CANCER DIAGNOSIS & PROGNOSIS
4: 315-319 (2024) doi: 10.21873/cdp.10326

Dose-escalated Salvage Whole-pelvic Radiotherapy for Biochemical Recurrence After Radical Prostatectomy for High-risk Prostate Cancer

SHUHEI MIYAZAKI[1], YUTARO TASAKI[1], MIKA NAKATAKE[1], KOICHI HONDA[1], DAISUKE NAKAMURA[1], AKIKO EGAWA[1], NOZOMI OKI[1], KENSUKE MITSUNARI[2], YUICHIRO NAKAMURA[2], RYOICHI IMAMURA[2] and RYO TOYA[1]

[1]*Department of Radiological Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan;* [2]*Department of Urology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan*

Abstract. *Background/Aim: To investigate the institutional experience of dose-escalated salvage whole-pelvic radiotherapy (WPRT) with the simultaneous integrated boost (SIB) technique in patients with biochemical recurrence (BCR) after radical prostatectomy for high-risk prostate cancer. Patients and Methods: This retrospective study included 21 patients with BCR who received radical prostatectomy for high-risk prostate cancer and underwent salvage RT. Clinical target volume (CTV) of the whole pelvis (CTV56) included the prostate bed, common iliac, external iliac, internal iliac, and obturator lymph node regions. The boost CTV (CTV66) included the prostate bed. Planning target volumes (PTV) were generated by adding a margin of 6-8 mm to CTV (PTV56 and PTV66). Doses of 56.1 and 66 Gy in 33 fractions were delivered to PTV56 and PTV66, respectively. Results: The 5-year biochemical progression-free survival, overall survival, and cause-specific survival rates were 72%, 94%, and 94%, respectively. A grade 3 late genitourinary toxicity event of gross hematuria was observed in one patient (4%). Acute and late toxicities of grade ≥3, other than gross hematuria, were not observed in any patient. Conclusion: Dose-escalated salvage WPRT using the SIB technique provides appropriate tumor control without increasing the incident of significant toxicities.*

Approximately 30% of patients who had undergone radical prostatectomy reportedly develop biochemical recurrence (BCR) (1). Salvage radiotherapy (RT) with or without androgen-deprivation therapy (ADT) is recommended for patients with BCR (2). Salvage prostate bed RT (PBRT) alone provides a certain effect on disease control in patients with BCR after radical prostatectomy; however, disease progression occurs in >50% of patients after treatment (3-5). Recent results of the NRG Oncology/RTOG 0534 SPPORT trial have suggested that salvage RT using WPRT and short-term ADT leads to significantly better treatment outcomes than PBRT with or without short-term ADT (6). WPRT as a salvage RT has been commonly performed using a conventional two-step three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT) technique, consisting of WPRT followed by PBRT (7-9).

Although a previous study has suggested that dose-escalated WPRT can be performed using IMRT (10), the WPRT dose of >50 Gy is not commonly performed (6, 11). Recently, a simultaneous integrated boost (SIB) technique using IMRT, which delivers a differential dose per fraction to selected subregions during the same treatment session that prescribes different total doses to target volumes in the same number of fractions, has been increasingly used for the treatment of definitive RT for prostate cancer (12, 13). However, the value of dose-escalated WPRT using the SIB technique in patients with postoperative prostate cancer has not been fully evaluated. The present study aimed to investigate the institutional experience of dose-escalated salvage WPRT using the SIB technique in patients with BCR after radical prostatectomy for high-risk prostate cancer.

Correspondence to: Ryo Toya, Department of Radiological Sciences, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel: +81 958197354, Fax: +81 958197357, e-mail: toya@nagasaki-u.ac.jp

Key Words: Prostate cancer, salvage radiotherapy, biochemical recurrence, whole-pelvic irradiation, intensity-modulated radiation therapy, simultaneous integrated boost, dose escalation.

