Original paper

A cold spot compensation technique using a combination of trans-rectal ultrasonography and intraoperative computed tomography for interstitial permanent prostate brachytherapy: a single-arm prospective trial

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Abstract

Purpose: To evaluate the efficacy of a cold spot compensation technique using a combination of trans-rectal ultrasonography (TRUS) and computed tomography (CT) for permanent interstitial prostate brachytherapy.

Material and methods: Sixty-five patients were treated with the cold spot compensation technique using TRUS-CT fusion. The prescribed dose was set at 145 Gy. The dose to 90% of prostate volume (D_{90}) was planned to be within 195 Gy (134%) and 205 Gy (141%). After implantation using the conventional technique, additional seeds were implanted if cold spots were detected on TRUS-CT fusion images.

Results: Cold spots were detected in 32 of 65 patients (49%) and were compensated by additional seeds. Median number of additional seeds was 3 (range, 1-5). A CT scan 1 month later revealed that the percentage of patients receiving an undesirably low D_{90} (160-180 Gy) was significantly reduced in the examination arm compared to historical controls. However, mean operation time was significantly longer in the examination arm (64 min) than in historical controls (49 min, $p < 0.001$). With median follow-up of 18 months (range, 9-24 months), no grade 3 or worse toxicity was encountered.

Conclusion: The cold spot compensation technique using TRUS-CT fusion appears effective for patients receiving permanent interstitial prostate brachytherapy.

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Key words: brachytherapy, low-dose-rate, intraoperative CT, O-arm system, prostate cancer.

Purpose

Trans-rectal ultrasonography (TRUS) is the standard imaging tool for interstitial prostate brachytherapy [1]. However, ultrasound is well known to be unsuitable for imaging implanted seeds, with computed tomography (CT) representing the standard for detecting seed positions and calculating post-implant dose-volume histograms (DVHs) [2,3].

The O-arm® surgical imaging system (Medtronic, Dublin, Ireland) was developed to provide real-time, intraoperative CT imaging with a large field-of-view. This system permits patients to remain in the lithotomy position even during image acquisition, because the bore diameter of this system (965 mm) is significantly larger than that of conventional CT systems (700-800 mm).

We combined TRUS with O-arm-based CT during surgery as a new strategy for intraoperative dosimetric evaluation. With this fusion dosimetry, we can compensate for the shortcomings of each modality, because accurate seed positions can be detected on CT, while accurate contours can be delineated by TRUS. Moreover, highly matched fusion images can be expected because of the removal of differences in patient and probe positions between the two modalities [4]. With this fusion dosimetry, we can check for the presence of cold spots and compensate with additional seeds during surgery.

The purpose of this prospective trial was to evaluate the efficacy of the cold spot compensation technique in interstitial prostate brachytherapy.

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Material and methods

Patients

The institutional review board approved this single-arm prospective study (C15-911). Eligible participants were all adults ≥ 20 years old with localized prostate cancer without lymph node or distant metastases. Exclusion criteria were no indications for anesthesia, refusal to participate, or a need for additional external radiation therapy.

A total of 89 patients were assessed as eligible between November 2015 and July 2016. Twenty-four patients were excluded because they declined to participate (n = 4), did not meet the criteria (n = 13), had excess height or weight (n = 2), and other reasons (n = 5). As a result, 65 patients were treated using the cold spot compensation technique following TRUS-CT fusion. In addition, data from 100 consecutive patients treated by conventional techniques using only TRUS just before the start of this study (from October 2014 to November 2015) were collected as historical controls. Patient characteristics are shown in Table 1.

