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Original Article

Safe dose escalation and reduction of the fraction number of uterine cervical brachytherapy using a gel spacer in the rectovaginal and vesicouterine septum: A planning study

Jun Takatsu[1], Naoya Murakami[1,*], Yoichi Muramoto[1], Tatsuki Karino[1], Masaki Oshima[1], Yasuo Kosugi[1], Terufumi Kawamoto[1], Yasuhisa Terao[2], Naoto Shikama[1]

[1] *Department of Radiation Oncology, Faculty of Medicine, Juntendo University, Tokyo, Japan*
[2] *Department of Obstetrics and Gynecology, Faculty of Medicine, Juntendo University, Tokyo, Japan*

ABSTRACT

PURPOSE: To evaluate the possibility of dose escalation and reduction of fraction number in cervical brachytherapy using a gel spacer.

MATERIAL AND METHODS: Twenty patients with uterine cervical cancer treated with image-guided adaptive brachytherapy (IGABT) were selected. Hyaluronic acid gel injection (HGI) was performed in the rectovaginal and vesicouterine septum for 10 patients. The other ten patients were not with HGI. Both groups were treated with IGABT involving tandem/ovoid or cylindrical applicators along with additional interstitial needles. Dose distributions approved by radiation oncologists were retrospectively analyzed, and a dose summation of 45 Gy/25 of external beam radiation therapy and IGABT was performed. Dose constraints for D_{2cc} of bladder, rectum, and sigmoid were 80, 70, and 70 Gy, respectively. Equivalent dose in 2-Gy fractions calculations used $\alpha/\beta = 10$ Gy for high-risk clinical target volume (CTV_{HR}) D_{90} and $\alpha/\beta = 3$ Gy for organs at risks (OARs). As a planning study, dose distribution rescaling was conducted to deliver as much dose to CTV_{HR} D_{90} as possible within the dose constraint limitation for OARs when IGABT was performed for four, three, and two fractions in both groups.

RESULTS: The median CTV_{HR} D_{90} was >80 Gy in the non-HGI group and >85 Gy in the HGI group for virtual two and three fractions. Rectum D_{2cc} was significantly lower in the HGI group for three fractions ($p < 0.01$).

CONCLUSIONS: In the HGI group, adequate dose delivery to CTV_{HR} could be achieved with a reduced IGABT fraction number while meeting the dose constraints of OARs.

Keywords: cervical cancer; image-guided brachytherapy; gel spacer; dosimetry; fractionation; treatment planning

Introduction

Traditionally, typical brachytherapy for uterine cervical cancer patients in primary settings consists of three to *six* sessions of intracavitary brachytherapy with or without additional interstitial needles following preceding whole pelvic radiation therapy (1–9). Recently, hypofractionation is being used in breast, or prostate cancer radiation therapy (10–13). However, such attempts to reduce the brachytherapy fractions are seldom performed due to the proximity of organs at risk (OARs), such as the rectum, bladder, and sigmoid colon, to the high-risk clinical target volume (CTV_{HR}). Nevertheless, if it is possible to reduce the brachytherapy fractions, it would alleviate patients' stress both physically and mentally and enable brachytherapy for more patients. The number of brachytherapy machines is normally limited within a certain medical care zone, so if the total treatment time can be shortened, patient throughput would increase, and clinical outcomes could potentially be improved (14).

Gel spacers, which are widely used in prostate radiotherapy (15,16), create a physical space between these OARs and the CTV_{HR} as well as widen the therapeutic window. Although gel spacers have limited use in man-

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* Corresponding author. Department of Radiation Oncology, Faculty of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Tel.: +81-3-3813-3111, fax: +81-3-3816-0958.

E-mail address: n.murakami.zi@juntendo.ac.jp (N. Murakami).

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aging gynecologic malignancies, their usefulness has been previously reported (15,17–24).