Patients and Methods

Patients. The present study was conducted in accordance with the guidelines stipulated in the Declaration of Helsinki and was approved by the Institutional Review Board of our hospital. This study was exempt from the requirement of obtaining informed consent from the patients because of its retrospective design. We enrolled 22 consecutive patients with histologically confirmed high-risk prostate adenocarcinoma who received salvage RT at our institution between September 2015 and March 2018. Among these patients, we excluded one patient from the analysis because he had a history of pelvic inflammation after surgery and underwent PBRT alone. Therefore, the study population ultimately comprised 21 patients with high-risk prostate cancer, as defined by the D'Amico risk classification system.

BCR was defined as a prostate-specific antigen (PSA) level of >0.2 ng/ml with a consecutive increase following radical prostatectomy (14-16). Three (14%) patients received neoadjuvant ADT before prostatectomy. No patient underwent concurrent or adjuvant ADT before or after salvage RT. Prior to salvage RT, computed tomography (CT) and laboratory tests (including an assessment of PSA levels) were performed in all patients.

Radiotherapy. Patients were instructed to void the bladder one hour before CT simulation and subsequent treatments. They were also instructed to void the rectum. Clinical target volume (CTV) of the whole pelvis (CTV56) included the prostate bed, common iliac, external iliac, internal iliac, and obturator lymph node regions based on the RTOG consensus guidelines (17, 18). The boost CTV (CTV66) included the prostate bed; the seminal vesicle bed was also included in the boost CTV for patients with seminal vesicle invasion (pT3b). Planning target volumes (PTV) were generated by adding a margin of 6-8 mm to CTV (PTV56 and PTV66). RT was delivered using a 7-field IMRT with the SIB technique. The doses of 56.1 and 66 Gy in 33 fractions were delivered to PTV56 and PTV66, respectively. The RT plans were approved when at least 95% of the PTV received the prescribed dose. The following dose constraints were used for organs at risk: 1) 35% and 65% of the rectal volume received <60 Gy and <40 Gy, respectively; 2) 65% of the bladder wall volume received <40 Gy; 3) 1, 20, and 50 ml of the small bowel received <60, <50, and <40 Gy, respectively; and 4) 1 ml of the large bowel received <65 Gy. For imaging guidance, cone-beam CT imaging was performed for each fraction.

Follow-up. Radiation oncologists examined patients once every week during salvage RT, and radiation oncologists or urologists performed a PSA test at 3-month intervals after salvage RT for 2 years and every 6 months thereafter. Events occurring during and within 6 months of the salvage RT completion were referred to as acute complications, whereas those that developed 6 months or more after salvage RT were termed late complications. The Common Terminology Criteria for Adverse Events version 5.0 by the National Cancer Institute was used to grade the toxicity events.

Statistical analysis. Biochemical progression (BCP) was defined as an increase in the PSA level of ≥0.2 ng/ml above the post-salvage RT nadir with a confirmation of subsequent increase (4, 9). The biochemical progression-free survival (BCPFS), overall survival (OS), and cause-specific survival (CSS) rates were calculated from RT initiation using the Kaplan–Meier method. JMP (SAS Institute, Cary, NC, USA) was used for analyses.

Table I. *Patient characteristics (n=21).*

Variables	N (%)
Age (years)	
Median (range)	66 (53-77)
Preoperative PSA level (ng/ml)	
Median (IQR)	10.01 (6-14)
PSA level before SRT (ng/ml)	
Median (IQR)	0.333 (0.245-0.480)
Gleason score	
Median (range)	8 (6-9)
6-7	9 (43)
8-10	12 (57)
pT-category	
pT2a-2c	8 (38)
pT3a	7 (33)
pT3b	6 (29)
pN-category	
N0	20 (95)
N1	1 (5)
Extracapsular extension	
Yes	12 (57)
No	9 (43)
Seminal vesicle invasion	
Yes	6 (29)
No	15 (71)
Lymphovascular invasion	
Yes	13 (62)
No	8 (38)
Surgical margin	
Negative	11 (52)
Positive	10 (48)

PSA: Prostate-specific antigen; SRT: salvage radiotherapy.

