Original paper

Subdermal injection of hyaluronic acid to decrease skin toxicity from radiation delivered with low-dose-rate brachytherapy for cancer patients

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Abstract

Purpose: To study the feasibility of hyaluronic acid (HA) injection to increase the distance between skin and radioactive sources, and dose reduction of skin during low-dose-rate (LDR) brachytherapy.

Material and methods: A total of 11 patients with subdermal malignant tumors were enrolled in this study. HA was injected after I-125 seed implantation, and dosimetric parameters were calculated by a brachytherapy treatment planning system (BTPS). The distance of the new space between radioactive sources and skin was measured on computed tomography (CT) and magnetic resonance imaging (MRI). Clinical signs were observed and followed up for every patient.

Results: After HA injection, the average of newly generated maximum distance was 1.0 cm along the entire length of the tumor. The D_{90} and V_{100} did not significantly change for tumors before or after injection ($p = 0.39$, $p = 0.50$, respectively). The maximum dose to a relatively small volume (0.1 cc) of the skin (OAR-Max) decreased from 100.66 Gy to 61.20 Gy ($p < 0.05$), and the mean skin dose (OAR-Mean) decreased from 49.20 Gy to 17.27 Gy ($p < 0.05$) after injection. On follow-up CT and MRI, HA was quite stable in shape and position for nearly 6 months.

Conclusions: Our study results showed that an additional 1.0 cm distance between the radioactive source and skin could be induced by HA injection in patients with subdermal tumor, and this distance could significantly decrease the skin dose in LDR brachytherapy. In addition, no obvious toxicity and side effects were produced by HA injection. Therefore, hyaluronic acid injection is a safe and effective technique.

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Key words: hyaluronic acid, low-dose-rate brachytherapy, subdermal malignant tumor.

Purpose

Percutaneous computer tomography (CT)-guided brachytherapy using permanent implants of I-125 seeds has been recently proposed as an effective treatment strategy for many malignant tumors such as prostate cancers [1,2] and nasopharyngeal carcinomas [3]. Compared with external beam radiation therapy (EBRT), brachytherapy has the ability to deliver a higher dose of irradiation to the tumor target while sparing normal tissues adjacent to the tumor lesion [4,5]. For low-dose-rate brachytherapy, the organs at risk (OARs) are the adjacent organs. To decrease the toxicity to the OARs from radiation delivered with brachytherapy, previous studies injected hyaluronic acid (HA) into the anterior perirectal fat of prostate cancer patients to decrease the dose to the rectum [6,7]. HA is also already used as a protective agent for at-risk organs in high-dose-rate brachytherapy [8,9]. In this study, we chose patients with a subcutaneous metastatic tumor, whose skin was the organ at risk. Hyaluronic acid was percutaneously injected into the right position after I-125 implantation, in order to increase the distance between the skin and the radioactive source. Finally, dosimetry of target volume and skin were evaluated before and after HA injection. Complications associated with the procedure, dermal toxicity, and the stability of HA were followed up. The purpose of this study was to investigate the feasibility to increase the distance between the skin and the radioactive source by HA injection, and to reduce the dose to the skin during low-dose-rate (LDR) treatment.

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Material and methods

Patients

Between August and December 2017, a total of 11 patients with a subdermal malignant tumor were enrolled. The enrollment criteria were as follows: histologically confirmed malignant tumor, subdermal malignant tumor visible on CT or magnetic resonance imaging (MRI), leukocyte count of 3.5×10^9 cells/l or higher, red blood cell count of 3.0×10^{12} cells/l or higher, platelet count of 80×10^9 cells/l or higher in peripheral blood, the partial thromboplastin time less than 50 s, the liver and kidney function within the normal range, the Karnofsky physical scores of ≥ 60.