Seed implantation and image fusion technique

We have previously reported the details of our fusion technique for TRUS and O-arm-based CT [4]. Briefly, patients were placed in the lithotomy position inside the O-arm system. TRUS images of the whole prostate gland were acquired using a biplane transrectal ultrasound probe (HI VISION Preirus, Hitachi Aloka Medical, Tokyo, Japan). Treatment plans were developed on TRUS images using Variseed version 8.0.2 software (Varian Medical Systems, Palo Alto, CA). The prescribed dose to the prostate with a 3- to 5-mm margin was set as 145 Gy. Table 2 shows dosimetric parameters for the planning phase. Both loose-seed and intraoperatively built custom-linked (IBCL) seeds were used for patients in this study. Loose seeds were placed one by one transperineally through needles attached to a Mick applicator (Mick Radio-Nuclear Instrument, Mount Vernon, NY, USA). IBCL seeds were connected to each other using the quick-link system (CR BARD, Murray Hill, NJ, USA) and inserted through a relay system [5]. No dosimetric difference has been reported between loose seeds and IBCL seeds [6]. Two types of ^{125}I source were used: either OncoSeed® model 6711 (GE Healthcare [Medi-Physics], Arlington Heights, IL, USA), or BrachySource® model STM125I (CR BARD, Murray Hill, NJ, USA). Source activities were 11.0 MBq or 13.1 MBq.

Following seed implantation, CT images were acquired using the O-arm system at 120 kV, 50 mA, and 200 mAs. Acquired CT images were transferred to the Variseed software. The end-fire probe was used as a landmark to fuse TRUS and O-arm-based CT images, due to clear recognition in both modalities. After image fusion, contours of

Table 1. Patient characteristics

Factor	Examination arm (n = 65)		Historical control (n = 100)		p
Age (y)	69	(7.3)	70	(7.4)	ns
T stage					ns
1c	24	(36.9%)	47	(47.0%)	
2a	25	(38.5%)	24	(24.0%)	
2b	8	(12.3%)	13	(13.0%)	
2c	8	(12.3%)	16	(16.0%)	
iPSA (ng/ml)	7.6	(2.1)	7.7	(3.1)	ns
Gleason score					ns
3 + 3	13	(20.0%)	29	(29.0%)	
3 + 4	21	(32.3%)	38	(38.0%)	
4 + 3	23	(35.4%)	27	(27.0%)	
4 + 4	7	(10.8%)	6	(6.0%)	
4 + 5	1	(1.5%)	0	(0.0%)	
Hormone therapy					ns
Yes	12	(18.5%)	23	(23.0%)	
No	53	(81.5%)	76	(76.0%)	
Number of sources	81.22	(14.6)	81.99	(14.6)	ns
Source activity (mCi)	0.338	(0.021)	0.341	(0.016)	ns

Values are means (standard deviation) or number (percentage).
iPSA – initial prostate-specific antigen, ns – not significant

Table 2. Dosimetric parameters for planning phase

Factor	Predetermined parameters	Examination arm		Historical control		*p*
Prescribed dose (Gy)	145	145		145		
D_{90} (Gy)	195-205	199.8	3.5	199.9	4.7	ns
V_{100} (%)	> 95	99.7	0.4	99.8	0.4	ns
V_{150} (%)	As low as possible	76.2	3.2	76.9	3.8	ns
UD_{90} (Gy)	> 160	174.5	12.2	175.8	15.9	ns
UD_{30} (Gy)	As low as possible	205.2	4.7	204.7	7.4	ns
RV_{100} (ml)	< 1	0.61	0.33	0.51	0.32	ns

D_{90} – dose to 90% of prostate volume, V_{100} – prostate volume receiving at least 100% of prescription dose, V_{150} – prostate volume receiving at least 150% of prescription dose, UD_{90} – dose to 90% of urethral volume, UD_{30} – dose to 30% of urethral volume, RV_{100} – rectal volume receiving at least 100% of prescription dose, ns – not significant

the prostate, urethra, and rectal wall were copied from TRUS to CT images. The same contours were thus available on both modalities.

Additional seed implantation for cold spots

The software automatically detected seed position on TRUS-CT fusion images. The quality of detection, however, is not perfect, perhaps due to the low contrast resolution of O-arm-based CT images. Manual correction of automatically recognized seed positions was needed for all patients. Both a radiation oncologist and a urologist, reviewed dosimetry on TRUS-CT fusion images and checked for the presence of cold spots. If cold spots were found, additional seeds were implanted under TRUS monitoring according to planned positions on TRUS-CT fusion images (Figure 1). As our previous study suggested that a dose to 90% of prostate volume (D_{90}) of 155 Gy on fusion images can be used as a surrogate for D_{90} > 170 Gy on 1-month follow-up CT analysis, we tried to reach around 155 Gy in the balance between urethral and rectal doses [4]. Parameters of D_{90} > 170 Gy (preferably > 180 Gy), V_{100} > 95%, V_{150} < 65%, and RV_{100} < 1 cc on 1-month CT were defined as the reference for "good quality implant" in this study, although there is no validated definition.

