Predictive Factors of Rectal Toxicity after Permanent Iodine-125 Seed Implantation: Prospective Cohort Study in 2339 Patients

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Conflict of interest: none
ABSTRACT

Purpose: To evaluate the incidence and the associated factors of rectal toxicity in patients with prostate cancer undergoing permanent seed implantation (PI) with or without external beam radiation therapy (EBRT) in a nationwide prospective cohort study in Japan (J-POPS) during the first 2 years.

Methods and Materials: 2,339 subjects were available for the analyses. Rectal toxicity was evaluated using the NCI-CTCAE version 3.0.

Results: The 3-year cumulative incidence for Grade ≥2 rectal toxicity was 2.88%, 1.76% and 6.53% in all subjects, PI group and EBRT combination therapy group, respectively. On multivariate analysis, among all subjects, Grade ≥2 rectal toxicity was associated with rectal volumes receiving 100% of the prescribed dose (R100) (p <0.0001) and EBRT combination therapy (p = 0.0066). R100 in the PI group (p = 0.0254), and R100 (p = 0.0011) and interactive planning (p = 0.0267) in the EBRT combination therapy group were also associated with Grade ≥2 toxicity. The 3-year cumulative incidence of Grade ≥2 rectal toxicity was 3.80% and 1.37% for R100 ≥1 mL and R100 <1 mL, respectively in the PI group (p = 0.0068), and 14.09% and 5.52% for R100 ≥1 mL and R100 <1 mL, respectively in the EBRT combination therapy group (p = 0.0070).

Conclusions: Rectal toxicity was relatively rare in this study compared to previous reports. For Japanese prostate cancer patients, R100 <1 mL in both PI and EBRT combination therapy groups and interactive planning in EBRT combination therapy group may be effective in decreasing the incidence of rectal toxicity.
KEYWORDS: Prostate cancer, Brachytherapy, Rectal toxicity, External beam radiation therapy, Dose-volume histogram parameters, Interactive planning

INTRODUCTION

Permanent seed implantation (PI) has become a standard treatment option for patients with localized prostate cancer, with long-term local and biochemical control similar to outcomes observed after radical prostatectomy and external beam radiation therapy (EBRT) (1).

However, PI can lead to rectal toxicity, because the rectum, fixed in position and close to the prostate, often receives a large radiation dose with PI (2). Rectal toxicity is the third late effect of brachytherapy, after the urinary and sexual toxicity. Rectal toxicity of PI is variable in its presentation and can range in severity from mild, self-limited proctitis to more severe cases of ulceration and fistula formation (3–5).

The number of patients with prostate cancer treated with PI has increased rapidly in Japan, and over 19,000 patients had been treated in 109 institutions at the end of 2011 (6). To evaluate the safety and efficacy of PI for prostate cancer, a nationwide prospective cohort study entitled the Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 (I-125) Seed Implantation (J-POPS; NCT00534196) was initiated in July 2005 (7). A total of 2,354 subjects were enrolled in the study during the first 2 years.

Ohashi et al. made the preliminary report evaluating the urinary and rectal toxicity in 2,339
subjects treated with PI enrolled in the J-POPS during the first 2 years (8). In this study, we describe rectal toxicity in more detail and evaluate factors associated with rectal toxicity in the same subjects.

METHODS AND MATERIALS

Although published previously (7, 8), a brief description of methods and materials are outlined below.

Patient eligibility

The J-POPS study is a large multi-institutional prospective cohort study to investigate the clinical effects of PI for localized prostate cancer in Japan (7). The enrollment of the subjects for this study has started in July 2005 and continued till December 2010. Finally, 6,927 participants in 46 institutes had been registered and been followed up still now.

All subjects were histologically confirmed as having adenocarcinoma of the prostate and clinically diagnosed as having localized disease. There was no limitation for age, and all subjects gave written informed consent for enrollment in the J-POPS study. Inclusion and exclusion criteria of the participants followed the recommendations of the American Brachytherapy Society (9).

A total of 2,354 participants were enrolled in this study during the first 2 years. Out of 2,354 participants, background characteristics and baseline data were available in 2,339 patients.
Treatment design

All participants were treated with loose I-125 seeds. Modified peripheral loading or modified uniform loading was generally recommended for seed placement. The clinical target volume (CTV) was defined as the prostate volume including an added treatment margin of 3–5 mm in all directions, except for less than 2 mm in the posterior direction.