The patient characteristics are shown in Table 1. The 11 patients comprised of 10 males and 1 female, with median age of 61 (range, 51-78). The cases included the following primary cancer sites: lung cancer – 5 cases, gastric cancer – 1 case, mesothelioma – 1 case, lymphoma – 2 cases, melanoma – 1 case, and 1 case of unknown cancer. The locations for I-125 implantation were the chest wall for 4 cases, the neck for 3 cases, the back for 1 case, the abdominal wall for 1 case, the arm for 1 case, and the groin for 1 case. All patients received combined treatment with chemotherapy and no radiotherapy.

The study was approved by the Ethics Committee of Shandong University School of Medicine, and written informed consent was obtained from all patients.

I-125 brachytherapy

I-125 seeds that were used in the procedures were produced by HTA Co., Ltd. in Beijing, China. Each I-125 seed was a single source, which was 4.5 mm long and 0.8 mm in diameter, and its radioactivity was $2.2\text{-}2.96 \times 10^7$ Bq. The prescription dose was 100-120 Gy. I-125 seeds were implanted into the tumor target according to the brachytherapy treatment planning system (BTPS) one by one. Once I-125 seeds were delivered into the tumor lesion, a CT scan was repeated to delineate the tumor and reconstruction source position, and display the dose distribution.

Hyaluronic acid injection

Hyaluronic acid was provided by Bloomage Freda Biopharm Co., Ltd. in Jinan, China. It is widely used in the medical field due to its biocompatibility and biodegradability [7,10,11]. After CT-guided seed implantation, the needle tip was placed in the space such that the OAR receives a significant overdose. At that point, the needle was connected to a syringe containing HA. After ensuring that the needle was not in a vessel, HA was injected within the space between the tumor and skin. The total amount of hyaluronic acid was decided by actual new space according to intraoperative planning. To decrease puncture injury, HA was injected through needles, by which the I-125 seeds were released, before the needle tip was removed out of skin. However, if the needle passage for HA injection was different from the passage used for seed implantation, we would make another puncture to create a passage for HA injection. This needle was only for HA injection. We recorded the amount of this kind of needles as a part of our results.

Magnetic resonance imaging protocol and image evaluation

MRI examinations were performed on a 3.0-T clinical system (Ingenia, Philips, The Netherlands), with a 32-channel ds Torso coil, and the following imaging sequences were acquired: T1-weighted (TR/TE1/TE2 = 166/1.15/2.3 ms; acquisition matrix = 376 × 235; NSA = 1; field of view = 425 × 372 mm; slice thickness = 6 mm, flip angle = 53°), and T2-weighted (TR/TE = 2725/78 ms; acquisition matrix = 296 × 296; NSA = 1; field of view = 400 × 400 mm; slice thickness = 6 mm, flip angle = 90°).

Brachytherapy treatment planning system

The brachytherapy treatment planning system (BTPS) used in this study was the seeds implanting brachytherapy system provided by the Image Processing Center of Beijing University of Aeronautics and Astronautics, in

Table 1. Patient characteristics

Patient	Gender	Age	Location	Diagnosis	Chemotherapy	Radiotherapy
1	Male	71	Abdominal wall	Gastric carcinoma	Y	N
2	Male	57	Chest wall	Mesothelioma	Y	N
3	Male	53	Neck	Lung cancer	Y	N
4	Male	51	Neck	Cancer of unknown primary	Y	N
5	Male	78	Arm	Lymphoma	Y	N
6	Male	58	Chest wall	Lung cancer	Y	N
7	Male	62	Groin	Lymphoma	Y	N
8	Female	53	Chest wall	Lung cancer	Y	N
9	Male	61	Neck	Lung cancer	Y	N
10	Male	67	Back	Melanoma	Y	N
11	Male	77	Chest wall	Lung cancer	Y	N

Peking, China. Its calculation algorithm is based on the American Association of Physicists in Medicine Task Group No. 43 Report.