This planning study aimed to use computed tomography (CT) images taken during cervical cancer brachytherapy performed with a gel spacer for protection of the rectum and bladder to investigate the possibility of reducing the number of brachytherapy sessions to less than four while observing the recommended dose constraints of CTV_{HR} D_{90} dose > 80–85 Gy equivalent dose in 2-Gy fractions (EQD_2) ($\alpha/\beta = 10$ Gy) while maintaining bladder D_{2cc}, rectum D_{2cc}, and sigmoid D_{2cc} doses of 80, 70, and 70 Gy EQD_2 ($\alpha/\beta = 3$ Gy), respectively.

Material and methods

Twenty patients who underwent CT-based image-guided adaptive brachytherapy to treat locally advanced cervical cancer at our institution were selected. This retrospective study was approved by our institutional review board. Since January 2023, we have used hyaluronic acid gel (MucoUp, Seikagaku Co., Tokyo, Japan) injected as a spacer into the rectovaginal and vesicouterine septum for patients without direct invasion to the rectum or bladder, guided by transrectal ultrasound, during each brachytherapy fraction. This procedure is known as hyaluronic acid gel injection (HGI). Unlike SpaceOAR, which remains in place for 2–3 months, MucoUp is absorbed within a few days (25). Therefore, it should be inserted in every brachytherapy procedure. However, while if SpaceOAR is inserted into the incorrect anatomical space, it would cause ulceration, because MucoUp is absorbed quickly, even if it is injected into a wrong anatomical space, it does not cause such severe adverse effects. A 5–10 mL volume of MucoUp was injected into the vesicouterine septum, and 10–30 mL of MucoUp was injected into the rectovaginal septum. A contrast-enhancement agent was injected into the hyaluronic acid gel to verify the location of the gel on the CT image. Ten consecutive patients who underwent HGI were selected. Ten consecutive cervical cancer patients before December 2022 who did not undergo HGI were also selected for assessing the CTV dose increase with gel spacers. The group that did not receive HGI was defined as a "conventional group."

Tandem/ovoid or vaginal cylinder applicators along with additional interstitial needles (IC/IS) were used to treat large or irregularly-shaped tumors. Planning CT images were acquired in the treatment room on Aquilion LB (Toshiba Medical Systems, Otawara, Japan). The treatment planning system used for brachytherapy was Oncentra version 4.6 (Elekta, Stockholm, Sweden). The bladder, rectum, sigmoid colon, small intestine, and CTV_{HR} were contoured by an experienced radiation oncologist. CTV_{HR} contouring was based on the Japanese Radiation Oncology Study Group guidelines (26). Figure 1 shows representative CT images of patients with and without HGI. Both patients in Fig. 1 were treated with tandem/ovoid and additional interstitial needles.

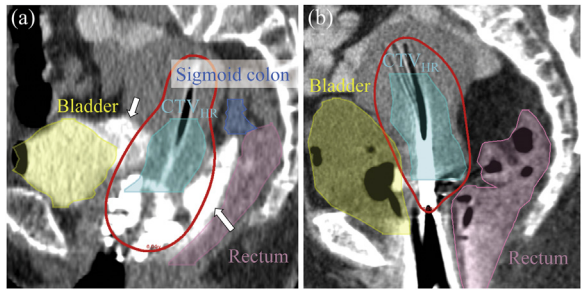

Fig. 1. Sagittal CT images of patients treated with tandem/ovoid applicators and extra needles with hyaluronic acid gel injection (HGI) (a) and without HGI (b). The prescription isodose line (6 Gy) is indicated in red. The dose distributions were those according to the treatment plan. The white arrow in (a) indicates the hyaluronate gel spacer.

The TG-43UI method was used to perform the dose calculations (27). In accordance with previous study (28), first, for the tandem/ovoid applicators, the prescription dose of 6 Gy was delivered at point A, whereas for the vaginal cylindrical applicator, the prescription dose of 6 Gy was delivered at a depth of 5 mm under the vaginal cylinder applicator. Next, the treatment plan was optimized to ensure that the CTV_{HR} was covered by the prescribed doses while reducing the dose to the OARs. HGI and treatment plan generation were performed on planning CT images for each session. The number of treatment fractions was determined by the radiation oncologist in three to four fractions. The basic number of brachytherapy fraction is four times. However, if it was possible to deliver an adequate high dose to the target volume while observing the dose constraints for OARs, the brachytherapy fraction was reduced to three times. In this way, the number of fractions is determined in current clinical practice.

