

## Scientific Article

# Effect of Hyaluronate Acid Injection on Dose-Volume Parameters in Brachytherapy for Cervical Cancer



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## Abstract

**Purpose:** Hyaluronate gel has been injected as a spacer into the rectovaginal fossa and vesicouterine fossa during brachytherapy for patients with cervical cancer at our institution. The effect of hyaluronate gel injection (HGI) on dose-volume parameters was investigated in this study.

**Methods and Materials:** Between July 2008 to January 2020, a total of 104 patients (non-HGI group: 52 patients; HGI group: 52 patients) who underwent curative radiation therapy for cervical cancer were selected. The total doses of external beam radiation therapy and brachytherapy for high-risk clinical target volume (CTV<sub>HR</sub>) D<sub>90</sub>, bladder D<sub>2cc</sub>, and rectal D<sub>2cc</sub> were converted to the equivalent dose in 2 Gy fractions (EQD2) and were analyzed for association with HGI.

**Results:** Median CTV<sub>HR</sub> D<sub>90</sub> (EQD2) in the non-HGI group was 76.0 Gy (63.7-99.5 Gy), and in the HGI group it was 79.4 Gy (52.6-97.5 Gy) ( $P = .017$ ). The median bladder D<sub>2cc</sub> and rectal D<sub>2cc</sub> (EQD2) were 62.9 Gy and 56.0 Gy in the non-HGI group and 63.7 Gy and 54.8 Gy in the HGI group, which had no significant difference.

**Conclusions:** In cases with HGI, a significant CTV<sub>HR</sub> D<sub>90</sub> dose increase was obtained with sufficient bladder and rectal doses suppression.

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Data for these analyses are included in the supplementary information files.

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## Introduction

Brachytherapy (BT) plays an essential role in radiation therapy for uterine cervical cancer, delivering a substantial dose to the tumor. It is important to reduce the dose of organs at risk (OARs) in the rectum and bladder while ensuring the dose of the high-risk clinical target volume (CTV<sub>HR</sub>). The transition from 2-dimensional BT to 3-dimensional BT allowed the improvement of high dose delivery to the clinical target volume (CTV) while reducing radiation doses to OARs.<sup>1</sup>

Groupe Européen de Curiothérapie—European Society for Radiotherapy and Oncology (GEC-ESTRO) guidelines recommend at least 85 Gy in the equivalent dose in 2 Gy fractions (EQD2) for CTV<sub>HR</sub> D<sub>90</sub>, and several studies showed the improvement of local control.<sup>2-4</sup>

However, even with image-guided brachytherapy (IGBT), sometimes it is challenging to deliver CTV<sub>HR</sub> D<sub>90</sub> >85 Gy while maintaining dose constraints for organs at risk in patients with large asymmetrical tumors or with little fat tissue around the tumor.

Since 2013, we have been injecting hyaluronic acid gel as a spacer into the rectovaginal fossa and vesicouterine fossa before every brachytherapy under the transrectal ultrasound (TRUS) guidance. In the BT treatment of multiple tumor sites, hyaluronic acid gel injection (HGI) has been proven to safely enhance the distance between OARs and target volumes, resulting in considerable OARs dose reduction.<sup>5,6</sup> Moreover, a phase 3 clinical trial found that SpaceOAR (Boston Scientific Corporation, Marlborough, MA), the polymerized type of polyethylene-glycol hydrogel, effectively reduced the rectal dose in patients with prostate cancer.<sup>7</sup>

Our research has previously reported on the efficacy of HGI in dose reduction for rectum and bladder and the incidence of rectal bleeding.<sup>8-10</sup> However, the association between HGI and CTV has not yet been reported. This study aims to report the effect of HGI on dose-volume parameters, especially on CTV, for patients with cervical cancer. We performed propensity score matching to select 2 groups—a non-HGI group and an HGI group—for additional analysis.

