

Dose-volume Histogram-based Predictors for Hematuria and Rectal Hemorrhage in Patients Receiving Radiotherapy After Radical Prostatectomy

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Abstract. *Aim: The aim of this study was to evaluate the dose-volume histogram parameters for late hematuria and rectal hemorrhage in patients receiving radiotherapy after radical prostatectomy. Patients and Methods: Data of 86 patients treated between January 2006 and June 2019 were retrospectively evaluated. The median radiation dose was 64 Gy in 32 fractions. Receiver operating characteristic (ROC) curves were used to identify optimal cut-off values for late adverse events. Results: Eleven patients experienced hematuria, and the 5-year cumulative rate was 18%. Four patients experienced rectal hemorrhage, and the 5-year cumulative rate was 7%. ROC curve analysis demonstrated the following significant cut-off values: bladder V50 Gy: 43% ($p=0.02$) and V40 Gy: 50% ($p=0.03$) for hematuria, and rectum V60 Gy: 13% ($p=0.04$) and V50 Gy: 33% ($p=0.03$) for rectal hemorrhage. Conclusion: This is the first study to identify dose constraints that may reduce hematuria and rectal hemorrhage in patients receiving radiotherapy in the postoperative setting.*

Prostate cancer is the most common malignancy in men worldwide (1). Surgery is the mainstay of curative treatment for prostate cancer (2). In recent years, robotic-assisted

radical prostatectomy (RARP), which offers minimally invasive treatment, has rapidly gained global popularity (3-5). However, positive surgical margins have been reported in 14-33%, with 5-year prostate-specific antigen (PSA) failure rates of 13-37% after surgery (4-8). Postoperative radiotherapy has been reported to improve overall and biochemical progression-free survival in patients with positive surgical margins and seminal vesicle invasion (9, 10). In addition, salvage radiotherapy has been found to improve prostate cancer-specific survival compared with observation in patients with PSA recurrence after radical prostatectomy (11). Therefore, radiotherapy plays a major role as adjuvant therapy in prostate cancer.

Radiotherapy is generally considered to be less invasive than surgery. The recent development of high precision radiotherapy for prostate cancer has improved dose conformity to the target (12-14). However, preventing adverse events remains a challenge, as the base of the prostate is located in close proximity to the organs at risk, which include the bladder and rectum. Late hematuria and rectal hemorrhage are particularly considered to be refractory and chronic conditions that decrease patient quality of life. Establishing appropriate dose constraints for minimizing these adverse events is therefore of particular necessity. The dose constraints for several organs, including the rectum, bladder, penile bulb, and femoral head have been reported from cases of prostate cancer treated with radical radiotherapy (15-18). However, reports regarding the association between dose-volume histogram (DVH) parameters and late hematuria and rectal bleeding in the postoperative setting are scarce (19).

Therefore, we evaluated the DVH parameters and clinical factors associated with late hematuria and rectal hemorrhage in patients treated with adjuvant radiotherapy.

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Key Words: Hematuria, rectal hemorrhage, prostate cancer, postoperative radiation therapy, dose-volume histogram.

Table I. Patient characteristics.

| Characteristics | | N | % |
|------------------------|----------------------------|------------|-----|
| Age, years | Median (range) | 67 (50-79) | |
| Pathological status | T2 | 24 | 28% |
| | T3a | 41 | 48% |
| | T3b | 20 | 23% |
| | Unknown | 1 | 1% |
| Surgical margin status | Positive | 61 | 71% |
| | Negative | 24 | 28% |
| | Unknown | 1 | 1% |
| Type of surgery | Open radical prostatectomy | 64 | 74% |
| | RARP | 22 | 26% |
| Gleason score | –6 | 17 | 20% |
| | 7 | 31 | 36% |
| | 8-10 | 38 | 44% |
| Type of RT | Salvage RT | 71 | 83% |
| | Postoperative RT | 15 | 17% |
| ADT | Yes | 24 | 28% |
| | No | 62 | 72% |
| Anticoagulant therapy | Yes | 11 | 13% |
| | No | 75 | 87% |

RARP: Robotic-assisted radical prostatectomy; RT: radiotherapy; ADT: androgen-deprivation treatment

Patients and Methods

A total of 94 consecutive postoperative patients with prostate cancer received radiotherapy at our institution between January 2006 and June 2019. This study was reviewed and approved by our Institutional Review Board (S18-081) and was performed in accordance with the Declaration of Helsinki; all patients provided informed consent. Eight patients, for whom the bladder or rectum were not included in the computed tomography (CT) simulation images used for treatment planning, were excluded; the remaining 86 patients were retrospectively evaluated. The clinical characteristics of the cohort are shown in Table I. The median patient age during radiotherapy was 67 years (range=50-79). Pretreatment evaluation to exclude lymph node and distant metastases included CT, magnetic resonance imaging, and bone scintigraphy.