For PI alone as radiation therapy (PI group), a dose of 144 Gy was prescribed. According to the planning goals, V100 for the CTV (the percent volume of the CTV receiving 100% of the prescription dose) had to be over 90% or D90 for the CTV (the minimal dose received by 90% of the CTV) had to be 144–180 Gy. The maximum urethral dose had to be <200 Gy, whereas that for the rectum had to be <200 Gy in any slice.

For EBRT combination therapy (EBRT combination therapy group), the prescription dose for PI was 100–110 Gy and that for EBRT was 40–50 Gy with 1.8–2.0 Gy/fraction. As for EBRT, the target volume consisted of the prostate gland, seminal vesicles, small pelvis, and/or whole pelvis. EBRT was performed either before PI or approximately 1 month after PI. The maximum urethral and rectal dose for PI had to be <150% of the prescription dose. All the treatment techniques, such as 2-dimensional radiation therapy, 3-dimensional conformal radiation therapy, and intensity-modulated radiation therapy were allowed in this protocol.

Computed tomography (CT) images, taken at 1–3 mm slice width, were obtained approximately 1 month after PI for postimplant dosimetric evaluation. Dose-volume histograms (DVH) for the
Prostate, urethra, and rectum were computed to obtain post-planning distribution data. The calculated dosimetry parameters were the percent volumes of the prostate receiving 100% and 150% of the prescribed dose (V100 and V150, respectively) and the values of the minimal dose received by 90% of the prostate volume (D90). The rectal dose was expressed as the rectal volume in cubic centimeters that received 100% and 150% of the prescribed dose (R100 and R150, respectively). The urethral dose was expressed as the values of the minimal dose received by 90% and 5% of the urethra volume (U-D90 and U-D5, respectively) and the urethral volume receiving 200% of the prescribed dose (U200).

Patient information is shown in Tables 1 and 2.

Toxicity scoring and follow-up protocol

The scheduled follow-up assessments involved prostate-specific antigen (PSA) blood tests and physical examinations every 3 months for the first 2 years, and every 6 months thereafter for 5 years. Toxicity was evaluated by physicians, mainly urologists, at 3, 12, 24, and 36 months after completion of radiation therapy.

The rectal toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0, for proctitis and rectal bleeding (10). In this system, Grade 1 toxicity included mild adverse events (rectal discomfort or rectal bleeding that did not require intervention). Grade 2 toxicity included moderate adverse events (proctitis or rectal bleeding requiring medical intervention or minor cauterization). Grade 3 toxicity included severe
adverse events (proctitis requiring operative intervention or rectal bleeding requiring transfusion, interventional radiology, or endoscopic or operative intervention). Grade 4 toxicity included life-threatening or disabling adverse events (rectal perforation or rectal bleeding requiring major urgent intervention).

Acute toxicity was defined as symptoms occurring by 3 months after radiation therapy, and late toxicity was defined as symptoms occurring beyond 3 months after radiation therapy.

Statistical analysis

We estimated the cumulative incidence rate for Grade $\geq 2$ rectal toxicity by the Kaplan Meier method to take into account of censored observations. We also identified the factors associated with Grade $\geq 2$ rectal toxicity by the Cox proportional hazard model. Probability ($p$) values of $<0.05$ were defined to be significant. Multivariate analysis was performed to analyze factors that were found to be significantly associated with Grade $\geq 2$ rectal toxicity in the univariate analysis.

Statistical analyses were performed by SAS 9.1.3 statistical software (SAS Institute Inc., Cary, NC, USA). All statistical analyses were carried out at the Translational Research Informatics Center (TRI) in the Foundation for Biochemical Research and Innovation (FBRI), a public interest incorporated foundation.

Ethical Considerations

The ethical review committee of the TRI (Approval no. 05-01; May 6, 2005) and all of the
Results of the participating facilities approved the study.

RESULTS

Incidence of acute and late rectal toxicity

The incidence of rectal toxicity was assessed at 3, 12, 24, and 36 months after completion of radiation therapy in 2,336, 2,310, 2,249, and 2,188 subjects, respectively.

The frequency of acute, late, and total rectal toxicity are shown in Table 3.

The 3-year cumulative incidence rate for Grade ≥2 rectal toxicity was 2.88% for all subjects, 1.76% for the PI group, and 6.53% for the EBRT combination therapy group (Fig. 1a). The 3-year cumulative incidence rate for Grade ≥2 proctitis was 1.57% for all subjects, 1.07% for the PI group, and 3.18% for the EBRT combination therapy group. The 3-year cumulative incidence rate for Grade ≥2 rectal bleeding was 1.71% for all subjects, 0.75% for the PI group, and 4.84% for the EBRT combination therapy group.

