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ORIGINAL ARTICLE

Retrospective Study

Correlation between dose-volume parameters and rectal bleeding after 12 fractions of carbon ion radiotherapy for prostate cancer

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Abstract

BACKGROUND

Carbon ion radiotherapy (CIRT) is currently used to treat prostate cancer. Rectal bleeding is a major cause of toxicity even with CIRT. However, to date, a correlation between the dose and volume parameters of the 12 fractions of CIRT for prostate cancer and rectal bleeding has not been shown. Similarly, the clinical risk factors for rectal bleeding were absent after 12 fractions of CIRT.

AIM

To identify the risk factors for rectal bleeding in 12 fractions of CIRT for prostate cancer.

METHODS

Among 259 patients who received 51.6 Gy [relative biological effectiveness (RBE)], in 12 fractions of CIRT, 15 had grade 1 (5.8%) and nine had grade 2 rectal bleeding (3.5%). The dose-volume parameters included the volume (cc) of the rectum irradiated with at least x Gy (RBE) (Vx) and the minimum dose in the most irradiated x cc normal rectal volume (Dx).

RESULTS

The mean values of D6cc, D2cc, V10 Gy (RBE), V20 Gy (RBE), V30 Gy (RBE), and V40 Gy (RBE) were significantly higher in the patients with rectal bleeding than in those without. The cutoff values were D6cc = 34.34 Gy (RBE), D2cc = 46.46 Gy (RBE), V10 Gy (RBE) = 9.85 cc, V20 Gy (RBE) = 7.00 cc, V30 Gy (RBE) = 6.91 cc, and V40 Gy (RBE) = 4.26 cc. The D2cc, V10 Gy (RBE), and V20 Gy (RBE) cutoff values were significant predictors of grade 2 rectal bleeding.

CONCLUSION
The above dose-volume parameters may serve as guidelines for preventing rectal bleeding after 12 fractions of CIRT for prostate cancer.

Key Words: Carbon ion radiotherapy; Prostate cancer; Rectal bleeding; Dose volume parameters; Prevention

Core Tip: This study identified the risk factors for rectal bleeding, including dose–volume parameters of 51.6 Gy [relative biological effectiveness (RBE)] in 12 fractions of carbon ion radiotherapy (CIRT) for prostate cancer. The cutoff values of D2cc = 46.46 Gy (RBE), V10 Gy (RBE) = 9.85 cc, and V20 Gy (RBE) = 7.00 cc were significant factors for the occurrence rate of grade 2 rectal bleeding. When planning CIRT for prostate cancer, the rate of rectal bleeding may decrease if these values are used.

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INTRODUCTION

Prostate cancer is the second most frequent cancer, with an estimated 1.4 million new cases, and is the most frequent cancer in 112 of 185 countries, including Japan. Although mortality rates have decreased in most high-income countries since the 1990s, they are expected to remain the fifth-leading cause of cancer-related deaths among men worldwide by 2020[1]. One well-established risk factor is older age[1,2]; therefore, the incidence of prostate cancer is expected to increase owing to Japan's aging society. Some patients with low-risk prostate cancer are allowed active surveillance to reduce overtreatment, and watchful waiting may be an option for frail patients. However, radical treatment should be considered for patients with medium- or high-risk prostate cancer and physicians should not refuse treatment based solely on age[2,3].

There are two radical treatments for prostate cancer: Radical prostatectomy and radiotherapy with or without androgen deprivation therapy (ADT)[2,3]. Retrospective studies have reported conflicting results regarding the superiority of radical prostatectomy or high-dose external X-ray radiotherapy, including biochemical failure[4-7]. Moreover, few randomized controlled trials have directly compared these two radical treatments[3]. Therefore, patients with good performance status can choose each treatment, considering their toxicities and advantages. However, many patients living in aging societies are unsuitable for surgery because of factors such as older age and comorbidities. Radiotherapy may be indicated in these cases. Moreover, radiotherapy avoids the substantial stress caused by urinary incontinence resulting from radical prostatectomy[3].