## Methods and Materials

A total of 163 patients who underwent curative radiation therapy for cervical cancer from July 2008 to January 2020 were included in the study. All patients underwent body computed tomography (CT), pelvic magnetic resonance image (MRI), and biopsy of the cervix for staging. The International Federation of Gynaecology and Obstetrics (2008) stage IB to IVA patients were included, and those with distant metastases were excluded except para-aortic lymph

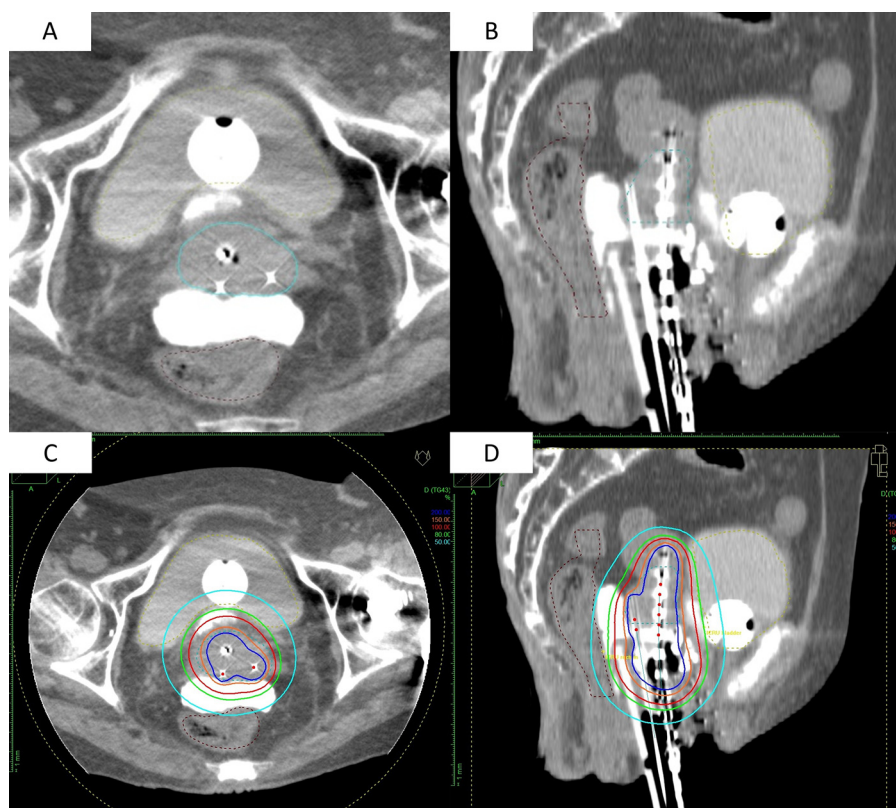
node metastasis. Concurrent weekly CDDP (40 mg/m<sup>2</sup>) was administered for regional node-positive patients or those with a >4 cm tumor diameter, except for those >80 years of age and with impaired renal function.

According to the Japan Society of Gynecologic Oncology Guidelines,<sup>11</sup> 20 to 50 Gy of whole pelvic irradiation (WPIR) was followed by 10 to 30 Gy WPIR with a central shield (CS) using a 4-cm width block to reduce the dose to the rectum and bladder until the pelvic sidewall received 50 Gy with 2 Gy per fraction. Since 2017, intensity modulated radiation therapy has been used for WPIR with no CS, which was delivered 45 Gy in 25 fractions. After WPIR, BT was administered using tandem and ovoid or cylinder with or without extra interstitial needles for large or irregularly shaped tumors (intracavitary and interstitial brachytherapy [IC/IS]).

Sacral anesthesia was administered in the treatment room before brachytherapy, and afterward, fentanyl and midazolam were used for analgesia and sedation. Before inserting the applicators, under the TRUS guidance, the 19 G needle (disposable ultrasonography compatible puncture needle; Create Medic Co, Ltd, Kanagawa, Japan) was advanced to the rectovaginal fossa and vesicouterine fossa through the anterior and posterior vaginal wall, respectively, while confirming the position of the needle tip with the sagittal image of the TRUS. After the final confirmation of the needle with the axial image, hyaluronate gel was injected in the spaces. Hyaluronate gel consists of 5 vials of Suvenyl (Chugai Pharmaceutical Co, Tokyo, Japan), 5 mL of saline, and 2 to 4 mL of contrast enhancement agent (Oiparomin 370; Fuji Pharmaceutical Company, Toyama, Japan). The gel was placed for every fraction as it was absorbed in 2 to 3 days. Figure 1. shows the case of CT images with HGI. We did not inject gel for patients with bladder or rectal invasion.