Only 3 subjects (0.55%; 3/547) in the EBRT combination therapy group experienced Grade 3 toxicity. Out of these 3 subjects, 2 had their symptoms resolved with argon plasma coagulation or hyperbaric oxygen therapy. One patient developed intractable bleeding and a rectourethral fistula, and a diverting colostomy was performed.

Factors associated with Grade ≥2 rectal toxicity
Tables 4, 5, and 6 show the results of the univariate and multivariate analyses using the Cox proportional hazard model for the effect of various factors on the incidence of Grade ≥2 rectal toxicity among all subjects, in the PI group, and in the EBRT combination therapy group, respectively.

On multivariate analysis, among all subjects, Grade ≥2 rectal toxicity was associated with rectal volumes receiving 100% of the prescribed dose (R100) (hazard ratio [HR], 1.885; 95% confidence interval [CI], 1.383–2.569; \(p < 0.0001\)) and EBRT combination therapy (HR, 2.815; 95% CI, 1.334–5.939; \(p = 0.0066\)). R100 in the PI group (HR, 1.655; 95% CI, 1.064–2.574; \(p = 0.0254\)), and R100 (HR, 1.977; 95% CI, 1.314–2.974; \(p = 0.0011\)) and interactive planning (HR, 0.472; 95% CI, 0.243–0.917; \(p = 0.0267\)) in the EBRT combination therapy group was also associated with Grade ≥2 toxicity.

In the PI group, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity exceeded 3% with R100 ≥ 1 mL; 3.80% for R100 ≥ 1 mL, and 1.37% for R100 < 1 mL (HR, 2.757; 95% CI, 1.282–5.929; \(p = 0.0068\)) (Fig. 1b). In the EBRT combination therapy group, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity exceeded 10% with R100 ≥ 1 mL; 14.09% for R100 ≥ 1 mL, and 5.52% for R100 < 1 mL (HR, 2.744; 95% CI, 1.286–5.857; \(p = 0.0070\)) (Fig. 1c). In the EBRT combination therapy group, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity was 4.87% for interactive planning and 10.25% for other plannings (Fig. 1d).
DISCUSSION

Rectal toxicity is the third late effect of brachytherapy, after the urinary and sexual toxicity, and many publications have described the incidence and severity of rectal toxicity after PI (3, 5, 11–15). However, no reports have included more than 1,000 patients and been prospectively designed. To our knowledge, this is the largest prospective report of rectal toxicity after PI.

Grade ≥2 rectal toxicity is reported to occur in 2.0–10.4% of patients treated with PI (5, 11–16) and in 8.0–18.0% of patients treated with EBRT combination therapy (11, 15–17). In our study, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity was 1.76% for the PI group and 6.53% for the EBRT combination therapy group. These findings were relatively favorable results as compared to other studies. We assume that this is largely attributable to the rectal dose being lower than those in other studies. The mean and median R100 in all patients was 0.48 mL and 0.30 mL in our study, whereas other studies have reported a mean or median R100 of 0.79–1.49 mL (5, 11, 18, 19). This might be explained by the superior quality of the technique used at these institutions. Training workshops have been held at regular intervals in Japan to maintain or improve the technical level of PI (6), and all the institutions in this study have participated the workshops. In each institution, PI treatment was performed with the strict aim of sparing the rectum. Additionally, a smaller prostate volume (PV) might result in a lower rectal dose. McNeely et al. (20) and Patil et al. (19) reported that the rectal dose increased in tandem with an enlarging PV. The mean and median PV in all subjects was 25.90 mL and 25.19 mL in our study, whereas the aforementioned studies have reported a mean or median PV of 28.0–38.5 mL (5, 11, 18, 19).
Factors reportedly associated with rectal toxicity in PI include the addition of EBRT (15, 17, 21–24), rectal dose (3, 11, 13–15, 25), prostate dose (15, 26, 27), advanced age (22, 21), inflammatory bowel disease (22), and smoking status (21). Prostate volume (19, 20) and body mass index (19) were reported to be associated with the rectal dose in PI. Diabetes mellitus, prior abdominal surgery, and androgen deprivation therapy were reported to be associated with rectal toxicity in EBRT (28). We performed this study on the basis of the hypothesis that these factors might be associated with rectal toxicity. Indeed, when we analyzed all 2,339 cases, Grade ≥2 rectal toxicity was associated with R100 and the addition of EBRT. R100 in the PI group and R100 and interactive planning in the EBRT combination therapy group were also associated with Grade ≥2 rectal toxicity. With regard to the planning process, several investigators have reported that DVH parameters are significantly better with intraoperative planning than preplanning (29). Zelefsky et al. (30) reported a more rapid resolution of Grade 2 urinary-related symptoms with interactive planning than preplanning. However, prior to our study, no reports have demonstrated that rectal toxicity was rarer with intraoperative planning than preplanning.