The dosimetric evaluation was performed by summing the minimum dose delivered to 90% (D_{90}) of the CTV_{HR} (CTV_{HR} D_{90}) for each session with EBRT and the D_{2cc} of OARs. EBRT and brachytherapy doses were converted to biological equivalent dose in 2 Gy (EQD_2). For EQD_2 conversions, $\alpha/\beta = 10$ Gy was used for CTV_{HR}, and $\alpha/\beta = 3$ Gy was used for OARs. All patients underwent EBRT of the whole pelvis (45 Gy/25 fractions) without central shielding. For EBRT, four-field box three-dimensional conformal radiotherapy (3D-CRT) plans were generated. The following formula was used to calculate the EQD_2:

$$EQD_2 = D \times (d + \alpha/\beta)/(2 + \alpha/\beta) \quad (1)$$

where D is the total dose and d is the dose per fraction. High-dose rate brachytherapy was performed with an I-192 remote after-loading system (Microselectron v3, Elekta, Stockholm, Sweden). The 2020 ASTRO clinical practice guideline recommends CTV_{HR} D_{90} > 80 Gy (7). In addition, the GEC-ESTRO GYN working group recommends CTV_{HR} D_{90} > 85 Gy (6).

Table 1
Dose constraints for OARs and required doses for CTV_{HR} for each session of brachytherapy.

No. of fractions	Fractional dose constraint (D_{2cc}, Gy)			Fractional required CTV_{HR} D_{90} (Gy)	
	Rectum	Bladder	Sigmoid	EQD2 > 80 Gy	EQD2 > 85 Gy
4	4.48	5.45	4.48	6.50	7.13
3	5.35	6.47	5.35	7.96	8.71
2	6.82	8.21	6.82	10.48	11.42

In this study, the dosimetric evaluation was performed retrospectively using dose distributions approved by radiation oncologists. As a planning study, dose distributions for each fraction were rescaled in similarity within the dose constraints of the OARs. Table 1 shows dose constraints for CTV_{HR} D_{90} and OARs expressed in physical dose units for each IGABT session required for the total number of IGABTs to be completed within two, three, or four fractions while achieving a cumulative CTV_{HR} D_{90} > 80 Gy or > 85 Gy as well as observing dose constraints of OARs. For a virtual two- and three-fraction dose evaluation, dose distributions from the first to the second or third fractions of treatments were used. For the calculation of virtual four fractions, when the clinical treatment was ended up to three fractions, it was assumed that the patient was treated twice with the third dose distribution. The dose–volume histogram (DVH) parameters were acquired for the rescaled dose distributions in the HGI group and the conventional group.

Organs at risks and CTV_{HR} are assumed to be uniformly irradiated with 45 Gy/25 fractions in external beam radiotherapy. The dose constraints for OARs D_{2cc} in the dose summation are 80, 70, and 70 Gy for the bladder, rectum, and sigmoid colon, respectively.

Welch's two-sample t test was performed to assess differences in DVH parameters between the HGI group and the conventional group. All tests were two-sided, and p values of <0.05 were used to determine statistical significance. R version 4.2.2 software (R Foundation, Vienna, Austria) was used to perform statistical analysis.

Results

Table 2 shows the DVH parameters for the summation doses of the plans used in actual clinical practice. Patient characteristics and applicators used in clinical practices are also listed in Table 3. In brief, the median age of the HGI group was 67 (range: 44–79) and the conventional group was 53 (40–82). The T stages for the HGI group were 0 for T1, 7 for T2, and 3 for T3, and for the conventional group were 1 for T1, 7 for T2, and 2 for T3. There were no major differences in patient characteristics between the two groups.

The average CTV_{HR} volumes of first fractions were 51.8 (range: 16.5–90.0) mL and 47.2 (range: 19.8–103.0) mL in the HGI group and the conventional group, respectively.