Overall, 64 and 22 patients underwent open radical prostatectomy and RARP, respectively. Surgical margin positivity and pathological T3b stage was noted in 61 (71%) and 20 (23%) cases, respectively. Fifteen patients received postoperative radiotherapy and 71 received salvage radiotherapy for PSA failure after surgery. The median interval between surgery and radiotherapy was 12 months (range=14-119). All patients received three-dimensional conformal radiotherapy based on CT simulation; the median radiation dose was 64 Gy in 32 fractions (range=60-66 Gy). The prostate floor was delineated for the clinical target volume. The planning target volume included the clinical target volume with a 5-10 mm margin for set-up error. All patients provided written informed consent prior to radiotherapy. Overall, 24 (28%) patients received neo-adjuvant or concurrent androgen-deprivation treatment (ADT). All DVH analyses were performed using the Monaco® (version: 5.11.02.) radiotherapy treatment planning system (Elekta AB, Stockholm, Sweden).

Table II. Dose-volume histogram parameters of the bladder for actual rates of hematuria.

| Characteristics | Cut-off values | Hematuria | n=86 | p-Value |
|-------------------|----------------|-----------|-------|---------|
| Bladder V60 Gy | ≥15% | 14% | 11/77 | 0.11 |
| | <15% | 0% | 0/9 | |
| Bladder V50 Gy | ≥43% | 17% | 11/69 | 0.02 |
| | <43% | 0% | 0/17 | |
| Bladder V40 Gy | ≥50% | 16% | 11/70 | 0.03 |
| | <50% | 0% | 0/16 | |
| Bladder mean dose | ≥42 Gy | 16% | 10/64 | 0.14 |
| | <42 Gy | 5% | 1/22 | |

Assessment of adverse events, physical examination, and PSA measurement were performed every 3 months after radiotherapy. Late hematuria and rectal hemorrhage were evaluated by the Common Terminology Criteria for Adverse Events (version 5.0). In cases with symptoms, the bleeding and inflamed areas of the bladder and rectum were evaluated by cystoscopy or proctoscopy.

Overall survival, biological progression-free survival, and cumulative rates of adverse events were calculated from the initiation of radiotherapy to individual events using the Kaplan-Meier method. Receiver operating characteristic (ROC) curves were used to identify optimal cut-off values for late adverse events. The chi-square test was used to compare the differences between two groups. A *p*-value of <0.05 was considered statistically significant. Analyses were performed using the SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA).

Results

The median follow-up period after radiotherapy was 49 months (range=2-157). No local recurrences were observed at the prostate floor. No deaths related to prostate cancer were observed during follow-up; 1 patient died at 75 months after radiotherapy owing to pancreatic cancer. The 5- and 10-year overall survival rates were 100% and 96%, respectively (Figure 1A); 29 patients experienced PSA recurrence during follow-up. The 5- and 10-year biological progression-free survival rates were 59% and 41%, respectively (Figure 1B). None of the cases of hematuria or rectal hemorrhage were related to cancers of the bladder or rectum.

Overall, 11 patients experienced hematuria (grade 1: n=5; grade 2: n=6), and the 5-year cumulative rates of grades ≥1 and ≥2 were 18% (95% CI=7-29%) and 12% (95% CI=3-21%), respectively (Figure 2A). Four patients experienced rectal hemorrhage (grade 1: n=3; grade 2: n=1), and the 5-year cumulative rates of grades ≥1 and ≥2 were 7% (95% CI=0-14%) and 2% (95% CI=0-5%), respectively (Figure 2B). No late adverse events of grade 3 or higher were observed.