Results

The patient characteristics are shown in Table I. The median follow-up duration was 62 months (range=14-98 months). One patient (5%) died of original prostate cancer due to multiple distant metastases of the lung, bone, and liver. During the follow-up period, five patients (24%) developed BCP; of these, two (10%) patients received ADT after BCP confirmation. The 3- and 5-year BCPFS rates were 85% and 72%, respectively, and the 3- and 5-year OS rates were 100% and 94%, respectively. The 3- and 5-year CSS rates were 100% and 94%, respectively (Figure 1).

The treatment-related toxicities are summarized in Table II. Acute ≥G2 and ≥G3 genitourinary (GU) toxicities were observed in one (5%) and 0 (0%) patients, respectively. Acute ≥G2 and ≥G3 gastrointestinal (GI) toxicities were observed in three (14%) and 0 (0%) patients, respectively, and late ≥G2 and ≥G3 GU toxicities in five (24%) and one (5%) patient, respectively. The G3 late toxicity observed in this study was gross hematuria. Late ≥G2 and ≥G3 GI toxicities were not observed in any patient. Grade ≥3 acute and late toxicities other than gross hematuria were not observed in any patient.

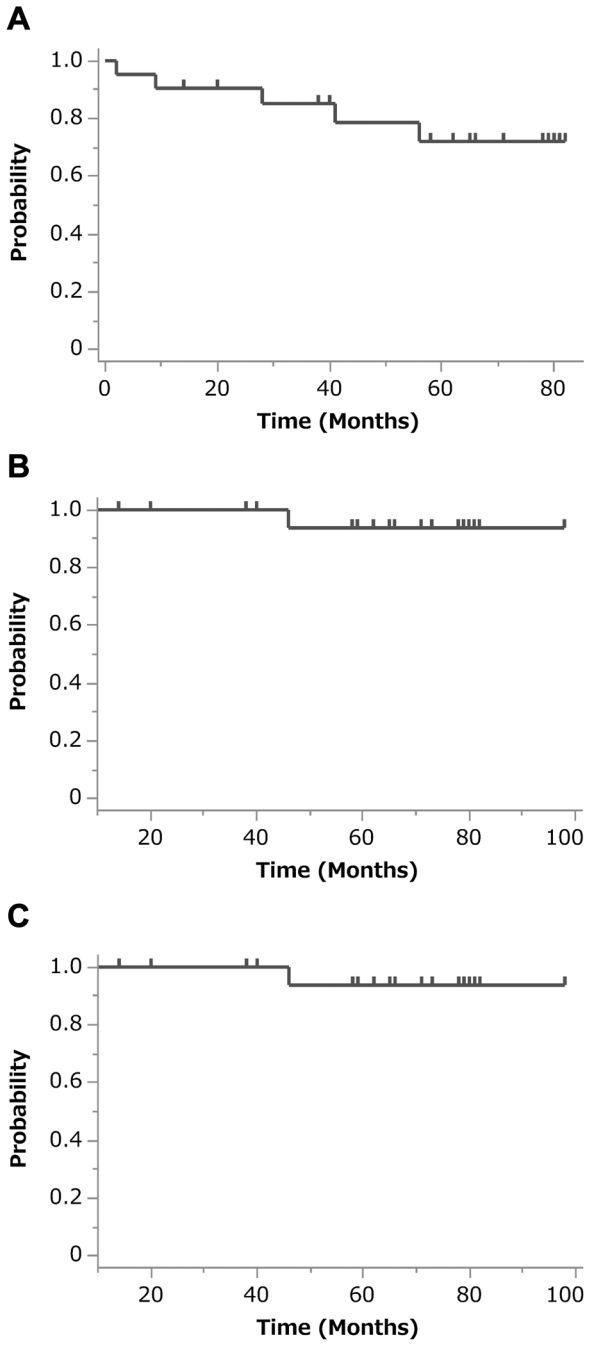

Figure 1. *Kaplan–Meier curves of (A) biochemical progression-free, (B) overall, and (C) cause-specific survival.*

Table II. *Acute and late toxicities.*

	Grade 1	Grade 2	Grade 3	Grade 4-5
Acute GU	12 (57%)	1 (5%)	0 (0%)	0 (0%)
Acute GI	3 (14%)	3 (14%)	0 (0%)	0 (0%)
Late GU	4 (19%)	4 (19%)	1 (5%)	0 (0%)
Late GI	0 (0%)	0 (0%)	0 (0%)	0 (0%)

GU: Genitourinary; GI: gastrointestinal.