DVH analysis

DVHs were calculated from TRUS images, TRUS-CT fusion images, and 1-month CT images. Urethral contouring was based on the outer rim of the urethral catheter, except for 1-month CT, in which the center of the prostate was used as a surrogate for urethral position. The rectal wall including sphincter muscle was fully contoured on 1-month CT images, but only the anterior one-third excluding the lumen (body of the TRUS probe) was contoured on TRUS and TRUS-CT fusion. The urethra and rectum were contoured in the same slices as the prostate contour.

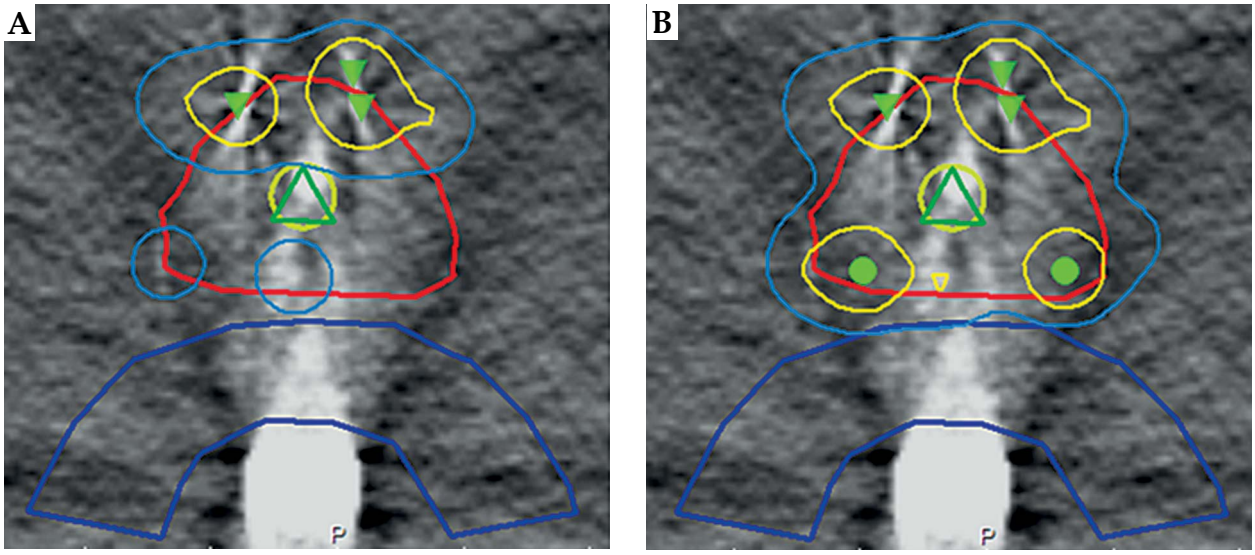

Fig. 1. Representative case of cold spot compensation. A significant cold area in the posterior apex of the prostate is evident in a trans-rectal ultrasonography–computed tomography (TRUS-CT) fusion image **(A)**. Two additional seeds were planned to cover this cold spot in the TRUS-CT image. Red line – prostate, dark blue line – anterior rectal wall, yellow circle with green triangle – Foley catheter, light blue line – 145 Gy, yellow line – 217.5 Gy

DVH parameters including D_{90}, prostate volume receiving at least 100% dose (V_{100}), prostate volume receiving at least 150% dose (V_{150}), dose to 90% of urethral volume (UD_{90}), dose to 30% of urethral volume (UD_{30}), rectal volume receiving at least 100% dose (RV_{100}), and rectal volume receiving at least 150% dose (RV_{150}) were collected from TRUS, TRUS-CT fusion, and 1-month CT.

Urinary and rectal morbidity were assessed using the Radiation Therapy Oncology Group (RTOG) scale and the National Cancer Institute Common Terminology Criteria (NCI-CTC), version 4.

Statistical analysis

Statistical analyses were performed using R version 3.2.0 software (R Foundation, Vienna, Austria). Fisher's exact test and independent t-test were used for comparisons of the examination arm and historical controls.