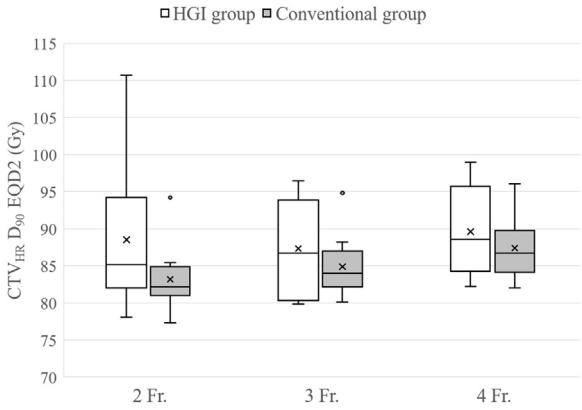

Fig. 2. Box plot of the high-risk clinical target volume D_{90} for each fraction number. The bottom and top of the box denote the 25th and 75th percentiles, respectively. The line inside the box shows the median, the crossmark shows the average, and the ends of the whiskers denote the maximum and minimum.

Figure 2 shows a box-and-whisker plot of CTV_{HR} D_{90} for each fraction number. The median CTV_{HR} D_{90} delivered in four fractions was 89.6 (range: 82.2–99.0) Gy for the HGI group and 87.4 (range: 82.0–96.0) Gy for the conventional group ($p = 0.36$). The median CTV_{HR} D_{90} was 86.7 (range: 79.8–96.4) Gy for the HGI group and 84.0 (range: 80.1–94.8) Gy for the conventional group for three fractions ($p = 0.35$), and 85.2 (range: 78.0–110.7) Gy for the HGI group and 82.2 (range: 77.3–94.2) Gy for the conventional group for two fractions ($p = 0.14$). The CTV_{HR} volumes and DVH parameters for the virtual 2, 3, and 4 fractions of CTV_{HR} and OARs are summarized in Table S1. The median of CTV_{HR} D_{90} was higher in the HGI group than in the conventional group for all fraction numbers. Even in the conventional group, the median CTV_{HR} D_{90} exceeded 85 Gy when given in four fractions. However, reducing the number of fractions resulted in insufficient dose delivery to CTV_{HR} D_{90}. In contrast, in the HGI group, the median CTV_{HR} D_{90} exceeded 85 Gy for all fraction numbers.

Figure 3 shows the box-and-whisker plot of the DVH parameters for each OAR in the case of three fractions. The median rectum D_{2cc} was 65.4 (range: 63.6–68.2) Gy in the HGI group and 68.7 (range: 66.9–69.6) Gy in the conventional group ($p < 0.01$). In addition, the median bladder D_{2cc} was 74.9 (range: 70.5–78.3) Gy in the HGI group and 73.9 (range: 60.9–77.0) Gy in the conventional group ($p = 0.25$), and the median sigmoid D_{2cc} was 59.5

Table 2
DVH parameters for CTV_{HR} and OARs for plans in clinical practice.

	Patient no.	Summation dose of clinical plans (EQD_2) (Gy)				No. of fraction
		CTV_{HR} D_{90}	Rectum D_{2cc}	Bladder D_{2cc}	Sigmoid D_{2cc}	
HGI group	1	80.0	64.2	73.1	54.3	3
	2	87.1	67.0	76.8	68.9	4
	3	81.8	64.9	72.5	51.5	3
	4	82.1	59.7	64.7	63.8	3
	5	79.8	62.5	72.8	58.0	3
	6	86.3	59.9	67.9	55.3	3
	7	85.0	69.6	79.3	66.6	4
	8	85.2	61.5	66.7	49.5	3
	9	84.5	60.7	68.5	57.3	3
	10	80.4	69.7	66.6	58.3	4
Conventional group	1	83.3	64.1	72.7	57.3	3
	2	82.5	68.3	75.0	63.2	3
	3	82.6	67.7	70.8	61.8	3
	4	86.3	63.7	70.7	61.7	3
	5	80.9	69.8	75.6	59.1	3
	6	83.3	69.6	68.8	61.5	3
	7	83.6	67.3	70.8	59.3	3
	8	81.8	67.9	70.6	61.9	3
	9	81.8	66.2	74.3	63.9	3
	10	80.6	67.5	72.9	60.8	3

HGI = hyaluronic acid gel injection.