In all cases, the prescribed reference dose per fraction was 6 Gy. After the applicators were placed, CT imaging was obtained with the patients in the lithotomy position, and planning was performed using the software Oncentra (Elekta, Veenendaal, The Netherlands). The CTV<sub>HR</sub> contouring was based on the Japanese Radiation Oncology Study Group guidelines,<sup>12</sup> which describe the contouring of the CT-based high-risk clinical target volume (CTV<sub>HR</sub>), and we also referred to GEC-ESTRO guidelines.<sup>2,13</sup> The plan was optimized to ensure that the 6 Gy isodose cover HR<sub>CTV</sub> while keeping OAR dose restrictions within guidelines. Our dosimetric constraints for OARs are as follows: <75 Gy for rectum D<sub>2cc</sub> and <85 Gy for bladder D<sub>2cc</sub> (EQD2). In the HGI group, dose-escalation was encouraged if the OARs doses were within the limit of the dose constraints, especially for patients with poor response.

To obtain the combined dose of EBRT and brachytherapy, the EQD2 was calculated according to the linear-



**Fig. 1** (A, B) Axial and sagittal computed tomography image with hyaluronate gel injection in the rectovaginal fossa and vesicouterine fossa. Tandem and ovoid are used with 2 interstitial needles for dorsal invasion of the tumor. (C, D) Distribution of the same case. The 100% isodose line (6 Gy) is indicated by the red line. The red line covers the high-risk clinical target volume (blue dotted line) as it avoids extending into the bladder and rectum.

quadrant model by the following formula, and the EQD2 of  $CTV_{HR} D_{90}$ , bladder  $D_{2cc}$  and rectal  $D_{2cc}$  were obtained:

$$EQD2 = D \left( d + (\alpha/\beta) \right) / \left( 2 + (\alpha/\beta) \right)$$

Here,  $D$  is the total dose,  $d$  is the dose per fraction,  $\alpha/\beta = 10$  Gy for  $CTV_{HR}$ , and  $\alpha/\beta = 3$  Gy for OARs.

Although many studies have not included the dose of CS, we referred to the report by Tamaki et al<sup>14</sup> and considered that 22% of the CS dose for  $CTV_{HR}$ , 15% of the CS dose for bladder, and 5% of the CS dose for rectum contributed to the total dose.

The time to local recurrence was defined as the time interval between the day when radiation therapy started and the date of local relapse or recurrence, and the local control rate of each group were compared. The Common Terminology Criteria for Adverse Events, version 5.0 was used to assess late genitourinary (GU) and gastrointestinal (GI) events, including rectum hemorrhage, cystitis, stenosis or stricture, and fistula.

A retrospective analysis of 163 patients with cervical cancer treated with RT showed a significant difference in the distribution of the use of IC/IS between the non-HGI and HGI groups. It is possible that the discrepancy was

because of the fact that the non-HGI group was primarily treated before 2013. Therefore, to extract confounding factors,  $CTV_{HR} D_{90}$ , age, International Federation of Gynecology and Obstetrics stage, the initial size of  $CTV_{HR}$ , the total dose of BT, the total dose of external beam radiation, the use of chemotherapy, and the use of IC/IS were subjected to multiple regression analysis. The results showed that 3 covariates were associated with  $CTV_{HR} D_{90}$ : initial size ( $P = .0480$ ), total BT dose ( $P < .0001$ ), and use of IC/IS ( $P < .0001$ ). Based on these three factors, 1:1 propensity score matching was performed to select non-HGI and HGI groups patients for further analysis.

The characteristics of the patients and each dosimetric parameter were compared between the non-HGI group and HGI group with the Fisher exact test for categorical variables and the Wilcoxon rank-sum test or Student  $t$  test for continuous variables. All tests were performed with JMP Pro 16.0 (SAS Institute, Cary, NC).  $P$  values  $< .05$  were considered statistically significant.