Table 3. Change of dose-volume histogram (DVH) parameters before and after compensation on trans-rectal ultrasonography–computed tomography (TRUS-CT) fusion images

Factor		Mean	SD	Minimum	Maximum	*p*
D_{90} (Gy)	Before	149.5	13.8	114.9	167.2	< 0.01
	After	164.3	7.0	150.5	177.2	
V_{100} (%)	Before	91.3	4.0	82.3	97.2	< 0.01
	After	96.0	1.9	91.6	99.3	
V_{150} (%)	Before	46.1	8.6	32.3	64.1	< 0.01
	After	50.0	8.1	36.5	66.0	
UD_{90} (Gy)	Before	126.3	16.5	82.0	156.2	< 0.01
	After	139.0	12.4	113.4	161.8	
UD_{30} (Gy)	Before	176.4	14.1	153.8	214.9	< 0.01
	After	181.5	12.8	160.1	216.5	
RV_{100} (ml)	Before	0.6	0.6	0.0	2.1	< 0.01
	After	0.7	0.6	0.0	2.2	

Abbreviations are the same as in Table 2

Table 4. Comparison between O-arm and conventional groups regarding post-implant computed tomography analysis

Factor		Mean	SD	Minimum	Maximum	*p*
D_{90} (Gy)	Historical control	183.2	17.5	128.7	222.8	< 0.05
	Examination arm	189.6	20.2	139.2	243.8	
V_{100} (%)	Historical control	97.7	2.6	86.4	100.0	ns
	Examination arm	98.1	2.2	88.6	100.0	
V_{150} (%)	Historical control	69.5	12.2	39.6	91.4	< 0.05
	Examination arm	74.2	11.7	46.9	95.5	
UD_{90} (Gy)	Historical control	167.0	21.3	107.8	218.7	ns
	Examination arm	169.1	23.0	123.4	221.3	
UD_{30} (Gy)	Historical control	211.3	19.3	165.3	257.9	< 0.01
	Examination arm	225.4	22.5	174.2	291.8	
RV_{100} (ml)	Historical control	0.9	1.0	0.0	7.3	ns
	Examination arm	1.0	0.8	0.0	3.4	
Prostate volume (ml)	Historical control	28.6	7.9	12.2	47.3	ns
	Examination arm	26.9	7.8	9.5	47.5	
Urethral volume (ml)	Historical control	0.4	0.1	0.3	0.5	ns
	Examination arm	0.4	0.1	0.2	0.5	
Rectal volume (ml)	Historical control	24.7	9.6	10.1	62.7	ns
	Examination arm	26.2	12.5	11.6	78.0	

Abbreviations are the same as in Table 2

Results

After reviewing TRUS-CT fusion images, cold spots were detected in 32 of 65 patients (49%) and were subsequently compensated with additional seeds. Median number of additional seeds was 3 (range, 1-5). Table 3 shows changes in DVH parameters on TRUS-CT fusion images of the 32 patients before and after compensation.

When the examination arm was compared to historical controls, no significant difference in patient characteristics or planning parameters were seen between groups (Tables 1 and 2). Meanwhile, 1-month CT analysis revealed significant differences between the two groups in D_{90}, V_{150}, and UD_{30} (Table 4). Table 5 shows a comparison of percentages of patients with good quality implant between groups. The percentage of patients receiving a D_{90} over 180 Gy was significantly increased in the examination arm. Figure 2 shows a comparison of histograms for each DVH parameter between groups. Histograms basically showed a rightward-shift from the historical control group to the examination arm group. The percentage of patients receiving a D_{90} of 160-180 Gy was significantly reduced in the examination arm (19%) compared with the control arm (35%), although no significant differences in patients in other dose ranges were identified. Likewise, the percentage of patients receiving a UD_{30} of 175-200 Gy

Table 5. Percentages of patients with good quality dosimetry on post-implant computed tomography analysis 1 month after implantation

	Reference parameters	Examination arm		Historical control		*p*
		n	%	*n*	%	
D_{90} (Gy)	> 170	54.0	83	75.0	75	ns
	> 180	47.0	72	56.0	56	< 0.05
V_{100} (%)	> 95	58.0	89	87.0	87	ns
V_{150} (%)	< 65	13.0	20	32.0	32	ns
UD_{90} (Gy)	> 160	25.0	38	36.0	36	ns
UD_{30} (Gy)	As low as possible	na		na		
RV_{100} (ml)	< 1	38.00	58	66.00	66	ns