Rectal bleeding is one of the most troublesome toxicities in high-dose radiotherapy, and previous studies have shown a 1.8%-13% occurrence rate of grade 2 or higher rectal bleeding[8-11]. Previous studies have also shown a correlation between rectal dose–volume parameters and occurrence rate[10,12-17]. Therefore, intensity-modulated radiotherapy, which can reduce the exposure dose for at-risk organs, including the rectum, has been reported to reduce the risk of gastrointestinal toxicities, including rectal bleeding, compared with three-dimensional radiotherapy[11]. As an alternative, hydrogel spacers have been used in some trials to reduce rectal bleeding by escalating prescription doses[18,19]. However, some reports have suggested clinical risk factors for grade 2 or higher rectal bleeding, such as diabetes mellitus (DM), anticoagulation therapy, ADT, and previous surgery[9,15,20-22].

Carbon ion radiotherapy (CIRT) is currently used to treat prostate cancer. In 2018, CIRT was approved by the national insurance as a curative treatment option for localized prostate cancer in Japan[23]. Multiple clinical trials have led to the development of novel therapies. The first clinical trial was a dose-escalation trial from 54 Gy [relative biological effectiveness (RBE)] in 20 fractions to 72 Gy (RBE) in 20 fractions conducted in December 1997 using the Heavy Ion Medical Accelerator in Chiba at the National Institute of Radiological Sciences[24]. Thereafter, treatment fractionations were gradually decreased from 20-16 to 12 fractions, and 51.6 Gy (RBE) in 12 fractions was used for curative CIRT for prostate cancer in Japan[25,26]. Favorable long-term results have been obtained using this schedule, including data for elderly patients[26,27].

Rectal bleeding is a major cause of toxicity even with CIRT. The incidence rates of grade 1 and 2 rectal bleeding are 1.8%-13% and 0%-2%, respectively[26-29]. There have been reports on the correlation between dose-volume parameters of 20 fractions of CIRT for prostate cancer and rectal bleeding[28]. Other reports have presented estimation data using normal tissue complication probability parameters[30,31]. However, to date, no correlation has been shown between the dose and volume parameters of the 12 fractions of CIRT for prostate cancer and rectal bleeding. Similarly, the clinical risk factors for rectal bleeding were absent after 12 fractions of CIRT. This study aimed to determine the correlation between the dose and volume parameters of 12 fractions of CIRT for prostate cancer and rectal bleeding.

MATERIALS AND METHODS

Ethics statement

This study was approved by the Institutional Ethics Committee of the Faculty of Medicine of Yamagata University (approval number: 2023-51). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients

Patients who underwent CIRT for prostate cancer between February 2021 and December 2021 at Yamagata University Hospital were retrospectively identified and analyzed. The prostate cancer stage was determined according to the Union for International Cancer Control (8th edition) using rectal examination, magnetic resonance imaging, computed tomography (CT), and bone scintigraphy. The inclusion criteria were as follows: Received 51.6 Gy (RBE) in 12 fractions at the East Japan Heavy Ion Center; no rectal invasion; no lymph node metastasis; and no distant metastasis to other organs or sites of uncontrolled cancer.

CIRT

For planning, CT images of the patients were acquired using an Aquilion One (Canon Medical Systems, Otawara, Japan) with a slice thickness of 2 mm. All patients were immobilized in the supine position using a HipFix thermoplastic solid and HipFix Baseplate (CIVCO, IA, United States). In cases where there was large air/fecal content, we performed gas removal or enemas and adjusted the laxatives. For cases that were considered hopeless, retreatment planning CT was performed after adjusting the prescription. Therefore, no patients were excluded from this study because of excessive air/fecal content. The clinical target volume (CTV) included the prostate volume, with reference to magnetic resonance imaging. In addition to the prostate, a part of the seminal vesicle was added for T3a or lower, excluding low-risk cases (≤ T2a, Gleason score was 3 + 3, and initial prostate-specific antigen ≤ 10 ng/mL), and the entire seminal vesicle was included in the CTV for T3b. The CIRT dose calculation algorithm uses a pencil beam. The planning target volume (PTV) was defined as the CTV plus 5-mm margins in the cranial, caudal, and posterior directions and 10-mm margins in the lateral and anterior directions. The CIRT plan was created using RayStation10A (RaySearch Laboratories, Stockholm, Sweden). A microdosimetric kinetic model was used to calculate the RBE dose[32,33]. The CIRT plan was created with the goal of > 51.55 Gy (RBE) for 95% of the PTV, accounting for the condition of each case and the rectal dose by each physician. CIRT was performed using a CI-1000 (Toshiba Energy Systems & Solutions Corporation, Kanagawa, Japan). The CIRT schedule was 51.6 Gy (RBE) in 12 fractions. Generally, CIRT is performed for 4 days in a week (generally Tuesday to Friday) and 6 days in 2 weeks if there are consecutive holidays, such as national holidays. The treatment plan was performed using 90- and 270-degree beams in six fractions each. Daily X-ray imaging and digitally reconstructed radiographs were used for positioning.