ROC curve analysis for hematuria revealed the following significant cut-off values (Table II): bladder V50 Gy: 43%

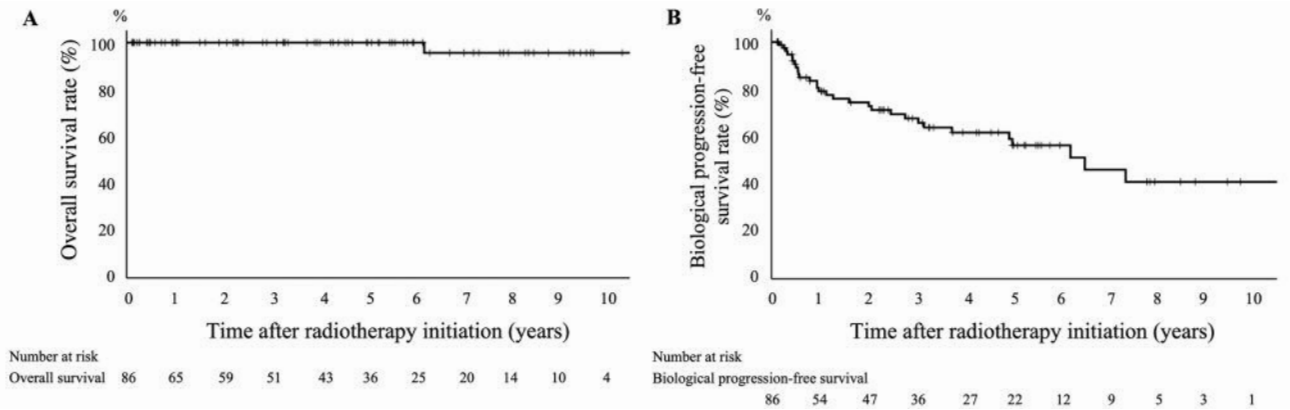


Figure 1. Overall survival and biological progression-free survival curves for all patients treated with radiotherapy. (A) The 5- and 10-year overall survival rates were 100% and 96%, respectively. (B) The 5- and 10-year biological progression-free survival rates were 59% and 41%, respectively.

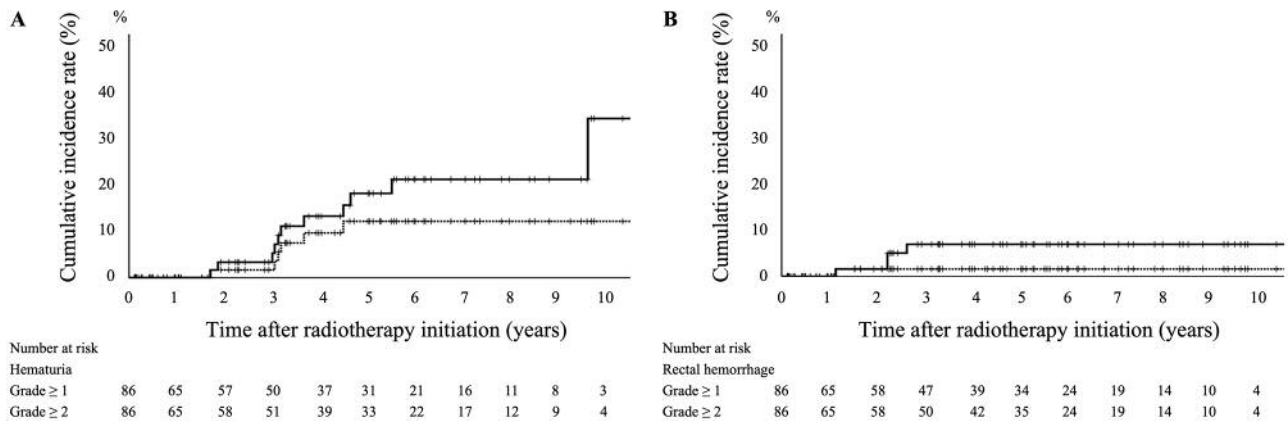


Figure 2. The cumulative curves of hematuria and rectal hemorrhage among all patients ($n=86$). (A) The 5-year and 10-year cumulative rates of grade ≥ 1 hematuria were 18% and 34%, respectively (solid line). The corresponding rates of grade ≥ 2 hematuria were 12% and 12%, respectively (dotted line). (B) The 5-year and 10-year cumulative rates of grade ≥ 1 rectal hemorrhage were 7% and 7%, respectively (solid line). The corresponding rates of grade ≥ 2 hematuria were 2% and 2%, respectively (dotted line).