Abbreviations are the same as in Table 2

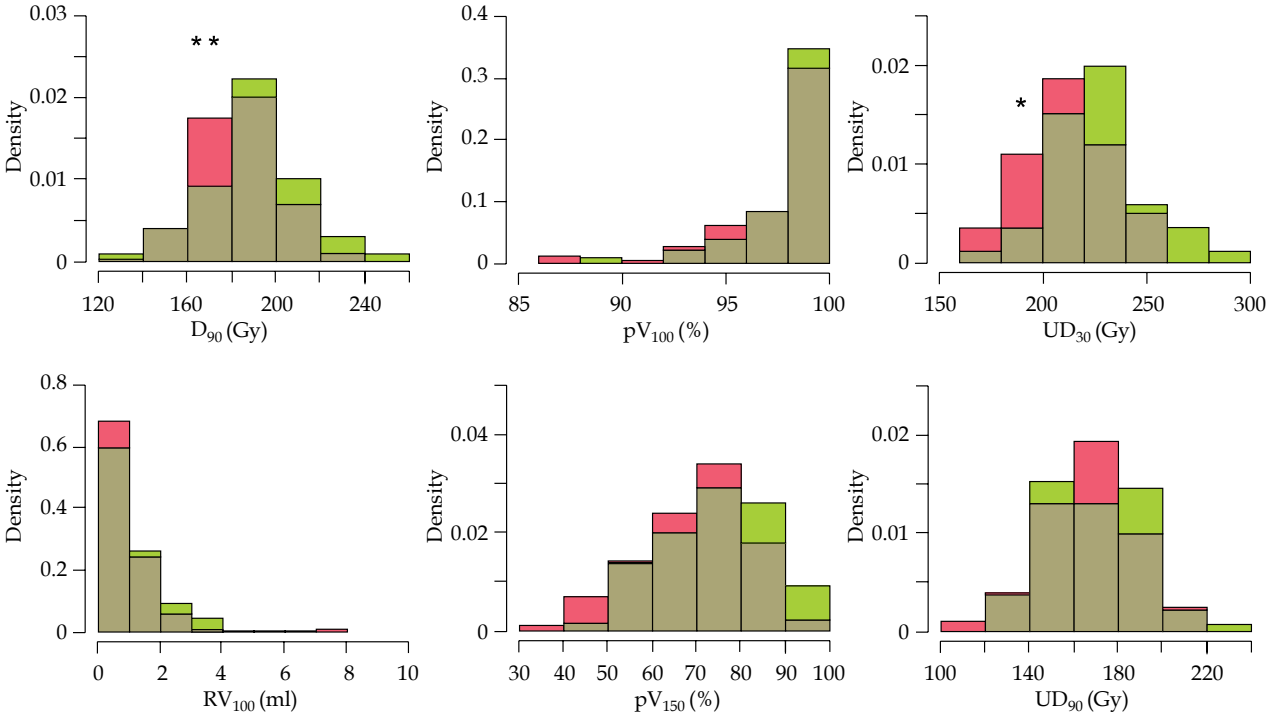

Fig. 2. Comparison of histograms for dose-volume histogram parameters between the examination arm and historical controls. Histograms show a mild right-shift from historical controls (red) to the examination arm (green). Percentages of patients receiving a D_{90} of 160-180 Gy and a UD_{30} of 175-200 Gy are significantly reduced in the examination arm. $^{**}p = 0.023$, $^{*}p = 0.032$

Table 6. Crude toxicity rate of examination arm and historical control

	Grade	Examination arm		Control		*p*
		n	%	*n*	%	
RTOG GU	1	44	68	69	69	ns
	2	8	12	16	16	
RTOG GI	1	14	22	24	24	ns
	2	1	2	0	0	
Miction pain	1	19	29	29	29	ns
	2	0	0	0	0	
Proctitis	1	11	17	17	17	ns
	2	0	0	0	0	
Incontinence (stool)	1	0	0	1	1	ns
	2	0	0	0	0	
Diarrhea	1	1	2	4	4	ns
	2	0	0	0	0	
Rectal bleeding	1	5	8	11	11	ns
	2	1	2	0	0	
Frequency	1	29	45	64	64	< 0.05
	2	6	9	12	12	
Incontinence (urine)	1	0	0	0	0	ns
	2	1	2	0	0	
Urinary retention	1	28	43	44	44	ns
	2	2	3	6	6	
Hematuria	1	4	6	1	1	ns
	2	0	0	0	0	
Stricture	1	0	0	0	0	ns
	2	0	0	0	0	

