Five-year Follow-up of Health-related Quality of Life after Intensity-modulated Radiation Therapy for Prostate Cancer

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Objective: We evaluated health-related quality of life (HRQOL) in patients with localized prostate cancer who underwent intensity-modulated radiation therapy (IMRT) or three-field conformal radiotherapy (3DCRT).

Methods: A total of 97 patients underwent 3DCRT and 36 underwent IMRT for localized prostate cancer between 2002 and 2004. We measured the general and disease-specific HRQOL with the Medical Outcomes Study 36-Item Health Survey and University of California, Los Angeles Prostate Cancer Index, respectively.

Results: There were no significant differences in the pre-operative characteristics of the two groups. The patients in the 3DCRT group were more likely to receive hormonal therapy compared with the IMRT group before and after radiation therapy (P < 0.001 and P = 0.011, respectively). With regard to general HRQOL domains, both the 3DCRT and IMRT group scores showed no significant difference between baseline and any of the observation periods. At 60 months after treatment, the 3DCRT group had significantly worse bowel function and bother scores than baseline (both P < 0.001). On the other hand, there were no significant differences between the baseline and any of the post-treatment time periods in the IMRT group. In the 3DCRT group, sexual function remained substantially lower than the baseline level (P = 0.023). The IMRT group tended to show a decrease in sexual function, which was not statistically significant (P = 0.11).

Conclusions: IMRT can provide the possibility to deliver a high irradiation dose to the prostate with satisfactory functional outcomes for long-term periods.

Key words: prostate cancer – intensity-modulated radiation therapy – radiotherapy – quality of life

INTRODUCTION

Men who are newly diagnosed with localized prostate cancer face a sometimes difficult choice between the principal treatments of watchful waiting, radical prostatectomy, radiation therapy (external beam or brachytherapy), hormonal ablation or a combination of these modalities. Recent research suggests that when clinical stage T1 or T2 prostate cancer is limited, biochemical outcomes are comparable for most men undergoing radical prostatectomy, external beam radiation or brachytherapy (1). Although the probability of eradicating prostate cancer increases by increasing the radiation dose, classic radiotherapy techniques at doses exceeding 70 Gy result in high rates of severe rectal and bladder toxicity (2–4). Intensity-modulated radiation therapy (IMRT) has been shown to improve the local control and disease-free survival in patients with localized prostate cancer (5). Zelefsky et al. (6) reported that IMRT reduced acute and rectal toxicities significantly compared with conventional radiotherapy techniques. With regard to conformal radiotherapy, Potosky et al. (7) reported survey results at three separate points—6, 12 and 24 months after treatment. According to their study, urinary function declined slowly for the first 6 months and then remained relatively stable. Rectal function decreased during the first 6 months and then improved.

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thereafter. Sexual function rapidly declined during the first 6 months and then continued to decline slowly thereafter. To evaluate treatment, not only genitourinary and gastrointestinal toxicity but also the impact on health-related quality of life (HRQOL) is important (8).

Several studies have addressed the impact of conformal radiation therapy or IMRT on the HRQOL scores within 3 years after treatment (9–11). To our knowledge, the present study is the longest-term prospective study to assess the impact of IMRT on general and disease-specific outcomes for localized prostate cancer.

PATIENTS AND METHODS

PATIENT POPULATION

Between 2002 and 2004, 97 patients were treated with three-field conformal radiotherapy (3DCRT) and 36 were treated with IMRT. The patients who suffered from localized prostate cancer (T1-T3N0M0) were treated at Tohoku University Hospital and two affiliated hospitals. Basically, we recommended radiotherapy with neoadjuvant hormonal therapy if the patient had a tumor with a clinical stage of T3 or higher. However, the final determination of the treatment modality was made by the patient after thorough discussion of the options. IMRT was performed at Tohoku University Hospital. Three gold markers were implanted transperineally through 18 G needles under transrectal ultrasound guidance before radiotherapy. Two markers were implanted toward the base of the prostate gland or at mid-gland, and one marker was implanted toward the apex. No noticeable complications from the implantation procedure occurred. Subsequently, the patients underwent computed tomography (CT) simulation in preparation for the treatment planning. Daily doses were delivered under an image guide using dual fluoroscopy with a flat panel on-board imager system which was developed at the department of radiation oncology at Tohoku University (12). Daily set-up error could be reduced to <1 mm using this system (13). A margin of 5 mm around the clinical target volume was added. Prescribed doses for the prostate and seminal vesicles were 78 Gy (range, 76–80 Gy) for IMRT. On the other hand, three-dimensional conformal external beam radiation therapy was performed at Miyagi Cancer Center and Osaki Citizen Hospital. For this group, a CT-planned three-dimensional conformal external beam technique was used to deliver a dose of 70 Gy at 2 Gy fractions (five fractions per week). All recruitment and research protocols were approved by Ethics Committee, Tohoku University School of Medicine. All patients were informed of their cancer diagnosis before being asked to fill out the HRQOL questionnaires. Those who agreed to participate in this study received from his urologist a questionnaire, an informed consent form and a prepaid envelope for returning the questionnaire.