Discussion

In the era of 2D-RT and 3D-CRT, elective nodal irradiation using WPRT with an RT dose of 44-46 Gy at 1.8-2 Gy fractions, which translates to a BED of 72-76.7 Gy_3 as the α/β ratio=3, has been commonly performed for patients with BCR (6, 7, 11). A modern technique, IMRT, which provides rapid dose drop-off beyond the target volumes, allows dose escalation to the target volumes without increasing the toxicities to normal tissues (19, 20). We prescribed a higher RT dose to the whole pelvis with 56.1 Gy in 33 fractions (1.7 Gy per fraction), which translates to a BED of 87.9 Gy_3, to achieve better treatment outcomes. Byun et al. treated 170 high-risk prostate cancer patients with BCR after prostatectomy (11). IMRT was performed with an RT dose of 44-46 Gy for the whole pelvis followed by an RT dose of 20-28.6 Gy for the prostate bed at 2-2.2 Gy fraction. Neoadjuvant, concurrent, or adjuvant ADT was administered with salvage RT in 97 (57%) patients. The 5-year BCPFS, OS, and CSS rates were 39%, 91%, and 97%, respectively. Although we did not perform neoadjuvant, concurrent, or adjuvant ADT, the BCPFS, OS, and CSS rates were comparable to the results of the previous study. This may be due to the dose-escalating prescription for the WPRT.

The problematic toxicities of salvage RT to prostate beds with or without WPRT are GU and GI toxicities (11, 21). Alongi et al. evaluated the acute toxicities of WPRT in patients treated with postoperative adjuvant or salvage RT after prostatectomy (21). Of the 172 patients, 81, 37, and 54 patients underwent 3D-CRT, Linac IMRT, and helical tomotherapy (HT), respectively. The median RT dose of WPRT was 50.4 Gy, and the median doses of prostate bed RT were 72.1, 72.5, and 70 Gy for 3D-CRT, Linac IMRT, and HT, respectively. The toxicity rates of 3D-CRT and IMRT (Linac IMRT and HT) for acute ≥G2 upper GI, ≥G2 lower GI, and ≥G2 GU toxicities were 22% and 7% (p=0.004), 9% and 3% (p=0.14), and 12% and 7% (p=0.19), respectively. They found that the risk of acute toxicities following postoperative WPRT delivered by IMRT was reduced as compared with that of 3D-CRT. In the NRG Oncology/RTOG 0534 SPPORT trial, 598 patients underwent salvage RT with short-term ADT (6). WPRT was performed at a dose of 45 Gy at 1.8-Gy fractions followed by PBRT at a dose of 19.8-25.2 Gy. Most patients underwent IMRT (87%). Acute ≥G2 and ≥G3 GU toxicities were observed in 67 (12%) and eight (1%) patients, respectively. Acute ≥G2 and ≥G3 GI toxicities were observed in 38 (7%) and four (1%) patients, respectively. Late ≥G2 and ≥G3 GU toxicities were observed in 223 (40%) and 45 (8%)

patients, respectively. Late ≥G2 and ≥G3 GI toxicities were observed in 51 (9%) and eight (1%) patients, respectively. Although our patients underwent WPRT with a higher dose, the toxicities were comparable or better than those in the NRG Oncology/RTOG 0534 SPPORT trial. The combination of higher-dose WPRT using the SIB technique and short-term ADT may provide excellent treatment outcomes.

Study limitations. First, this was a retrospective study with a relatively small number of patients. Second, RT was delivered using fixed-field IMRT, and volumetric modulated arc therapy, which is a more modern and sophisticated RT delivery method that has rapidly become popular in recent years, was not performed. Further investigations are underway to address these limitations.