Evaluation and follow-up

Patients were followed-up every 2-6 months in the first year and every 6-12 months thereafter. Rectal bleeding was evaluated using the rectal hemorrhage item within the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics software (version 24; SPSS Inc., Chicago, IL, United States). The Kaplan–Meier algorithm was used to estimate the cumulative incidence of rectal bleeding from the start of CIRT to the occurrence of rectal bleeding or last follow-up. The mean values of the dose-volume parameters were compared using the Mann-Whitney *U* test. Pretreatment clinical factors included DM, anticoagulation therapy, and ADT. Previous surgeries were not included in this study because not all patients had a sufficient surgical history. The entire rectal area was evaluated. The dose-volume parameters included the volume (cc) of the rectum irradiated with at least x Gy (RBE) (Vx) (V10-50 Gy [RBE]) and the minimum dose in the most irradiated x cc normal rectal volume (Dx) (D6cc, D2cc, and D0.2cc). The relationship between the occurrence of rectal bleeding and pretreatment factors was compared using the χ^2 test. Receiver operating characteristic (ROC) curves and sensitivity and specificity calculations were performed to determine the cutoff value of the significant dose-volume parameter with the highest sum of sensitivity and specificity. The χ^2 test was used for evaluation. All *P*-values were two-sided, and *P*-values < 0.05 were considered statistically significant.

RESULTS

Patients

In total, 259 patients received 51.6 Gy (RBE) in 12 fractions of CIRT for prostate cancer, including two patients with bladder invasion (Table 1). All patients completed the planned treatment. The median follow-up time was 31 months (range, 14-40 months), and > 94% of living patients were followed up for at least 24 months. Five patients died of unrelated illnesses between 14 and 24 months after CIRT (two with heart disease, one with bacterial pneumonia, and two with pancreatic cancer).

Table 1 Patient characteristics, *n* (%)

Characteristics (*n* = 259)	
Age (years)	
Median (range)	71 (54-87)
Karnofsky performance status	
100	232 (89.5)
90	24 (9.3)
80	1 (0.4)
60	2 (0.8)
Follow-up time (months)	
Median (range)	31 (14-40)
Initial prostate-specific antigen (ng/mL)	
Median (range)	8.23 (0.62-1354)
T category	
1b	1 (0.4)
1c	39 (15.1)
2a	99 (38.2)
2b	34 (13.0)
2c	57 (22.0)
3a	19 (7.3)
3b	8 (3.1)
4	2 (0.8)
Gleason score	
6	39 (15.1)
7	119 (45.9)
8	65 (25.1)
9	35 (13.5)
10	1 (0.4)
Diabetes mellitus	
Yes	29 (11.2)
No	230 (88.8)
Anticoagulation therapy	
Yes	38 (14.7)
No	221 (85.3)
Androgen deprivation therapy	
Yes	234 (90.3)
No	25 (9.7)
Planning target volume (cc)	
Median (range)	80.71 (43.24-202.60)

Rectal bleeding

Fifteen patients had grade 1 rectal bleeding (5.8%), and nine patients had grade 2 rectal bleeding (3.5%). Figure 1 shows the cumulative incidence. The median time between CIRT and rectal bleeding was 8 months (1-19 months). Approximately three-quarters of the patients developed rectal bleeding within 12 months, excluding six of the 24 patients. Only two patients had grade 1 rectal bleeding after 18 months. Eight of the nine patients experienced grade 2 rectal bleeding,

