.

Results: The modality of XRT was the only factor to independently predict erectile dysfunction following XRT. The maintenance rates of erectile function were 47.6% at 1 year and 19% at 3 years in patients who received the 3-dimensional conformal radiotherapy, which were significantly higher than in those who received conventional radiotherapy ($P = 0.026$).

Conclusions: XRT significantly reduced the maintenance rate of erectile function during the follow-up period, with the rate being 19% at 3 years in patients who received 3-dimensional conformal radiation. The XRT modality was involved in the reduction of erectile function. These results suggest that erectile dysfunction is a possible adverse event following XRT.

Key words: external beam radiotherapy – erectile dysfunction – prostate cancer

INTRODUCTION

Radical prostatectomy and external beam radiotherapy (XRT) are standard treatments for clinically localized prostate cancer and they help in achieving favorable cancer control. However, these treatments are not free of adverse events that may decrease the quality of life (QOL) in such cancer patients. Preservation of erectile function following XRT for prostate cancer is controversial (1–8). Especially in Japanese men, the influence of XRT on erectile function has not been investigated, partly because their attitude toward sexual function is somewhat different from that of American men (9) and partly because only a small proportion of patients receive XRT for prostate cancer.

The aim of this study is to clarify the impact of XRT on erectile function and to determine predictive factors of erectile dysfunction (ED) following the treatment.

SUBJECTS AND METHODS

We evaluated 84 Japanese patients with clinically organ-confined or locally invasive prostate cancer who underwent XRT between August 1995 and June 2002. We assessed the erectile function following XRT by a simple mailed questionnaire that was especially developed for this study in July 2002 (see Appendix). Questions 2 and 3 of this questionnaire were designed to inquire about erectile function before XRT, and questions 4 and 5, the onset of ED. To evaluate these aspects, we modified the questions regarding frequency and rigidity in our Japanese questionnaire that was previously validated (10).

During the study period, two patients died of prostate cancer and three patients died of diseases other than prostate cancer. Of the remaining 79 patients, only 72 (91.1%) responded to the questionnaire. To assess the influence of XRT on erectile function, we excluded 38 patients from the study because of the reasons listed below; therefore, only 34 were evaluable in the study. Those excluded were five patients with neoadjuvant hormonal therapy, three with immediate adjuvant or concomitant hormonal therapy, and 30 with ED before the treatment. In this
study, ED was defined as the erection not being sufficiently firm to penetrate, or it swelled but was not at all firm.

XRT was delivered to the prostate using the conventional four-field box (anterior, posterior and right and left laterals) technique and the 3-dimensional conformal technique (3-D CRT). The total dose ranged from 65 to 66 Gy (median, 66.0 Gy) in 24 to 30 fractions within 6 to 7.5 weeks in the conventional technique, and 65 to 70 Gy (median, 70.0 Gy) in 33 to 35 fractions within 6.5 to 7 weeks in the conformal technique. Conventional XRT was used in one institution, and 3-D CRT in the other two institutions. At each institution, the treatment modality for all patients who underwent XRT depended on the institutions’ setting; therefore, radiologists could not choose another modality.

To determine the predictive factors of ED following XRT, data were analyzed by multivariate analysis with the Cox proportional hazards model. The variables for this multivariate analysis were determined according to previous reports (11, 12). They included age (continuous), pretreatment prostate-specific antigen (PSA) (<10 ng/ml versus ≥10 ng/ml), clinical stage (T1 versus T2 and T3), XRT modality (conventional XRT versus 3-D CRT), the Brinkmann Index (continuous), alcohol intake (every day or frequently versus occasionally or never), hypertension (yes versus no), diabetes (yes versus no), and history of transurethral resection of the prostate (TURP) (yes versus no). In this analysis, we used ‘T1 versus T2 and T3’ as the clinical stage variables because pathological overlap between T2 and T3 clinical stages was more frequent than that between T1 and T2. To assess the history of smoking, we used the Brinkmann Index, which includes the number of cigarettes smoked per day and duration (years) of smoking history, although it does not distinguish between past smokers and current smokers.

Pretreatment serum PSA concentrations were measured by radioimmunoassay (Hybritech Inc., San Diego, CA). Clinical stages were classified on the basis of TNM classification of the American Joint Committee on Cancer (AJCC) (13).

We used Stat View 5.0 for Windows (SAS Institute, Cary, NC) for the statistical analyses. The maintenance rate of erectile function was determined by the Kaplan–Meier method, and the log-rank test was used for statistical analysis. Mann–Whitney U test was used for comparison of the questionnaire scores and characteristics between the two groups. A P-value of <0.05 was considered to be statistically significant.