The National Cancer Center Hospital's institutional review board approved this retrospective study (approval number 2017-091) following the Declaration of Helsinki's ethical principles.

## Results

Between July 2008 and January 2020, according to 1:1 propensity score matching (confounding factors: initial size of tumor, total BT dose, the use of IC/IS), 104 patients (non-HGI group: 52 patients; HGI group: 52 patients) were included. Patients' characteristics are summarized in Table 1. In both groups, the median dose of EBRT was 50 Gy, and the median dose of BT was 24 Gy. IC/IS was used in 43 cases in the non-HGI group and 40 cases in the HGI group, about 80% of the entire group. There were no differences in baseline tumor characteristics, dose prescription, and the use of interstitial brachytherapy across groups. A significant difference in age and use of chemotherapy was observed, but it was not considered to affect the assessment of dose-volume parameters. The median follow-up period for all the patients was 32.6 months (4.6-147.2 months). Since the use of HGI was started in 2015, the observation period was also significantly longer

in the non-HGI group (50.4 months vs 25.4 months,  $P < .001$ ).

Table 2 and Figure 2 show the dose-volume parameters of CTV<sub>HR</sub>, rectum, and bladder. The median doses for CTV<sub>HR</sub> D<sub>90</sub> were 76.0 Gy (range, 63.7-99.5) in the non-HGI group and 79.4 Gy (range, 52.6-97.5) in the HGI group. CTV<sub>HR</sub> D<sub>90</sub> was significantly higher in the HGI group ( $P = .017$ ; 95% confidence interval [CI], 0.69-6.82). The median rectal dose in the non-HGI group was 56.0 Gy (range, 38.7-68.9) and 54.8 Gy (range, 39.7-71.0) in the HGI group ( $P = .628$ ; 95% CI,  $-1.96$  to 3.23), and the median bladder dose in the non-HGI group was 62.9 Gy (range, 41.3-81.2) and 63.7 Gy (range, 45.2-80.4) in the HGI group ( $P = .272$ ; 95% CI,  $-4.22$  to 1.20), which showed no significant difference.

The 2-year local control rate was 85.9% in the non-HGI group and 91.9% in the HGI group, which was not significantly different ( $P = .313$ ; hazard ratio, 1.98; 95% CI, 0.51-7.71). There were no adverse events related to

**Table 1 Patient characteristics**

	Total	Non-HGI group	HGI group	P value
Number of patients	104	52	52	
Age, median (range)	60 (23-88)	55 (23-85)	66 (35-88)	.032*
FIGO (2008)				.966
IB1	5	2	3	
IB2	10	6	4	
IIA2	3	1	2	
IIB	31	15	16	
IIIA	2	1	1	
IIIB	43	21	22	
IVA	10	6	4	
Initial tumor size (cm), median (range)	5.5 (1.5-9.2)	5.5 (1.5-8.9)	5.5 (2.3-9.2)	.834
Histology				.473
Squamous cell carcinoma	94	47	47	
Adenocarcinoma	9	4	5	
Adenosquamous cell carcinoma	1	1	0	
EBRT dose (Gy), median (range)	50 (40-50.4)	50 (40-50.4)	50 (42-50.4)	.191
BT dose (Gy), median (range)	24 (12-36)	24 (12-30)	24 (12-36)	.296
Type of BT				.463
Intracavitary brachytherapy		9	12	
IC/IS		43	40	
Chemotherapy				<.002*
Concomitant chemotherapy	74	45	29	
Nonchemotherapy	30	7	23	
Follow-up time (mo), median (range)	32.6 (4.6-147.2)	50.4 (9.7-147.2)	25.4 (4.6-52.7)	<.001*
Abbreviations: BT = brachytherapy; EBRT = external beam radiation therapy; FIGO = International Federation of Gynaecology and Obstetrics; HGI = hyaluronate gel injection; IC/IS = intracavitary and interstitial brachytherapy.				
* Statistically significant.				