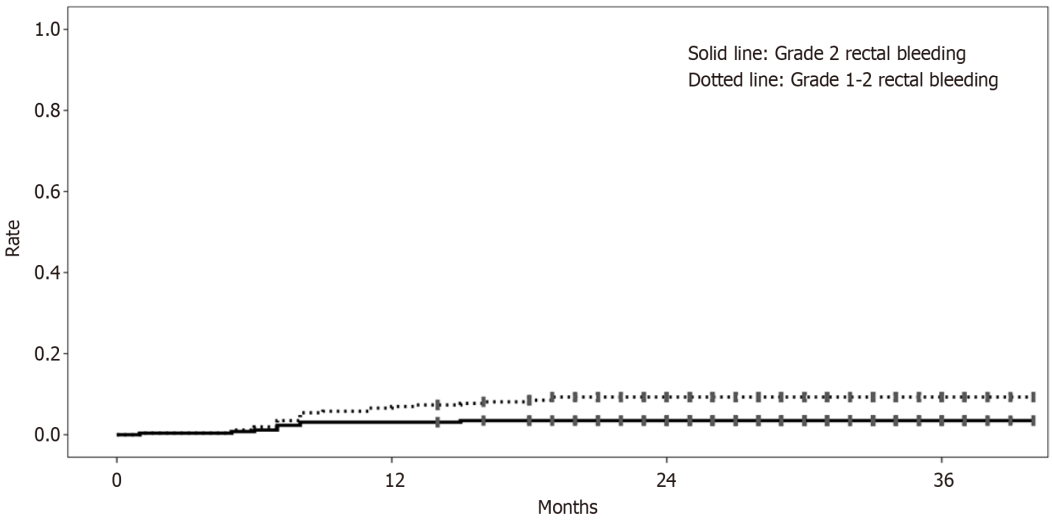

Figure 1 The cumulative incidence of rectal bleeding after carbon ion radiotherapy.

all eight of whom experienced bleeding within 8 months post-CIRT.

Correlation between pretreatment clinical factors and rectal bleeding

Grade 1 or 2 rectal bleeding occurred in four of 29 patients (14%) with DM, five of 38 patients (13%) using anticoagulation therapy, and four of 25 patients (16%) who received concomitant ADT. There were no significant differences in rectal bleeding in any of the pretreatment clinical factors.

Correlation between dose-volume parameter and rectal bleeding

Regarding dose-volume parameters, the mean values of D6cc, D2cc, V10 Gy (RBE), V20 Gy (RBE), V30 Gy (RBE), and V40 Gy (RBE) in patients with grade 1 or 2 rectal bleeding were significantly higher than in those without (Table 2). The data were used for the ROC curves. The cutoff values of parameters were D6cc = 34.34 Gy (RBE) (sensitivity 50.0%, specificity 85.5%), D2cc = 46.46 Gy (RBE) (sensitivity 54.2%, specificity 77.9%), V10 Gy (RBE) = 9.85 cc (sensitivity 79.2%, specificity 50.2%), V20 Gy (RBE) = 7.00 cc (sensitivity 83.3%, specificity 49.4%), V30 Gy (RBE) = 6.91 cc (sensitivity 50.0%, specificity 84.7%), and V40 Gy (RBE) = 4.26 cc (sensitivity 58.3%, specificity 80.9%), respectively, by using ROC curves. Analysis of the correlations between these cutoff values and the occurrence rates of grade 2 rectal bleeding showed that parameters below the cutoff values of D2cc, V10 Gy (RBE), and V20 Gy (RBE) were significant factors for lower occurrence rates (Table 3).

DISCUSSION

To the best of our knowledge, this is the first report showing a correlation between dose-volume parameters and rectal bleeding after 51.6 Gy (RBE) in 12 fractions of CIRT for prostate cancer.