($p=0.02$) and V40 Gy: 50% ($p=0.03$). The 5-year cumulative hematuria rates for bladder V50 Gy $\geq 43\%$ and $<43\%$ groups were 20% and 0%, respectively ($p=0.37$, HR=22.6) (Figure 3A). On ROC curve analysis, rectum V60 Gy: 13% ($p=0.04$) and V50 Gy: 33% ($p=0.03$) were significant cut-off values for rectal hemorrhage (Table III). The 5-year cumulative rectal hemorrhage rates for rectum V50 Gy $\geq 33\%$ and $<33\%$ groups were 11% and 0%, respectively ($p=0.12$, HR=43.2) (Figure 3B). The other characteristics were not associated with late adverse events (Table IV).

Discussion

In this study, we analyzed the DVH parameters and clinical factors associated with hematuria and rectal hemorrhage in

86 patients receiving radiotherapy after radical prostatectomy. The treatment was safe, and the 5-year cumulative rates of hematuria and rectal hemorrhage of grade ≥ 2 were 12% and 2%, respectively. Previous studies have demonstrated that the rates of late genitourinary and gastrointestinal toxicities of grade ≥ 2 are 9-17% and 0-12%, respectively (Table V) (20-24); our results agreed with these findings. However, most previous studies did not report the incidence of grade 1 adverse events; ours is probably the only study to perform a detailed analysis on the incidence of grade 1 hematuria and rectal hemorrhage in the postoperative setting. The present study identified the dose constraints (bladder V50, V40 Gy: $\leq 43\%$, $\leq 50\%$, respectively; rectum V60, V50 Gy: $\leq 13\%$, $\leq 33\%$, respectively) that might help minimize hematuria and rectal

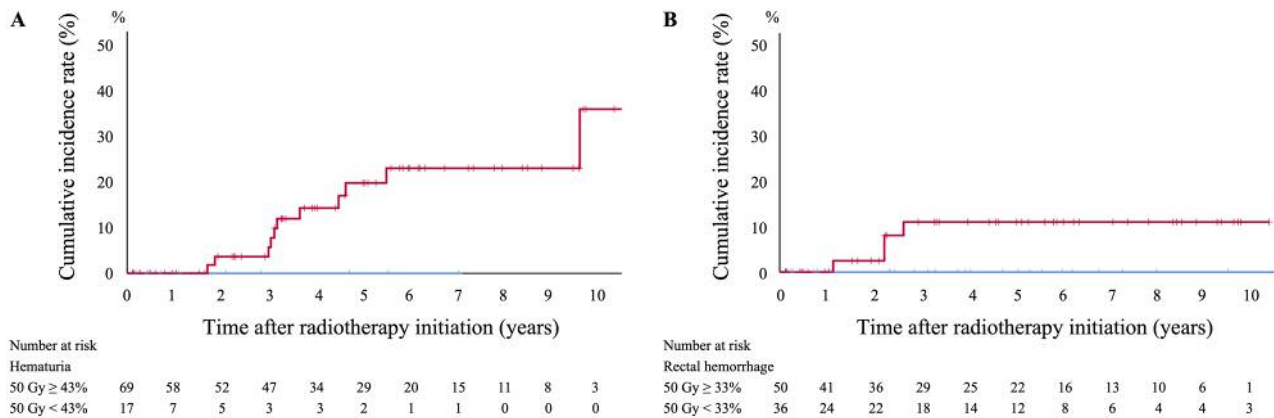


Figure 3. The cumulative curves for hematuria and rectal hemorrhage according to cut-off values of bladder and rectum. (A) The cumulative curves for hematuria according to bladder V50 Gy of \geq 43% (n=69) and V50 Gy of <43% (n=17). The 5-year cumulative hematuria rates for the higher and lower dose groups were 20% and 0%, respectively. (B) The cumulative curves for rectal hemorrhage according to rectum V50 Gy of \geq 33% (n=50) and V50 Gy of <33% (n=36). The 5-year cumulative rectal hemorrhage rates for the higher and lower dose groups were 11% and 0%, respectively.

hemorrhage of grade 1 in patients with prostate cancer receiving postoperative radiotherapy.