Post-implant dosimetry

We routinely performed postoperative dosimetric verification for each patient. The CT images obtained immediately after seed implantation was transferred to the BTPS. First, we outlined the gross tumor volume as GTV. Then, clinical target volume (CTV) was generated by adding a margin of 5-mm to gross tumor volume (GTV) in all directions. The CTV was equal to the target volume [12,13,14]. We outlined a 2-mm thick contour below the skin surface standing for skin [15]. Based on the recommendations of the American Brachytherapy Society (ABS) [16], the tumor volumes, the D_{90} (the dose delivered to 90% of the target volume), and V_{100} (the percentage of the target volumes receiving 100% of the prescription dose) values were calculated through the BTPS both pre- and post-HA injection as well as the OAR-Max (0.1 cc of skin receiving the highest dose) and OAR-Mean (the mean skin dose) values. The isodose curves for each slice and the dose-volume histograms (DVHs) of the target were generated by the BTPS.

Follow-up

All patients were followed up at 1, 3, and 6 months post-HA injection. The radiation morbidity of skin was assessed by the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria (Table 2) [17].

Statistical analysis

The D_{90}, V_{100}, OAR-Max, and OAR-Mean values (pre- and post-HA injection) were documented at the end of the present study, as were the complications. The statistical analyses were performed with SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA). We chose one-tailed paired *t*-test for the comparison of dosimetric parameters before and after HA injection. A p value of less than 0.05 was defined as significant.

Results

New space between tumor and skin following hyaluronic acid injection

For the patients, the mean volume of HA injection was 4.2 ml (range, 1.6-8.0 ml) and the mean new space after HA injection was 1.0 cm (range, 0.6-1.5 cm) (Table 3). Figure 1 illustrates the process of HA injection between tumor and skin. The patients' MRIs before and after HA injection showed a newly formed space between tumor and skin. The technique of HA injection is additionally shown in Figure 1. The new space was measured on a CT image or MRI. There were 3 patients who were evaluated by MRI, 7 patients by CT scan, and 1 patient who accepted MRI in first month, and then CT scan.

Table 2. RTOG acute radiation morbidity scoring criteria of skin [17]

Score 0	Score 1	Score 2	Score 3	Score 4
No change over baseline	Follicular faint or dull erythema, epilation, dry desquamation or decreased sweating	Tender or bright erythema, patchy moist	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage or necrosis

Table 3. Volume of hyaluronic acid (HA) injection and the distance of the new space

Patient	HA (ml)	Increased distance[1] (cm)	Increased time[2] (min)	Increased[3] needles
1	3.0	0.8	36	1
2	4.0	1.5	16	1
3	1.6	0.6	19	1
4	5.0	1.2	17	1
5	3.0	0.8	11	2
6	5.0	1.0	24	2
7	8.0	1.0	20	0
8	4.5	1.4	17	3
9	2.0	0.8	5	0
10	5.0	1.0	10	0
11	5.0	1.0	14	1
Average	4.2	1.0	17.2	1.1

[1]measurement of increased distance is defined as the maximum distance induced by HA; [2]prolonged operating time for HA injection; [3]more needles needed only for HA injection