**Table 2** Dose-volume parameters of CTV<sub>HR</sub>, rectum, and bladder by treatment groups

	Non-HGI group	HGI group	P value
Median CTV <sub>HR</sub> D <sub>90</sub> , Gy (range)	76.0 (63.7-99.5)	79.4 (52.6-97.5)	.017*
Median rectal D <sub>2cc</sub> , Gy (range)	56.0 (38.7-68.9)	54.8 (39.7-71.0)	.272
Median bladder D <sub>2cc</sub> , Gy (range)	62.9 (41.3-81.2)	63.7 (45.2-80.4)	.628

Abbreviations: CTV<sub>HR</sub> = high-risk clinical target volume; HGI = hyaluronate gel injection.  
 \* Statistically significant.

HGI, such as bleeding, hematuria, bladder wall injury, or urethral injury requiring hospitalization. One patient (nephritis) in the non-HGI group and 1 patient (vesicovaginal fistula) in the HGI group had late adverse events of GU ≥grade 3. Five patients (rectal bleeding: 2, rectovaginal fistula: 2, ileus:1) in the non-HGI group and 2 patients (rectovaginal fistula:1, ileus:1) in the HGI group experienced late adverse events of GI grade ≥3. None of the adverse events were caused by the tumor, but by the treatment. There were no significant differences in morbidity between these 2 groups (GU: *P* = .65; 95% CI, −0.01 to 0.06; GI: *P* = .29; 95% CI, −0.16 to 0.05).

### Discussion

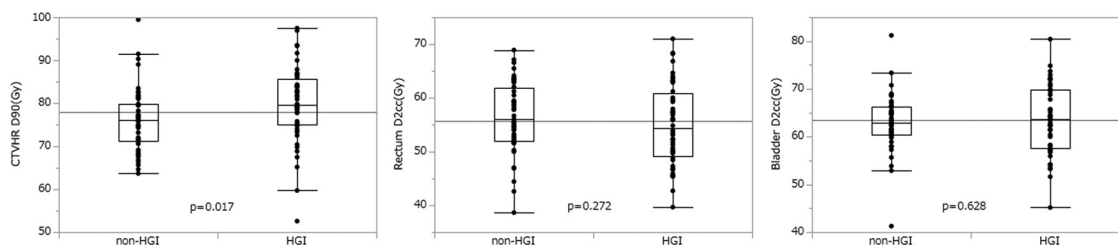
In this study, we have shown that HGI into the rectovaginal fossa and vesicouterine fossa resulted in a significant increase in CTV<sub>HR</sub> D<sub>90</sub> without an increase in the dose of OARs in uterine cervical cancer brachytherapy. It has been shown that spacers can reduce the dose of OARs, but no one has mentioned the dose of the target volume.<sup>15,16</sup> To the best of our knowledge, this is the first study concerning the dose parameters of CTV when spacers are used.

IGBT is vital in the curative treatment of locally advanced cervical cancer and in combination with external beam radiation and chemotherapy can obtain favorable local control. The outcome of the EMBRACE-I, which used MRI-based IGBT, showed that the median dose of CTV<sub>HR</sub> D<sub>90</sub> was 90 Gy (range, 85-94 Gy) and 5-year local control was 92% (95% CI, 90%-93%).<sup>17</sup> In comparison, the median dose of CTV<sub>HR</sub> D<sub>90</sub> in Japan has been reported to be 65 to 74 Gy, a relatively lower dose.<sup>18-20</sup> The median

dose of the HGI group in our study was 79.4 Gy, which seems to be relatively high in Japan. However, it did not achieve CTV<sub>HR</sub> D<sub>90</sub> >85 Gy recommended by the GEC-ESTRO.