Histopathologically, late radiation cystitis and proctitis are characterized by significant submucosal and mucosal changes. Vascular abnormalities, such as focal distortion, destruction of small arteries, intimal fibrosis, and fibrin thrombi within vessels are characteristic findings (25–27). These chronic microvascular injuries reduce the vascularity of the bladder and rectal walls, leading to secondary ischemic changes, which include submucosal fibrosis, crypt distortion, and focal mucosal ulceration. Telangiectatic vessels are often observed, causing repeated episodes of bleeding. Severe symptoms result in restrictions in the patient's lifestyle, and dramatically decrease the quality of life. In clinical practice, corticosteroids, endoscopic approaches, and hyperbaric oxygen have been used to arrest bleeding or reduce inflammation (28–30). However, there is no evidence to support the routine use of these treatments. Radical treatments (*e.g.*, rectal or urinary diversion) are considered in cases that progress despite conservative management. It is therefore essential to prevent radiation induced hematuria and rectal hemorrhage.

The identification of optimal dose constraints for the bladder and rectum is particularly necessary to prevent severe adverse events. Akthar *et al.* verified the utility of the parameters proposed by the Radiation Therapy Oncology Group (RTOG) 0534 (bladder-CTV V65, 40 Gy: \leq 50, 70%, and rectum V65, 40 Gy: \leq 35, 55%) and their institutional dose constraints (bladder V70, 65, 40 Gy: \leq 30, 60, 80%, and rectum V70, 65, 40 Gy: \leq 20, 40, 80%) in postoperative patients (20). However, neither RTOG 0534 nor their institutional dose constraints were significantly associated

Table III. Dose-volume histogram parameters of the rectum for actual rates of rectal hemorrhage.

| Characteristics | Cut-off values | Rectal hemorrhage | n=86 | p-Value |
|------------------|----------------|-------------------|------|---------|
| Rectum V60 Gy | \geq 13% | 8% | 4/51 | 0.04 |
| | <13% | 0% | 0/35 | |
| Rectum V50 Gy | \geq 33% | 8% | 4/50 | 0.03 |
| | <33% | 0% | 0/36 | |
| Rectum V40 Gy | \geq 51% | 7% | 4/54 | 0.05 |
| | <51% | 0% | 0/32 | |
| Rectum mean dose | \geq 40 Gy | 2% | 1/41 | 0.34 |
| | <40 Gy | 7% | 3/45 | |

with late adverse events; therefore, DVH-toxicity relationships in the postoperative setting could not be established. The present study revealed the following significant cut-off values: bladder V50 Gy: 43% and V40 Gy: 50% for hematuria, and rectum V60 Gy: 13% and V50 Gy: 33% for rectal hemorrhage, respectively. We were probably able to identify the dose constraints as we focused solely on the symptoms of bleeding, and excluded other symptoms associated with surgery. Since the postoperative tissues are fragile, several adverse events (*e.g.*, urinary incontinence and urinary stricture) are often observed after radiotherapy; these are not considered to be directly associated with radiotherapy. Another possible explanation for the differences between the present and previous studies is the selection of endpoints; the previous study aimed to predict grade 2 adverse events, whereas the present study aimed to predict those of grade 1. Akthar *et al.* found grade

Table IV. Actual rates of hematuria and rectal hemorrhage based on clinical characteristics.

| Characteristics | | n=86 | Hematuria | | Rectal hemorrhage | |
|-----------------------|----------------------------|------|-------------|---------|-------------------|---------|
| | | | Actual rate | p-Value | Actual rate | p-Value |
| Type of RT | Salvage RT | 71 | 14% | 0.40 | 6% | 0.21 |
| | Postoperative RT | 15 | 7% | | 0% | |
| RT dose | ≥64 Gy | 73 | 14% | 0.52 | 6% | 0.25 |
| | <64 Gy | 13 | 8% | | 0% | |
| ADT | Yes | 24 | 13% | 0.96 | 0% | 0.10 |
| | No | 62 | 13% | | 7% | |
| Type of surgery | Open radical prostatectomy | 64 | 16% | 0.14 | 6% | 0.12 |
| | RARP | 22 | 5% | | 0% | |
| Pathological stage | T2, T3a | 66 | 15% | 0.19 | 6% | 0.14 |
| | T3b | 20 | 5% | | 0% | |
| Age | ≥67 years | 43 | 7% | 0.10 | 2% | 0.30 |
| | <67 years | 43 | 19% | | 7% | |
| Anticoagulant therapy | Yes | 11 | 18% | 0.58 | 9% | 0.50 |
| | No | 75 | 12% | | 4% | |