Conclusion

Dose-escalated salvage WPRT using the SIB technique provides appropriate tumor control without increasing the risk for significant toxicities.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

SM developed the study design, collected, analyzed, and interpreted the data, performed the statistical analysis, and drafted the manuscript. YT developed the study design, analyzed and interpreted the data, and drafted the manuscript. MN, KH, DN, AE, NO, KM, and YN developed the study design and interpreted the data. RI analyzed and interpreted the data. RT developed the study design, collected, analyzed, and interpreted the data, and revised the manuscript. All Authors have read and approved the final version of the manuscript.

Funding

No funds, grants, or other support were received.

References

1 Bianco FJ Jr, Scardino PT, Eastham JA: Radical prostatectomy: Long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology 66(5): 83-94, 2005. DOI: 10.1016/j.urology.2005.06.116

2 National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncology, prostate cancer (version 4; 2023). 2018. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines [Last accessed on December 23, 2023]

3 Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, Klein E, Michalski J, Roach M, Sartor O, Wolf JS Jr, Faraday MM: Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO guideline. J Urol 190(2): 441-449, 2013. DOI: 10.1016/j.juro.2013.05.032

4 Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, Anscher MS, Michalski JM, Sandler HM, Lin DW, Forman JD, Zelefsky MJ, Kestin LL, Roehrborn CG, Catton CN, DeWeese TL, Liauw SL, Valicenti RK, Kuban DA, Pollack A: Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 25(15): 2035-2041, 2007. DOI: 10.1200/JCO.2006.08.9607

5 Choo R: Salvage radiotherapy for patients with PSA relapse following radical prostatectomy: issues and challenges. Cancer Res Treat 42(1): 1-11, 2010. DOI: 10.4143/crt.2010.42.1.1

6 Pollack A, Karrison TG, Balogh AG, Gomella LG, Low DA, Bruner DW, Wefel JS, Martin AG, Michalski JM, Angyalfi SJ, Lukka H, Faria SL, Rodrigues GB, Beauchemin MC, Lee RJ, Seaward SA, Allen AM, Monitto DC, Seiferheld W, Sartor O, Feng F, Sandler HM: The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet 399(10338): 1886-1901, 2022. DOI: 10.1016/S0140-6736(21)01790-6

7 Kim BS, Lashkari A, Vongtama R, Lee SP, Parker RG: Effect of pelvic lymph node irradiation in salvage therapy for patients with prostate cancer with a biochemical relapse following radical prostatectomy. Clin Prostate Cancer 3(2): 93-97, 2004. DOI: 10.3816/cgc.2004.n.018

8 Spiotto MT, Hancock SL, King CR: Radiotherapy after prostatectomy: Improved biochemical relapse-free survival with whole pelvic compared with prostate bed only for high-risk patients. Int J Radiat Oncol Biol Phys 69(1): 54-61, 2007. DOI: 10.1016/j.ijrobp.2007.02.035

9 Moghanaki D, Koontz BF, Karlin JD, Wan W, Mukhopadhay N, Hagan MP, Anscher MS: Elective irradiation of pelvic lymph nodes during postprostatectomy salvage radiotherapy. Cancer 119(1): 52-60, 2013. DOI: 10.1002/cncr.27712

10 Guerrero Urbano T, Khoo V, Staffurth J, Norman A, Buffa F, Jackson A, Adams E, Hansen V, Clark C, Miles E, McNair H, Nutting C, Parker C, Eeles R, Huddart R, Horwich A, Dearnaley D: Intensity-modulated radiotherapy allows escalation of the radiation dose to the pelvic lymph nodes in patients with locally advanced prostate cancer: preliminary results of a phase I dose escalation study. Clin Oncol (R Coll Radiol) 22(3): 236-244, 2010. DOI: 10.1016/j.clon.2010.01.005