Table 3
Patient and treatment characteristics.

	Patient ID	Tumor histology	TNM	Age	Applicator	No. of needles
HGI group	1	Adenocarcinoma	T3aN0M0	66	Cylinder	2
	2	Adenocarcinoma	T2bN0M0	75	Cylinder	3
	3	SCC	T2bN0M0	79	Tandem/Ovoid	1
	4	SCC	T2bN1M0	78	Tandem/Ovoid	2
	5	SCC	T2bN1M0	78	Cylinder	2
	6	SCC	T2bN1M0	56	Tandem/Ovoid	1
	7	Adenocarcinoma	T3bN1M0	61	Cylinder	2
	8	SCC	T2bN0M0	64	Tandem/Ovoid	1
	9	SCC	T2bN1M0	44	Tandem/Ovoid	2
	10	SCC	T3abN1M0	67	Cylinder	2
Conventional group	1	Adenocarcinoma	T2bN0M0	82	Tandem/Ovoid	4
	2	Adenocarcinoma	T2bN0M0	54	Tandem/Ovoid	6
	3	SCC	T3aN1M0	44	Tandem	8
	4	Adenocarcinoma	T2bN0M0	51	Ovoid	3
	5	Adenocarcinoma	T1bN0M0	51	Tandem/Ovoid	2
	6	Adenocarcinoma	T2bN1M0	40	Tandem/Ovoid	2
	7	SCC	T2bN1M0	62	Ovoid	3
	8	SCC	T2bN1M0	81	Tandem/Ovoid	4
	9	SCC	T2bN0M0	58	Ovoid	3
	10	SCC	T3aN1M1	51	Tandem	6

SCC = squamous cell carcinoma; HGI = hyaluronic acid gel injection.

(range: 51.8–68.7) Gy in the HGI group and 61.9 (range: 59.1–65.6) Gy in the conventional group ($p = 0.12$). Although not shown in the manuscript, the DVH parameters of the OAR at virtual two and four fractions are shown in Fig. S1. HGI significantly reduced the rectum dose while maintaining the CTV_{HR} D_{90} doses at a high level. The main limiting factor for dose escalation was the rectum D_{2cc} in the conventional group (Fig. 3) and was the bladder D_{2cc} in the HGI group. In some cases, the sigmoid colon D_{2cc} was the limiting factor for dose escalation in both the HGI group and the conventional group.

Discussion

This study demonstrates the feasibility of HGI of the rectovaginal and vesicoureteral septum in brachytherapy for cervical cancer, which can help reduce the number of fractions while achieving the dose constraints of OAR.

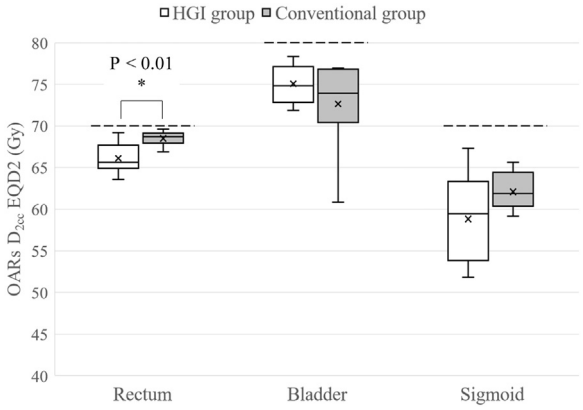

Fig. 3. Box plot of the D_{2cc} values of the rectum, bladder, and sigmoid for three fractions. The bottom and top of the box denote the 25th and 75th percentiles, respectively. The line inside the box shows the median, the cross mark shows the average, and the ends of the whiskers denote the maximum and minimum. The black dashed line indicates the dose constraints of each OAR (accumulated EQD_2 values of the rectum, bladder, and sigmoid; 70, 80, and 70 Gy, respectively). Asterisks indicate a statistically significant difference ($p < 0.05$).