The cutoff value of rectal bleeding after CIRT for prostate cancer should be defined using clinical data, completely separate from reports on X-ray therapy, although dose-volume parameters appear to be related to rectal bleeding in CIRT, as with X-ray therapy. This is because carbon ions do not have the characteristics of photons. Carbon ions have a higher RBE and a lower oxygen enhancement ratio[34]. Owing to this advancement, CIRT is expected to achieve eradication of radioresistant tumors and a smaller variation in radiation sensitivity with the position of the cells in the replication cycle, unlike X-ray therapy. Although this property may have positive therapeutic effects, it may also affect toxicity. Moreover, the physical dose (Gy) decreases as the RBE increases to achieve a uniform dose [Gy (RBE)] across the irradiated field in CIRT[35]. As mentioned above, CIRT often has different properties from those of X-ray therapy, which has been widely used until now, and it is unclear whether the common sense that physicians use for X-ray therapy still applies. In addition, the areas of the rectum irradiated with low and medium doses of X-ray radiotherapy are much wider than those irradiated with CIRT[36]. This is because CIRT is applied mainly in the left and right directions, including the plan of the present study[26,28,36]. These differences may result in different outcomes for each treatment method. Therefore, a concrete discussion is needed using actual clinical results, as in the present study.

Methods using absolute and relative values have been reported for evaluating rectal doses. Most studies have discussed the proportion of the rectum or rectal wall irradiated with doses of V40-70 Gy[10,12-16]. However, this evaluation method varies greatly depending on the rectal area and degree of rectal dilatation. In contrast, Kotabe *et al*[17] reported that the absolute rectal volume irradiated at 60 Gy was the only significant factor for rectal bleeding, although relative rectal volume was not. The present study also analyzed the absolute volume owing to rectal volume uncertainty, as reported by Kotabe *et al*[17]. Indeed, the present study found a significant difference between the absolute rectal volume and occurrence rate of rectal bleeding, and it seems appropriate to evaluate it using absolute values, even for

Table 2 The correlation between dose–volume parameter of rectum and rectal bleeding, mean ± SD

	Grade 0	Grade 1/2	*P* value
D 6cc	25.40 ± 7.56 Gy (RBE)	30.93 ± 6.75 Gy (RBE)	0.001[a]
D 2cc	44.54 ± 2.88 Gy (RBE)	45.93 ± 1.71 Gy (RBE)	0.005[a]
D 0.2cc	49.73 ± 0.98 Gy (RBE)	49.80 ± 0.34 Gy (RBE)	0.592
V 10 Gy (RBE)	10.45 ± 2.72 cc	11.89 ± 2.79 cc	0.010[a]
V 20 Gy (RBE)	7.46 ± 2.05 cc	8.90 ± 2.29 cc	0.002[a]
V 30 Gy (RBE)	5.32 ± 1.57 cc	6.56 ± 1.78 cc	0.001[a]
V 40 Gy (RBE)	3.34 ± 1.05 cc	4.15 ± 1.12 cc	0.001[a]
V 50 Gy (RBE)	0.18 ± 0.10 cc	0.17 ± 0.12 cc	0.590

[a]$P < 0.05$.
RBE: Relative biological effectiveness.

Table 3 The comparison of ratio of rectal bleeding before and after cutoff values of dose-volume parameters calculated by using receiver operating characteristic curves

	Comparison	Number of patients	Ratio of grade 2 rectal bleeding (%)	*P* value
D 6cc	≥ 34.34 Gy (RBE)	54	5.3	0.42
	< 34.34 Gy (RBE)	202	3.0	
D 2cc	≥ 46.46 Gy (RBE)	65	7.7	0.047[a]
	< 46.46 Gy (RBE)	194	2.1	
V 10 Gy (RBE)	≥ 9.85 cc	136	5.9	0.038[a]
	< 9.85 cc	123	0.8	
V 20 Gy (RBE)	≥ 7.00 cc	139	5.8	0.040[a]
	< 7.00 cc	120	0.8	
V 30 Gy (RBE)	≥ 6.91 cc	48	6.0	0.374
	< 6.91 cc	211	6.3	
V 40 Gy (RBE)	≥ 4.26 cc	59	1.7	0.689
	< 4.26 cc	200	4.0	

[a]$P < 0.05$.
RBE: Relative biological effectiveness.

CIRT. Moreover, there is a report on CIRT for cervical cancer rather than prostate cancer, which was evaluated based on the absolute values of Vx and Dxcc. In this study, these were identified as significant factors for rectal bleeding[37], which is consistent with the results of the present study.