In this study, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity was 3.80% for R100 ≥1 mL and 1.37% for R100 <1 mL, respectively, in the PI group (HR, 2.757; 95% CI, 1.282–5.929; \( p = 0.009 \)), and 14.09% for R100 ≥1 mL and 5.52% for R100 <1 mL, respectively, in the EBRT combination therapy group (HR, 2.744; 95% CI, 1.286–5.857; \( p = 0.009 \)). Snyder et al. (13) have shown that Grade ≥2 proctitis at 5 years was seen in 18% of patients with R100 >1.3 mL and in 5% of patients with R100 ≤1.3 mL among patients receiving PI (\( p = 0.001 \)). Keyes et al. (5) have
shown that, for PI, late Grade ≥2 rectal toxicity was seen in 10.6% of patients with R100 ≥1 mL and in 6.7% of patients with R100 ≤1 mL. Shiraishi et al. (31) have shown that, for EBRT combination therapy, Grade 2 rectal bleeding was seen in 22.0% of patients with R100 >1 mL and in 8.1% of patients with R100 ≤1 mL. Keyes et al. (5), Tran et al. (32), and Han et al. (33) suggested keeping R100 <1 mL. These reports are consistent with our data in terms of association of R100 with rectal toxicity.

This study has some limitations. First, interobserver variability in postimplant dosimetry exists because this study was a multicenter study. Contouring the prostate and rectum on postimplant CT images can be challenging (34). However, because the above-mentioned training workshops in which all the institutions in this study have participated include the technical instruction of postimplant dosimetry, interobserver variability in this study should be minimized. Secondly, we did not analyze the rectal DVH parameters for EBRT in the EBRT combination therapy group, although Shiraishi et al. (31) reported that rectal V30 (the percent volumes receiving doses higher than 30 Gy) for EBRT was associated with Grade 2 rectal bleeding in patients receiving EBRT combination therapy and rectal DVH parameters were reported to be associated with rectal toxicity in patients receiving EBRT (28). Finally, the follow-up period may be too short to observe late rectal toxicity. The final follow-up of toxicity was at 36 months in our protocol, although rectal toxicity could appear after more than 3 years.
CONCLUSIONS

Rectal toxicity after PI with and without EBRT was relatively rare in our study as compared to previous reports. For Japanese patients with prostate cancer treated with PI, R100 < 1 mL both in PI and EBRT combination therapy and interactive planning in EBRT combination therapy may be effective in decreasing the incidence of rectal toxicity.

FIGURE CAPTIONS

Fig. 1. (a) Cumulative Grade ≥2 rectal toxicity rates for the PI group and the EBRT combination therapy group. (b) Cumulative Grade ≥2 rectal toxicity rates for R100 ≥ 1 mL and R100 < 1 mL in the PI group. (c) Cumulative Grade ≥2 rectal toxicity rates for R100 ≥ 1 mL and R100 < 1 mL in the EBRT combination therapy group. (d) Cumulative Grade ≥2 rectal toxicity rates for interactive planning and other plannings in the EBRT combination therapy group.

PI = permanent seed implantation; EBRT = external beam radiation therapy; R100 = the rectal volume in cubic centimeters that receiving 100% of the prescribed dose.

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Table 1  Descriptive statistics of patient information

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SD = standard deviation; PI = permanent seed implantation; EBRT = external beam radiation therapy; BMI = body mass index; PSA = prostate-specific antigen; VXX = the percent volumes receiving XX% of the prescribed dose; DXX = the values of the minimal dose received by XX% of the volume; RXX = the rectal volume in cubic centimeters that receiving XX% of the prescribed dose; U200 = the urethral volume receiving 200% of the prescribed dose