QOL METHODOLOGY

We measured the general and prostate-specific HRQOL using two types of instruments. The general HRQOL was assessed with the Medical Outcomes Study 36-Item Short Form (SF-36) (14). The general scales cover eight domains, four physical and four emotional. The eight scales are scored separately from 0 to 100, a higher score representing a better quality of life. The prostate-specific HRQOL was assessed with the University of California, Los Angeles Prostate Cancer Index (UCLA PCI), which is a 20-item questionnaire that quantifies prostate cancer-specific HRQOL in six separate domains of urinary function, urinary bother, bowel function, bowel bother, sexual function and sexual bother (15). The six scales are scored separately from 0 to 100, a higher score representing a better outcome. Both questionnaires have already been translated into Japanese and the validity and reliability were previously tested (16,17). All patients were informed of their cancer diagnosis before being asked to fill out the HRQOL questionnaires. The baseline interview was conducted after the diagnosis. Follow-up interviews were conducted in person at scheduled study visits of 3, 6, 12, 18, 24 and 60 months after treatment.

STATISTICS ANALYSIS

Quality of life scores for the various domains are shown as mean ± standard deviation (SD) in scales of 0–100, with a higher score always representing a better HRQOL. Differences in the distributions of the background variables were evaluated by non-parametric procedures ($\chi^2$ or Mann–Whitney tests). The inspection value was shown by using average ± SD and statistical analysis was performed using the Mann–Whitney U-test. A value of $P < 0.05$ was considered significant.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Table 1 presents information on the background characteristics of the patients with localized prostate cancer who subsequently underwent IMRT or 3DCRT. The two groups were comparable in terms of mean patient age, serum prostate-specific antigen (PSA) values, Gleason scores and clinical tumor stage. The two groups showed similar levels of co-morbidities and socio-demographic characteristics. At the time of the study entry, no national guidelines for hormonal treatment were available and hormonal therapy was commonly used before, during and after radiation therapy. The patients in the 3DCRT group were more likely to receive hormonal therapy compared with the IMRT group before and after radiation therapy ($P < 0.001$ and $P = 0.011$, respectively). The median duration periods of neoadjuvant hormonal therapy were 6.5 months (range 3–24 months) and 3 months (range 1–39 months) in the IMRT and 3DCRT
group, respectively. As for adjuvant hormonal therapy, the median duration periods were 8 months (range 6–15 months) and 12 months (range 2–48 months) in the IMRT and 3DCRT groups, respectively.

HRQOL ASSESSMENT

A comparison of HRQOL scores between the IMRT and 3DCRT groups is shown in Fig. 1 (general scales) and Fig. 2 (disease-specific scales). The total numbers of questionnaires returned were 133 (36 and 97), 115 (28 and 87), 109 (26 and 83), 110 (32 and 76), 114 (30 and 84) and 96 (24 and 72) at baseline, 3, 6, 12, 18, 24 and 60 months after radiotherapy (for the IMRT and 3DCRT groups, respectively), respectively.