RTOG – Radiation Therapy Oncology Group, GU – genitourinary, GI – gastrointestinal, ns – not significant

was significantly reduced in the examination arm (7%) compared with the control arm (28%).

However, mean operation time (from first needle insertion to end of operation) was significantly longer in the examination arm (64 min) than in historical controls (49 min, $p < 0.001$).

Table 6 shows acute toxicity until 12 months after treatment in the examination arm and historical controls. With a median follow-up of 18 months (range, 9-24 months) for the examination arm and of 19 months (range, 6-32 months) for historical controls, no significant difference was evident between groups except for urinary frequency. No instances of grade 3 or worse toxicity were encountered. Biochemical failure was seen in no patients from the examination arm and in 4 historical controls.

Discussion

By compensating for cold spots during surgery, a significant percentage of patients were salvaged from poor dosimetry on 1-month CT analysis. Our system enables checking for the presence of cold spots during surgery and permits implantation of additional seeds without second anesthesia. We believe that this system is useful not only for experts, but also for beginners lacking experience in brachytherapy, providing an extra margin of safety for favorable dosimetry.

Adaptive planning for interstitial permanent prostate brachytherapy using intraoperative CT was already reported from the Netherlands in 2007 [7]. The same group recently reported not only improvement of dosimetric results [8], but also of biochemical control with their technique from a large database of over 1,600 patients [9]. Their surprising improvement in clinical results (28% increase in 7-year biochemical control for high-risk patients) encouraged us to continue with this technique and to promote its spread to other hospitals.

As shown in Figure 2, however, patients with a low D_{90} did not disappear with our technique. One of the shortcomings of our technique is the lack of a method for adapting to changes in prostate volume. Although prostate volume usually decreases from the intraoperative phase to 1-month CT, some patients inversely show an increase, or no change compared to the intraoperative phase. These patients inevitably show a low D_{90} on 1-month CT because we set dosimetric parameters in the

planning phase on the assumption that prostate volume would decrease by 1 month after treatment [4]. In addition, prostate contours might be ambiguous in some patients and contouring errors might have some effects on 1-month CT analysis [4].

The other key shortcoming of our technique was operation time. Our software takes a long time to recognize implanted seed positions from TRUS-CT fusion images. Furthermore, the quality of recognition is imperfect and manual correction is needed for all patients. Operation time was thus extended by 15 min compared to historical controls. However, we believe this represents an acceptable cost, considering the utility of cold spot compensation.

One of the strong points of our technique is highly matched fusion of TRUS and CT images, due to the identical patient and probe positions. In reports on the utility of intraoperative CT from other institutions [8,9,10,11], positions of patients and probes changed from operation to intraoperative CT acquisition. This can result in significant changes to prostate shape [12,13]. The positions of the legs also seem certain to have some effect on prostate shape. Although these differences may seem small, such small differences might cause large differences in the results of brachytherapy because of the very sharp dose gradient. The bore size of the O-arm system may be problematic for American or European individuals, who are relatively taller than Japanese population. Although most of our patients could remain in the lithotomy position, two patients taller than 190 cm or weighing over 137 kg could not undergo O-arm CT due to positioning difficulties.

Toxicity was acceptable with our compensation technique. The crude rate of urinary frequency was lower in the examination arm than in historical controls. Although the reasons for this were not clear, the short follow-up of the examination arm might have underestimated urinary frequency.

Conclusions

This prospective study showed that our cold spot compensation technique can salvage a significant percentage of patients from poor dosimetry with acceptable toxicity and operation time.

Disclosure

Authors declare no conflict of interest. Dr. Ishiyama reports personal fees from Medicon, Inc., personal fees from Nihon Medi-Physics Co., Ltd., outside the submitted work.

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