*PSA was measured before the latest biopsy.
†Prostate volume was measured pre-implantation.
<p>| Factors                        | PI group |  | EBRT combination group |  | Total |  |
|-------------------------------|----------|------------------|----------------------|------------------|
|                               | n        | %                | n                    | %                | n     | %     |
| Diabetes                      |          |                  |                      |                  |
| Yes                           | 113      | 6.31             | 44                   | 8.04             | 157   | 6.72  |
| No                            | 1678     | 93.69            | 503                  | 91.96            | 2181  | 93.28 |
| Rectal cancer                 |          |                  |                      |                  |
| Yes                           | 12       | 0.67             | 5                    | 0.91             | 17    | 0.73  |
| No                            | 1779     | 99.33            | 542                  | 99.09            | 2321  | 99.27 |
| Bladder cancer                |          |                  |                      |                  |
| Yes                           | 10       | 0.56             | 6                    | 1.10             | 16    | 0.68  |
| No                            | 1781     | 99.44            | 541                  | 98.90            | 2322  | 99.32 |
| Smoking status                |          |                  |                      |                  |
| Yes                           | 239      | 14.60            | 74                   | 13.83            | 313   | 14.41 |
| No                            | 1398     | 85.40            | 461                  | 86.17            | 1859  | 85.59 |
| Drinking status               |          |                  |                      |                  |
| Yes                           | 1111     | 68.03            | 394                  | 73.78            | 1505  | 69.45 |
| No                            | 522      | 31.97            | 140                  | 26.22            | 662   | 30.55 |
| Gleason score                 |          |                  |                      |                  |
| 8 or more                     | 12       | 0.67             | 72                   | 13.16            | 84    | 3.60  |
| 7                             | 545      | 30.46            | 384                  | 70.20            | 929   | 39.77 |
| 6 or less                     | 1232     | 68.87            | 91                   | 16.64            | 1323  | 56.64 |
| Clinical stage: T Stage       |          |                  |                      |                  |
| T3                            | 2        | 0.11             | 16                   | 2.93             | 18    | 0.77  |
| T2                            | 394      | 22.02            | 207                  | 37.84            | 601   | 25.73 |
| T1                            | 1388     | 77.59            | 324                  | 59.23            | 1712  | 73.29 |
| TX                            | 5        | 0.28             | -                    | -                | 5     | 0.21  |
| Clinical stage: N Stage       |          |                  |                      |                  |
| N0                            | 1776     | 99.27            | 546                  | 99.82            | 2322  | 99.40 |
| NX                            | 13       | 0.73             | 1                    | 0.18             | 14    | 0.60  |
| Clinical stage: M Stage       |          |                  |                      |                  |
| M0                            | 1774     | 99.16            | 546                  | 99.82            | 2320  | 99.32 |
| MX                            | 15       | 0.84             | 1                    | 0.18             | 16    | 0.68  |
| Androgen deprivation therapy  |          |                  |                      |                  |
| Yes                           | 764      | 42.63            | 390                  | 71.30            | 1154  | 49.34 |
| No                            | 1028     | 57.37            | 157                  | 28.70            | 1185  | 50.66 |
| Planning process              |          |                  |                      |                  |
| Interactive                   | 772      | 43.08            | 374                  | 68.37            | 1146  | 49.00 |
| Others                        | 1020     | 56.92            | 173                  | 31.63            | 1193  | 51.00 |</p>
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<td>Late</td>
<td>Acute</td>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
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PI = permanent seed implantation; EBRT = external beam radiation therapy.

* One patient was missing due to loss to follow up.
Table 4  Univariate and multivariate analyses for Grade $\geq 2$ rectal toxicity among all patients

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<tr>
<td>Rectal cancer</td>
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</table>

HR = hazard ratio; CI = confidence interval; Other abbreviations as in Table 1.

*: Significant risk factor

†: R150 is the collinearity factor of R100; therefore, R150 is excluded in the multivariate analysis.

One patient was treated but lacked the data for the rectal toxicity; as a censored sample the patient was included for the calculation of HR. Therefore, total n=2339 if explanatory variables were measured for all the patients.
### Table 5  Univariate and multivariate analyses for Grade ≥ 2 rectal toxicity in the PI monotherapy group

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<td>95% CI</td>
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<td>0.919–1.010</td>
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<td>Prostate volume (ml)</td>
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<td>0.903–1.006</td>
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<td>0.997</td>
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<td>1781</td>
<td>0.997</td>
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<td>1685</td>
<td>1.655</td>
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Abbreviations as in Table 4.

*: Significant risk factor

†: R150 is the collinearity factor of R100; therefore, R150 is excluded in the multivariate analysis.

One patient was treated but lacked the data for the rectal toxicity; as a censored sample the patient was included for the calculation of HR. Therefore, total n=1792 if explanatory variables were measured for all the patients.
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Abbreviations as in Table 4.

*: Significant risk factor

†: R150 is the collinearity factor of R100; therefore, R150 is excluded in the multivariate analysis.
REFERENCES