Kobayashi et al. (20) investigated whether the use of HGI in the rectovaginal and vesicouterine septum can increase the dose to CTV_{HR} without increasing the dose to OARs. Their findings were consistent with those of our study, which indicates that the use of gel spacers in cervical cancer brachytherapy is an important technique that contributes significantly to safe radiation therapy. Murakami et al. (21) also found that a gel spacer was useful in reducing late radiation-related toxicity.

In addition, we found that dose delivery to CTV_{HR} could be achieved even with a reduced number of IGABT fractions when HGI was performed. In the conventional group, the median in CTV_{HR} D_{90} exceeded 85 Gy when treated with four fractions, but it was not possible to achieve the same level of safe dose delivery with two or three fractions. However, in the HGI group, the median CTV_{HR} D_{90} was >85 Gy even in two and three fractions. When adequate distance is created by HGI and dose escalation to the CTV_{HR} is possible, further reduction of the IGABT fraction down to two could have been accomplished by referring to Table 1. With the COVID-19 pandemic, there has been a need to reduce the number of patient visits to hospitals or treatment centers to minimize the risk of exposure to the virus. In this context, reducing the number of brachytherapy fractions can help to reduce the treatment time and therefore the number of hospital visits for patients while still achieving the required dose delivery to CTV_{HR}. Chopra et al. (29) also recommend reducing the treatment time during the COVID-19 pandemic. After the COVID-19 pandemic, radiotherapy, including EBRT, is expected to move toward shorter fraction numbers in the future. Menon et al. (30) reported the latest brachytherapy dose prescription for locally advanced cervical cancer in Canada. The survey results showed that 7 Gy × four fractions was the most common regimen followed by 8 Gy × three fractions. Moreover, a shorter total treatment time has been known as a favorable prognostic factor in cancer treatment (31). Pain management is also an important aspect of patient care during brachytherapy. While sedation and analgesia can help alleviate discomfort, reducing the number of fractions can help improve patient experience and satisfaction. HGI is expected to be a technique that safely reduces the number of fractions in brachytherapy. As shown in Fig. 2, even with two fractions, the HGI group delivered 85 Gy to CTV_{HR} D_{90}. This result suggests that two fractions of IGABT with HGI could be a treatment option depending on a future infection pandemic or patient request. When treated in four fractions, tumor shrinkage over the course of treatment is expected to lead to a reduction in the doses of OARs in the latter part of treatment. Adequate distance between CTV_{HR} and OARs using HGI is important because such tumor shrinkage over the treatment period cannot be expected by shortening the treatment period by reducing brachytherapy fractions. The decision to use HGI and reduce the fraction number should always be made by a qualified radiation oncologist in consultation with the patient. While a recent study has reported outcomes with three fractions (32) and such three fractions of brachytherapy is even commonly used as standard of care in some countries. However, two fractions of brachytherapy is seldom practiced as a standard practice. As in stereotactic body radiation therapy, it is theoretically acceptable to further reduce the brachytherapy fraction if doses to the OARs surrounding the target volume are within the recommended dose constraints. Obviously, it is important to approach the clinical application of reduced fraction numbers with caution. Further research, including clinical trials, is needed to validate the safety and efficacy of this approach in larger patient populations.

When CTV_{HR} D_{90} exceeds 85 Gy, it means that the dose requirement for CTV_{HR} has been achieved and further dose escalation is no longer unnecessary, as demonstrated by >90% local control regardless of T-stage in the EMBRACE-I study (33). In such patients, the OAR dose could be even lower than that shown in Fig. 3 because the dose-optimization process would prioritize reducing the OARs doses while keeping the CTV_{HR} dose above the recommended threshold. In the 2020 ASTRO clinical practice guideline, the recommended D_{2cc} in the rectum is 65–75 Gy (7). Figure 3 shows that the rectum dose was significantly lower in the HGI group than in the conventional group, even when the CTV_{HR} dose was increased.