11 Byun SJ, Kim YS, Ahn H, Kim CS: Image-guided, whole-pelvic, intensity-modulated radiotherapy for biochemical recurrence following radical prostatectomy in high-risk prostate cancer patients. PLoS One 13(1): e0190479, 2018. DOI: 10.1371/journal.pone.0190479

12 Fink CA, Wegener D, Sauer LD, Jäkel C, Zips D, Debus J, Herfarth K, Koerber SA: Whole-pelvic irradiation with boost to involved nodes and prostate in node-positive prostate cancer-long-term data from the prospective PLATIN-2 trial. Strahlenther Onkol 200(3): 202-207, 2024. DOI: 10.1007/s00066-023-02129-y

13 Masson I, Larriviere L, Mahé MA, Azria D, Pommier P, Mesgouez-Nebout N, Giraud P, Peiffert D, Chauvet B, Dudouet P, Salem N, Noël G, Khalifa J, Latorzeff I, Guérin-Charbonnel C, Supiot S: Prospective results for 5-year survival and toxicity of moderately hypofractionated radiotherapy with simultaneous integrated boost (SIB) in (very) high-risk prostate cancer. Clin Transl Radiat Oncol 44: 100702, 2023. DOI: 10.1016/j.ctro.2023.100702

14 Freedland SJ, Sutter ME, Dorey F, Aronson WJ: Defining the ideal cutpoint for determining PSA recurrence after radical prostatectomy. Urology 61(2): 365-369, 2003. DOI: 10.1016/s0090-4295(02)02268-9

15 Trock BJ, Han M, Freedland SJ, Humphreys EB, DeWeese TL, Partin AW, Walsh PC: Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 299(23): 2760-2769, 2008. DOI: 10.1001/jama.299.23.2760

16 Cotter SE, Chen MH, Moul JW, Lee WR, Koontz BF, Anscher MS, Robertson CN, Walther PJ, Polascik TJ, D'Amico AV: Salvage radiation in men after prostate-specific antigen failure and the risk of death. Cancer 117(17): 3925-3932, 2011. DOI: 10.1002/cncr.25993

17 Lawton CA, Michalski J, El-Naqa I, Buyyounouski MK, Lee WR, Menard C, O'Meara E, Rosenthal SA, Ritter M, Seider M: RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 74(2): 383-387, 2009. DOI: 10.1016/j.ijrobp.2008.08.002

18 Michalski JM, Lawton C, El Naqa I, Ritter M, O'Meara E, Seider MJ, Lee WR, Rosenthal SA, Pisansky T, Catton C, Valicenti RK, Zietman AL, Bosch WR, Sandler H, Buyyounouski MK, Ménard C: Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 76(2): 361-368, 2010. DOI: 10.1016/j.ijrobp.2009.02.006

19 Matsumoto T, Toya R, Shimohigashi Y, Watakabe T, Matsuyama T, Saito T, Fukugawa Y, Kai Y, Oya N: Plan quality comparisons between 3D-CRT, IMRT, and VMAT based on 4D-CT for gastric MALT lymphoma. Anticancer Res 41(8): 3941-3947, 2021. DOI: 10.21873/anticanres.15190

20 Toya R, Watakabe T, Kai Y, Matsuyama T, Fukugawa Y, Matsumoto T, Shiraishi S, Shimohigashi Y, Saeki S, Sakagami T, Hirai T, Oya N: Implementation of (99m)Tc-GSA SPECT image-guided inverse planning into palliative radiotherapy for diffuse liver metastases: a novel approach. In Vivo 36(3): 1523-1526, 2022. DOI: 10.21873/invivo.12862

21 Alongi F, Fiorino C, Cozzarini C, Broggi S, Perna L, Cattaneo GM, Calandrino R, Di Muzio N: IMRT significantly reduces acute toxicity of whole-pelvis irradiation in patients treated with post-operative adjuvant or salvage radiotherapy after radical prostatectomy. Radiother Oncol 93(2): 207-212, 2009. DOI: 10.1016/j.radonc.2009.08.042

Received February 5, 2024
Revised March 5, 2024
Accepted March 6, 2024