There have been some reports of rectal bleeding with CIRT using clinical data from a certain number of patients. Using clinical data from 172 patients, Ishikawa *et al*[28] reported that the V50% of the prescribed dose (33 Gy [RBE]) was a significant factor for rectal bleeding. In contrast, factors other than a high rectal dose were identified as significant in the present study. The reason may be the difference in the evaluation methods, such as the absolute value in the present study, unlike the relative value in the previous study, and the difference in the dose per fraction. However, Okonogi *et al* [37] reported that D5cc and D2cc for the rectum were significantly higher in patients with ≥ grade 1 rectal bleeding, although the V10-50 were not, using 139 patients' clinical data. In the present study, D6cc and D2cc were significant risk factors for rectal bleeding, as in their study. The different results of the Vx data may be due to differences in the irradiation method, as CIRT was applied only from the left and right directions in the present study; however, CIRT may also be applied in other directions for cervical cancer, as well as differences in total dose and dose per fraction. Beams from other sides likely worsen the absolute exposure to radiation of the rectal wall compared with a more dispersed beam, given an equal rectal volume, including its contents (gas and feces). Previous evaluations of X-ray therapy have shown that an area irradiated with a slightly higher dose affects rectal bleeding, unlike the present results, for example, V50-70[10,12-16]. In this study, the area of the rectum irradiated with low-dose radiation was identified as a significant

factor in the incidence of rectal bleeding. Moreover, no significant difference was observed in the pinpoint high-dose areas as D0.2cc in the present study. The tendency of the significant factor to be the area of the rectum irradiated with a low dose was more clearly observed in patients with grade 2 rectal bleeding. This may be because a small dose must be delivered to a certain area of the rectum for rectal bleeding, especially problematic bleeding.

DM, anticoagulation therapy, and ADT, the clinical factors examined in the present study, have been suggested as risk factors for rectal bleeding after X-ray therapy for prostate cancer[9,15,20,21,28]. Herold *et al*[20] reported that DM is a significant risk factor for grade 2 gastrointestinal toxicity. However, Feigenberg *et al*[21] reported that ADT was an independent predictor of ≥ grade 2 gastrointestinal toxicity, adding to the total dose. Ishikawa *et al*[28] reported that anticoagulation therapy was a significant risk factor for grade 1-2 rectal bleeding after 20 fractions of CIRT. However, these factors were not significant predictors of rectal bleeding in the present study. This may be because only a small number of patients received DM or anticoagulation therapy, whereas most patients in the present study received ADT. Other reasons may include cases in which the attending physician adjusted the dose to the rectum, taking into account risk factors; however, this could not be evaluated in this retrospective study.

This study had two limitations. First, the follow-up period was relatively short. However, more than 94% of patients were followed for at least 2 years. Moreover, Ishikawa *et al*[28] reported that > 80% of rectal bleeding cases occurred within 2 years, and most patients with rectal bleeding in the present study experienced it within 1.5 years. Second, this study was based on retrospective data from a single institution. However, the number of patients in the present study was larger than those in previous clinical studies that examined dose-volume parameters[28,36]. Therefore, despite its limitations, the present study is meaningful.

CONCLUSION

In conclusion, D2cc = 46.46 Gy (RBE), V10 Gy (RBE) = 9.85 cc, and V20 Gy (RBE) = 7.00 cc may be indicators for preventing both all-grade and grade 2 rectal bleeding after 51.6 Gy (RBE) in 12 fractions of CIRT for prostate cancer.

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FOOTNOTES

Author contributions: Ono T designed and performed the research and wrote present paper; Sato H designed and supervised the report; Miyasaka Y provided clinical advice; Hagiwara Y, Yano N, Akamatsu H, Harada M, and Ichikawa M contributed to data analysis.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Faculty of Medicine at Yamagata University (approval number: 2023-51).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written informed consent. When consenting to treatment, we also informed patients of the possibility of their use in research, and they agreed to this, so we do not believe it is necessary to obtain new consent for this study. For full disclosure, the details of the study are published on the home page of Faculty of Medicine at Yamagata University.

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