The mean general HRQOL scores are shown in Fig. 1. At baseline, there were no significant differences in any of the general HRQOL domains between the two groups. Both the 3DCRT and IMRT group scores showed no significant difference between baseline and any of the observation periods. Figure 2 presents the mean UCLA PCI scores at each time point. The two treatment groups showed similar urinary function and bother scores throughout the follow-up period. With regard to the domain of bowel function and bother, no significant difference was observed at baseline. At 60 months after treatment, the 3DCRT group had significantly worse bowel function and bother scores than baseline (both \( P < 0.001 \)). In particular, patients who received 3DCRT were more likely to suffer from rectal urgency, diarrhea or crampy pain in abdomen and pelvis compared with those who received IMRT. On the other hand, there were no significant differences between the baseline and any of the post-operative time periods in the IMRT group. In the 3DCRT group, sexual function decreased at 3 months and remained substantially lower than the baseline level (\( P = 0.023 \)). The IMRT group showed no significant difference for 2 years. At 60 months, the IMRT group tended to show a decrease in sexual function, which was not statistically significant (\( P = 0.11 \)). No significant differences between the 3DCRT and the IMRT group were observed at the baseline and any of the post-operative time periods for sexual bother.

Since endocrine therapy might have affected the recovery of sexual function and bother, the impact of IMRT alone on HRQOL was further analyzed, resulting in a study cohort of 12 patients. The sexual function score continued to show a modest decline from baseline (27.8) at 2 years (19.8) and 5 years (17.4). When assessing sexual bother, it appeared to be equivalent at every point among those who received IMRT alone (Fig. 3).

DISCUSSION

The current study has several important findings. First, there was overall stability in the general HRQOL in the 3DCRT...
and IMRT groups, and no significant differences among the two radiation groups were observed throughout the long follow-up period. These findings were consistent with those of several investigators who have reported that general HRQOL is relatively good after radiotherapy (18,19). Among those treated with radiotherapy, fatigue appears to be the most common complication. Radiotherapy has been associated with increases in fatigue from pre-treatment until 3 to 12 months post-treatment, particularly in those receiving ‘whole pelvis radiation’ (20). However, relatively low levels of depression were indicated at both of these time points. Hence, although fatigue may increase during the year of treatment, it does not appear to be particularly distressing to men with localized prostate cancer.

Second, although bowel impairment was more common among subjects who received 3DCRT, IMRT showed no significant differences in the bowel function and bother even after 5 years from the baseline levels. IMRT has the added potential of reducing the treatment-related toxicity by the conformal avoidance of normal tissue. Zelefsky et al. reported acute toxicity in 772 patients treated with at least 81 Gy. Acute grade 2 genitourinary toxicity was observed in 4% (6). In our questionnaire study, there were no significant differences in bowel function and bother scores between baseline and any post-treatment period. Lips et al. (9) described that the increase in gastrointestinal and genitourinary toxicity did not cause changes in HRQOL. This could be because the incidence of severe toxicity was too low to be detected by the HRQOL questionnaire. Another explanation might be that patients had time to adapt to the radiotherapy-induced complaints and developed coping skills (21). Our report shows that improved technical possibilities, regarding IMRT and accurate position verification, provide the possibility of dose escalation with comparable QOL results. Therefore, to minimize the risk of QOL deterioration, an accurate radiotherapy technique should be used when further increasing the radiation dose to the prostate.

Third, consistent with previous analyses, we identified a progressive decline in sexual function among patients with external beam radiation therapy. In a study of 287 men who reported acute toxicity in 772 patients treated with at least 81 Gy. Acute grade 2 genitourinary toxicity was observed in 4% (6). In our questionnaire study, there were no significant differences in bowel function and bother scores between baseline and any post-treatment period. Lips et al. (9) described that the increase in gastrointestinal and genitourinary toxicity did not cause changes in HRQOL. This could be because the incidence of severe toxicity was too low to be detected by the HRQOL questionnaire. Another explanation might be that patients had time to adapt to the radiotherapy-induced complaints and developed coping skills (21). Our report shows that improved technical possibilities, regarding IMRT and accurate position verification, provide the possibility of dose escalation with comparable QOL results. Therefore, to minimize the risk of QOL deterioration, an accurate radiotherapy technique should be used when further increasing the radiation dose to the prostate.