RESULTS

The median age of the 34 patients in this study was 71 years (range, 57–81 years), and the median follow-up period was 24 months (range, 1–85 months). More than 60% of the patients had either a past history of TURP or current association of hypertension or diabetes (Table 1). The pretreatment median PSA level was widely distributed between the levels of 0.5 to 81.9 ng/ml, reflecting clinical stage distribution. Conventional radiotherapy was administered to six patients and 3-D CRT to 28 patients. There were no major complications that required specific surgical or medical management during or after treatment. Four patients (1; conventional, 3; 3-D CRT) experienced mild diarrhea and eight (2; conventional, 6; 3-D XRT) experienced a slight increase in urinary frequency as acute reactions. All these complications were transient and did not compromise the scheduled plan of radiotherapy. Seven patients had PSA recurrence as defined by the American Society of Therapeutic Radiology and Oncology (ASTRO) Consensus Panel (14). Although they received hormone therapy after the recurrence, their data on erectile function before the start of the therapy were included in the study.

Before initiation of XRT for the 34 patients, 16 had erectile function sufficiently firm to penetrate, while in 18 it was almost sufficiently firm to penetrate, as evaluated by question 3 of the current questionnaire. Of the 28 patients who received 3-D CRT, sufficient erectile function was observed in 13, and an almost sufficient function in 15. Of the six patients with conventional XRT, three had sufficient function and three did not. The median ages were 72 years (range, 61–81 years) in the conventional XRT group, and 71 years (range, 57–79 years) in the 3-D CRT group. No difference in age distribution was found between the two groups (P = 0.541; the Mann–Whitney U test). However, the median follow-up periods were significantly different: 39.6 months (range, 25.2–86.4 months) for conventional XRT and 18.1 months (range, 1.0–60.2 months)

### Table 1. Clinical and pathological characteristics of the 34 patients

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past history and associated diseases (%)</td>
<td></td>
</tr>
<tr>
<td>TURP</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>Smoking – current and previous smoker (%)</td>
<td>18 (52.9)</td>
</tr>
<tr>
<td>Median serum PSA; ng/ml (range)</td>
<td>13.1 (0.5–81.9)</td>
</tr>
<tr>
<td>Clinical stage (%)</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>T1c</td>
<td>10 (29.4)</td>
</tr>
<tr>
<td>T2a</td>
<td>11 (32.4)</td>
</tr>
<tr>
<td>T2b</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>T3a</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Gleason sum; biopsy (%)</td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>15 (44.1)</td>
</tr>
<tr>
<td>7</td>
<td>10 (29.4)</td>
</tr>
<tr>
<td>8–10</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Data not available</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Patients with PSA failure during follow-up (%)</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>Radiation modality (%)</td>
<td></td>
</tr>
<tr>
<td>3-dimensional conformal radiotherapy</td>
<td>28 (52.9)</td>
</tr>
<tr>
<td>Conventional</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Median radiation dose; Gy (range)</td>
<td>70.0 (65–70)</td>
</tr>
</tbody>
</table>
for the 3-D CRT group (P = 0.010, Mann–Whitney U test). Although most patients with ED following XRT responded to questions 4 and 5, four patients did not respond. In this situation, we arbitrarily determined that ED started at the time of the current study to avoid a bias toward a worse maintenance rate.

Multivariate analysis with the Cox proportional hazards model revealed that the modality of radiation was the only predictive factor for ED after XRT, with a statistically significant odds ratio of 3.7 (Table 2). When patients were divided into two groups, conventional XRT and 3-D CRT, those who received 3-D CRT had a significantly higher maintenance rate of erectile function than those with conventional XRT (Fig. 1). The estimated maintenance rates of the function were 0% at 1 year in the conventional XRT group, and 47.6% at 1 year and 19.0% at 3 years in the 3-D CRT group.

**DISCUSSION**

The preservation rate of erectile function varies widely from 1 to 63% at 3 years following XRT (1–7). The wide range can be attributed to the differences in the definition of ED, pretreatment erectile function and modality of XRT across the studies.

As for the definition of ED, the National Institutes of Health (NIH) consensus on ED defined impotence as the consistent inability to attain and maintain a penile erection sufficient to permit satisfactory sexual intercourse (15). In this study, we focused on patients who had normal erectile function sufficient to penetrate, as defined by the NIH, at the onset of XRT treatment, and assessed its function over time after the treatment. Thus, more than half of the cases were excluded in order to assess the direct impact of the radiotherapy on normal erectile function.

In the study by Goldstein et al. (16) that assessed the causes of ED following XRT, color-Doppler ultrasonography indicated abnormal vascularity in all patients with ED while hormone levels and neurologically tests were normal. Moreover, selective pudendal arteriography performed on two patients revealed bilateral narrowing of the internal iliac arteries, and tortuosities and occlusions of the internal pudendal and penile arteries. Merlin et al. (17) have also reported that ED following XRT is arteriogenic because radiation damages the wall and endothelium of the blood vessels.

Another aspect of XRT, which supports the idea that ED following XRT is vasculogenic, is the efficacy of sildenafil. Sildenafil is effective for vasculogenic ED rather than neurogenic ED. Its efficacy in ED following XRT is reported to be as high as 71 to 77% (18–20).