RT: Radiotherapy; ADT: androgen-deprivation treatment; RARP: robotic-assisted radical prostatectomy.

Table V. Previous studies of late genitourinary and gastrointestinal toxicities in the postoperative setting.

| Author (Year) (Reference) | Type of RT | Median RT dose | Study design | Patient number | Genitourinary toxicity | | Gastrointestinal toxicity | |
|------------------------------|------------|-------------------|-----------------|-------------------|---------------------------|--------------------|------------------------------|--------------------|
| | | | | | 5-year Grade ≥1 | 5-year Grade ≥2 | 5-year Grade ≥1 | 5-year Grade ≥2 |
| Akthar (2018) (20) | IMRT | 66 Gy | Retrospective | 164 | - | 9% (4-year) | - | 9% (4-year) |
| Berlin (2015) (21) | IMRT | 66 Gy | Prospective | 68 | - | 11% | - | 12% |
| Hunter (2013) (22) | IMRT | 70 Gy | Prospective | 104 | - | 12% (3-year) | - | 0% (3-year) |
| Goenka (2011) (23) | 3DCRT+IMRT | - | Retrospective | 285 | - | 17% | - | 5% |
| Nath (2010) (24) | IMRT | 68 Gy | Retrospective | 50 | - | 16% (2-year) | - | 2% (2-year) |
| Present study | 3DCRT | 64 Gy | Retrospective | 86 | 18% | 12% | 7% | 2% |

RT: Radiotherapy; 3DCRT: three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy.

2 adverse events for gastrointestinal and genitourinary toxicities to be less than 10% (20); these rates were considerably low for obtaining any statistical association between DVH parameters and events. The relatively higher incidence of grade 1 events may facilitate the analysis of statistical significance of dose constraints for these events. Certain researchers advocate the use of established dose constraints to avoid severe adverse events; however, we also support the avoidance of mild bleeding symptoms as far as practicable, because grade 1 events may potentially increase the incidence of more severe effects.

In our study, cut-off values in the middle range of 40 to 60 Gy demonstrated statistical significance. This may be attributed to the fact that most patients were treated with total doses of 64 Gy, which was not a high dose. Higher doses of ≥70 Gy using intensity-modulated radiotherapy

have been recommended in recent years to reduce biological failure in the postoperative setting (31, 32). Further studies are required to verify the utility of our dose constraints in the treatment planning using higher radiation doses.

Hypofractionated radiotherapy, that is the administration of fewer fractions with a higher dose per fraction, is being increasingly used for the definitive treatment of prostate cancer owing to benefits of shorter treatment schedules and patient convenience (33). This has been reported to be safe and effective in the postoperative setting (34). In view of the different dose fraction between hypofractionated and conventional schedules, a different set of dose constraints will need to be established when hypofractionated regimens are employed in the postoperative setting in future.

The present study has several limitations. It was a retrospective single-center study with a small sample size.

Cumulative evidence on additional cases of bleeding may alter the interpretation of our analysis.

In conclusion, the present study identified the dose constraints that may reduce the incidence of hematuria and rectal hemorrhage in patients receiving radiotherapy after radical prostatectomy. Further large-scale prospective studies are needed to validate the clinical utility of the bladder and rectal dose constraints obtained from the present study.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Shirai K, Suzuki M and Akahane K designed and directed the analysis. Takahashi Y, Kawahara M and Yamada E analyzed the data. Ogawa K, Takahashi S, Minato K and Hamamoto K contributed to the analysis of the results and performed the statistical analysis. Saito K, Oshima M, Konishi T, Nakamura Y and Washino S generated a database and performed data collection. Shirai K, Wakatsuki M and Miyagawa T supervised the project.

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