**Figure 1.** Longitudinal changes in the mean general health-related quality of life (HRQOL) scores over time by type of radiation treatment. High scores indicate better outcomes. Treatment consisted of intensity-modulated radiation therapy (IMRT) or three-field conformal radiotherapy (3DCRT). (A) Physical function, (B) physical role restriction, (C) bodily pain, (D) general health perception, (E) mental health, (F) emotional role restriction, (G) social function and (H) vitality.
underwent 3DCRT for localized prostate cancer, Mantz et al. noted an actuarial potency rate of 96%, 75%, 59% and 53% at 1, 20, 40 and 60 months, respectively, after treatment (22). Our findings confirm the longitudinal trends in sexual function observed by Litwin et al. (23), in which the patients undergoing 3DCRT for localized prostate cancer began to show declining sexual function during the second year after treatment. Concomitant with primary therapy, men who receive external radiation therapy may have received androgen deprivation therapy. Those with more aggressive tumor characteristics more commonly receive androgen deprivation with radiation, which impair both general and disease-specific HRQOL including sexual activity. In our sample, hormonal therapy was administered to 93% of the 3DCRT group and 67% of the IMRT group. Yoshimura et al. (11) even reported an improvement in sexual function during the follow-up, probably resulting from reduced sexual function before the start of radiation therapy, as a result of neoadjuvant hormonal therapy. Thus, the persistent deterioration in sexual function might be due to not only late radiation effects but also rate of androgen deprivation, which might have influenced sexual activity. Previously, we reported that IMRT did not cause a loss of potency in men with localized prostate cancer during the first 2 years (10). At 60 months, however, subjects who received IMRT alone appeared to show decreased sexual function to the same extent as those who received IMRT plus hormonal therapy, and the difference was not statistically significant. Given the small subset of patients on which the results are based, future confirmatory studies will be necessary to assess the impact of IMRT on sexual domain-related HRQOL.

Our study found that erectile dysfunction after treatment was not a burden to the patients, although a deterioration of sexual function was observed in both treatment groups. The demonstrated trends in sexual function and bother suggest that they are discrete independent variables. Hamilton et al. (19) found that 43% of men who were potent before diagnosis were impotent 2 years after radiotherapy, yet more than two-thirds of the men were satisfied with their treatment and would choose the same option again, implying that their sexual dysfunction was not a major problem. In addition, the
median age of over 70 years in our cohort likely influenced the sexual function and bother scores (24).

Our study has several limitations. First, our study had relatively few patients, especially in the IMRT group, consistent with its design as a feasibility study of longitudinal collection. Second, we did not assess HRQOL before the initiation of hormonal ablation, which may constitute another potential flaw in our study. Third, the treatment was not in a randomized fashion but patients were treated according to their physicians and institutions’ practice. This may have introduced a sampling bias if the two groups had apparent or unapparent baseline differences. Because there were no significant differences in regard to age, pre-treatment PSA level, tumor stage distribution, morbidity or socio-demographic characteristics between the two treatment groups, the substantial differences in the post-operative HRQOL could be attributed mainly to the treatment approach. Furthermore, we did not separately examine subjects whose cancer recurred, which also impacts both general well-being and cancer-specific domains (25). However, we sought to characterize long-term HRQOL after treatment for clinically localized prostate cancer, inclusive of factors inherent to the treatment choice. This method of analysis certainly introduces bias, but it also facilitates valid comparison of expected outcomes of an average subject undergoing treatment for localized prostate cancer. Fourth, it is important to remember that the urinary function scale of UCLA PCI is designed to measure urinary leakage symptoms often seen after surgery and not irritative symptoms often seen after radiation. Hence, the instrument does not detect urinary function impairments that would be expected after radiation. Further investigation is needed to comment on this aspect of urinary disability. Finally, since no data are included on the use of phosphodiesterase-5 inhibitors or other erection aids, it would be very difficult to interpret the information about sexual satisfaction.

Despite these limitations, our observations have important implications for men who are faced with the choice of radiation for localized prostate cancer. In the future, it will be important for randomized studies of further dose escalation to measure HRQOL, as well as toxicity, with long-term follow-up.

CONCLUSION

For 5 years following IMRT using gold marker-based position verification, none of the HRQOL items showed significant deterioration compared with the HRQOL scores before the start of radiation therapy. Thus, IMRT can offer satisfactory functional outcomes for long-term periods.

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Conflict of interest statement

None declared.

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