Our study revealed that the modality of XRT was the only predictive factor of ED following XRT. Inevitable exposure of tissues surrounding the prostate to radiation may produce an unfavorable effect on erectile function. Indeed, the modality of XRT has been reported to affect preservation of erectile function. The preservation rate for conventional XRT was as low as that of radical prostatectomy (5). A 3-D CRT showed a favorable outcome of erectile function in 100% of patients at 1 year and 63% of the patients at 3 years following XRT (4). A comparative study between conventional XRT and 3-D CRT with the same questionnaire showed that preservation of erectile function was higher in 3-D CRT than in the conventional therapy (3), which is similar to the result of our study. These results also suggest that 3-D CRT possibly contributes to a better outcome of erectile function because critical structures receive low radiation exposure. However, even 3-D CRT may not guarantee complete preservation of the function because approximately 43% of the total dose for the prostate is delivered to the cavernous (21).

![Figure 1. Maintenance of erectile function following radiotherapy. Log-rank test: P = 0.026; 3-D CRT: 3-dimensional conformal radiotherapy; Conventional: conventional radiotherapy; (): patients at risk.](https://academic.oup.com/jjco/article-abstract/34/5/269/790351)

**Table 2. Factors involved in erectile dysfunction following radiotherapy**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.91–1.09</td>
<td>0.89</td>
</tr>
<tr>
<td>Pretreatment PSA</td>
<td>0.41</td>
<td>0.14–1.18</td>
<td>0.10</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>1.44</td>
<td>0.39–5.26</td>
<td>0.58</td>
</tr>
<tr>
<td>Radiation modality</td>
<td>3.70</td>
<td>1.07–12.83</td>
<td>0.04</td>
</tr>
<tr>
<td>Brinkmann index</td>
<td>1.00</td>
<td>1.00–1.001</td>
<td>0.40</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>2.78</td>
<td>0.53–14.52</td>
<td>0.22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.02</td>
<td>0.36–2.93</td>
<td>0.97</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.30</td>
<td>0.46–11.52</td>
<td>0.31</td>
</tr>
<tr>
<td>TURP</td>
<td>0.76</td>
<td>0.10–6.0</td>
<td>0.79</td>
</tr>
</tbody>
</table>
Massachusetts Male Aging Study (23). However, the results of the present study suggest that the influence of aging led to approximately 1% increase in ED over 3 years. Thus, even though our study population was old, the impact of aging on erectile function was minimal during the 3-year follow-up period.

Japanese elderly men were found to differ with regard to QOL in a community-based study comparing Japan and United States (9). They might have less interest in their sexual life, and ED did not contribute to deterioration of the QOL (24). This can be possibly attributed to the difference in culture and customs between Japan and Western countries. Thus, elderly Japanese men might not seek ED treatment aggressively even if they have ED. Therefore, in this study group, very few ED patients following XRT sought highly effective oral medicine.

The current study has some limitations. The study is retrospective and used a mailed questionnaire that depended on the patient’s memory concerning erectile function before and after treatment. The questionnaire used in this study has only been partially validated. We developed a new questionnaire for this study for the purpose of assessing the subjective quality of erectile function regardless of sexual activity, and the onset of ED. The different outcomes between 3-D CRT and conventional XRT might be influenced by confounding variables among institutions. However, in the two institutions where 3-D CRT was used for treatment, there was no statistically significant difference in the maintenance rates of erectile function following XRT.

Another limitation of this study is the small number of patients who received conventional XRT and the significantly different follow-up period compared to those with 3-D CRT. The difference in the follow-up period might have influenced the outcomes of patients. Recently, 3-D CRT has become a mainstream modality of administering XRT for localized prostate cancer. Thus, a large-scale prospective trial is crucial to draw a definitive conclusion for ED following well-designed 3-D CRT using a validated questionnaire.

CONCLUSION

The only predictive factor of ED following XRT was the modality of XRT. However, even patients who received 3-D CRT achieved only a 19% preservation rate for erectile function at 3 years following XRT. This study suggests that XRT does not always guarantee preservation of erectile function.

Appendix

QUESTIONS FOR ERECTILE FUNCTION

1. How often did you have sexual intercourse before initiating radiotherapy?
   Never
   Less than once a month
   Once or twice a month
   More than three times a week
   More than three times a week

2. How often did you notice your erection regardless of sexual activity before initiating radiotherapy?
   Never
   Less than once a month
   Once or twice a month
   Once or twice a week
   More than three times a week

3. How firm was your erection? (except for the persons who answered never in question 2)
   Swollen but not firm at all
   Insufficient to penetrate
   Sufficient to penetrate but not satisfactory
   Sufficient to penetrate satisfactorily

4. When did you notice that your erection was not firm enough after initiating radiotherapy?

5. When was your erection insufficient to penetrate after initiating radiotherapy?

QUESTION FOR QOL

6. How do you feel about your current erectile function condition lasting for the rest of your life?
   Very dissatisfied
   Rather dissatisfied
   Slightly dissatisfied
   Satisfied
   Rather satisfied
   Very satisfied

References

8. Egawa S, Shimura S, Irie A, Kitano M, Nishiguchi I, Kuwao S, et al. Toxicity and health-related quality of life during and after high dose rate...