There are several possible reasons for the low dose of CTV<sub>HR</sub> D<sub>90</sub> in Japan, including the results of this study. First, the cumulative dose schedule used in Japan is lower than those of the United States and Europe. This is because the prospective study in Japan has shown that the clinical outcomes of this schedule are comparable with those of global dose schedule while adverse events were low.<sup>21</sup> Second, the uncertainty of CS in evaluating doses is a concerning issue. In general practice, the CS dose is not included in the total dose calculation, and subsequently, the dose of CTV<sub>HR</sub> may have been underestimated. Tamaki et al reported that when the CS is 4 cm width, 13% to 35% of the CS dose contributes to the total dose of CTV<sub>HR</sub>.<sup>14</sup> Therefore, although it is not precise and contains inherent uncertainty, dose contribution from CS was included in this study to obtain a cumulative dose as accurate as possible. Of course, such calculations have not been widely used; additional discussion is needed in the community which uses CS. Lastly, the combined IC/IS technique has not been used in many facilities in Japan. When the tumor is massive or has an irregular form, it is difficult to cover the dose to CTV with ICBT alone; thus, combining interstitial needles can improve coverage of the CTV<sub>HR</sub> while adhering to OAR dose constraints.<sup>22</sup> In the present study, IC/IS was used in 80% of cases, and HGI was also used, resulting in a significant increase in CTV<sub>HR</sub> dose compared with the Japanese standards but still lower than 85 Gy.

Although the dose goal is lower than 85 Gy, several Japanese reports demonstrated favorable clinical



**Fig. 2** A box plot shows the dose-volume histogram parameters of the high-risk clinical target volume (CTV<sub>HR</sub>), rectum, and bladder. The 50% interquartile range, median, and range of data are displayed. All cases were divided into 2 groups: a group without hyaluronate gel injection (non-HGI) and a group with hyaluronate gel injection (HGI).

outcomes.<sup>19,23,24</sup> In our previous study, the LC rate was more than 90% even if the dose did not reach 85 Gy in the following low-risk cases: squamous cell carcinoma, reduction ratio before brachytherapy  $\geq 29\%$ , tumor size before brachytherapy  $\leq 4$  cm, and total treatment time  $< 9$  weeks.<sup>25</sup> Risk stratification may be necessary to identify cases requiring more than 85 Gy for CTV<sub>HR</sub> (eg, large tumor size, adenocarcinoma), and should strive to increase the dose of CTV<sub>HR</sub> in such cases, in which HGI may be a helpful tool. Reviewing the results of our study, we were overly concerned with the OARs dose, which was low enough. The CTV<sub>HR</sub> dose may have been increased much further, but we cannot simply increase the dose because we sometimes face severe radiation-related toxicity even in cases with low CTV<sub>HR</sub> doses.

While the incidence of late adverse events was sufficiently low, we could not accomplish a significant dose reduction of OARs in the HGI group because of our prioritization of increasing the dose in the CTV<sub>HR</sub> within the OARs dose constraints. Due to the lower dose schedule and use of CS, the incidence of late adverse events in Japan are lower than in other countries. Pötter et al<sup>17</sup> reported that actuarial cumulative 5-year incidence of grade 3 to 5 morbidity was 6.8% (95% CI, 5.4–8.6) for GU events, 8.5% (6.9–10.6) for GI events in the EMBRACE-I study. In comparison, even though the follow-up period was short in the present study, rates of late adverse events were low (GU: 1.9%; GI: 3.8%) in the HGI group, and HGI is expected to reduce the dose of OARs and adverse events further by widening the physical space between OARs and CTV.

The limitations of this study are that the study was retrospective from single institution study with inherent information and selection bias, the presence of confounding factors and the difference of follow-up period between the 2 groups. Although patients did not complain of any pain or discomfort caused by HGI during follow-up visits, patient-reported toxicities were not evaluated in this article. Therefore, prospective studies are required to validate its effectiveness in cervical cancer brachytherapy, through which we would also like to promote the technique of HGI to other facilities. Long-term observation is also needed to analyze the relationship between CTV<sub>HR</sub> D<sub>90</sub> and local control rate. Even with those limitations, HGI enables a safe increase in the CTV<sub>HR</sub> D<sub>90</sub> dose and also be helpful for institutions where the total dose already is  $> 85$  Gy in contributing to the reduction of late severe rectal or bladder side effects.

## Conclusion

Using HGI in the rectovaginal fossa and vesicouterine fossa for patients with cervical cancer increased the dose of CTV<sub>HR</sub> D<sub>90</sub> while the quantity of rectum and bladder D<sub>2cc</sub> was within the constraints.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.adro.2022.100918](https://doi.org/10.1016/j.adro.2022.100918).

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