As shown in Fig. 3, in the HGI group, the rectum dose was greatly decreased by the gel spacer, allowing the CTV_{HR} dose to increase up to the tolerable bladder dose. As shown in Fig. 3, the bladder D_{2cc} was the limiting factor for dose escalation in the HGI group, suggesting that vesicovaginal spacing was ineffective. We previously reported that HGI into the vesicovaginal septum reduced the bladder dose using another hyaluronic acid agent, Suvenyl, whose

molecular weight ranges from 1500 to 3900 kDa. However, because it was announced that the pharmaceutical company would discontinue the production of Suvenyl, we regrettably chose to use MucoUp, whose molecular weight is 500 to 1200 kDa. As a result, it is true that the thickness of MucoUp is somewhat thinner than Suvenyl (25). Therefore, if we had a better material that could be used for gynecologic brachytherapy spacers, we would like to switch to it in the future. However, in this study, the CTV_{HR} D_{90} did not reach 85 Gy in a few cases because of dose limitations in the sigmoid, not the bladder or rectum. Gel spacers can be inserted only in the rectovaginal or vesicouterine septum. When the sigmoid is close to the CTV_{HR}, dose increases were difficult to achieve, even in the HGI group. However, in most cases, the dose constraints of the rectum and bladder were the factors limiting an increase in the CTV_{HR} dose, and HGI was used to minimize the dose to these organs while still achieving the recommended CTV_{HR} dose. These findings indicated that HGI is a useful technique for cervical cancer brachytherapy. Karube et al. (34) reported that artificial ascites infusion allowed a reduction of the sigmoidal dose by increasing the distance between the target and the sigmoid. In the future, further study will be required to combine HGI and artificial ascites infusion to reduce the fraction number more safely.

A limitation of this study is that it was a single-center retrospective planning study. It would have been better if we collected more patients with HGI and used specific statistical techniques such as propensity score matching to further minimize the potential selection bias between the HGI group and the conventional group. However, because it was only a preliminary study and we only had ten patients with HGI at this moment, therefore, we selected 10 consecutive patients in the conventional group to minimize the selection bias and tried to avoid arbitrariness as much as possible. Although MRI-based IGABT is the basic core concept of original IGABT for uterine cervical cancer (1), and the results of the EMBRACE-I study are also based on MRI-based IGABT, due to logistical issues, MRI-based IGABT is not widely available internationally, where the majority of cervical cancer cases occur, and CT-based IGABT is also recognized as an acceptable alternative to IGABT (35). However, it has been previously reported that there can be discrepancies between the MRI-based and CT-based CTV_{HR} delineation, particularly in the lateral direction (36), and our results are based on CT-based IGABT; therefore, caution should be exercised when interpreting the results of this study. Technique and experience can vary among radiation oncologists, resulting in potential variability in gel spacer and needle insertion. In order to comprehensively assess the safety and efficacy of combining high-grade interstitial techniques with a gel spacer in reduced-fraction brachytherapy, it is imperative to conduct further prospective clinical studies. These studies should encompass multiple institutions to enhance the generalizability of the findings and provide a broader understanding of the benefits and potential risks associated with this combined approach. Through such studies, valuable insights can be gained regarding the optimal utilization of high-grade interstitial techniques and gel spacers in the context of reduced-fraction brachytherapy, ultimately contributing to improved treatment outcomes for patients. Because of the limited number of patients in this study, it was not feasible to categorize patients based on applicator type, tumor volume, and other relevant factors. In our forthcoming study, we want to assess the efficacy of MucoUp through the examination of its applicator functionality and its impact on tumor volume.

Conclusions

The findings of this study highlight two important observations within the field of cervical cancer brachytherapy. The use of HGI in the rectovaginal and vesicouterine sept can be expected to safely deliver dose to the CTV_{HR} while maintaining the dose constraints in OARs. This result highlights the safety and feasibility of this technique. Additionally, this study suggests that HGI may be a safe and effective approach by widening the therapeutic window to reduce the number of fractions in cervical cancer brachytherapy.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.brachy.2023.10.003.

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