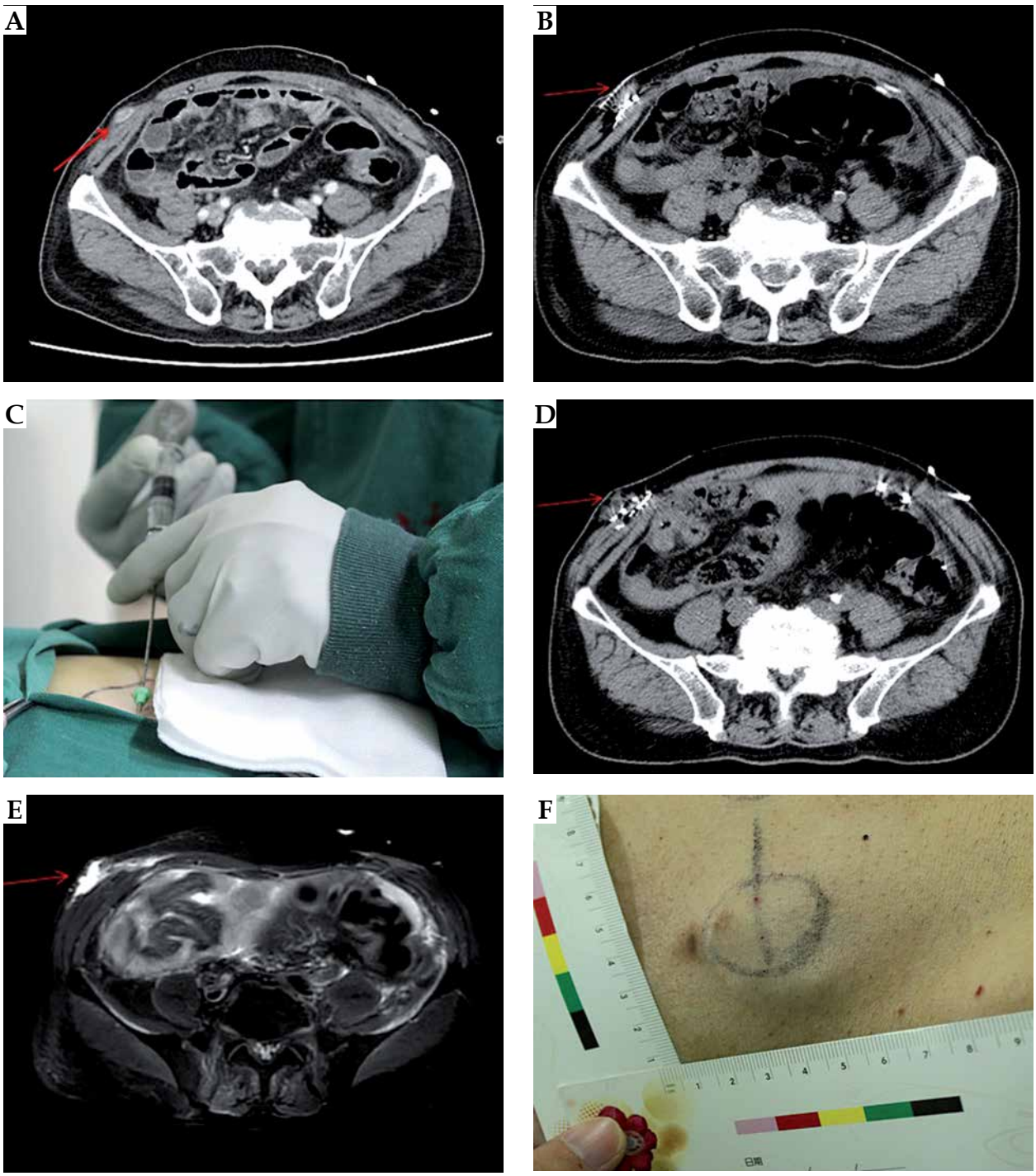

Fig. 1. Process of hyaluronic acid (HA) injection between the tumor and skin. **A**) Subdermal malignant tumor on a CT scan (red arrow); **B**) The needle tip for HA injection was placed between the skin and the tumor (red arrow); **C**) HA injection; **D**) The new space caused by HA injection is shown in the CT image (red arrow); **E**) The new space caused by HA injection is shown on T2 MRI (red arrow); **F**) Skin appearance after HA injection

Dosimetric outcomes before and after hyaluronic acid injection

To assess the effect of HA injection on tumor's dose coverage and radiation exposure to skin, D_{90} and V_{100} of CTV were calculated as well as OAR-Max and the OAR-Mean. The mean CTV V_{100} prior to HA injection was 91.18% (range, 69.6-100%). The mean V_{100} after HA injection was 91.17% (range, 70.7-100%). The mean D_{90} prior to HA injection was 142.47 Gy (range, 65.96-208.52 Gy). The mean D_{90} after HA injection was 141.44 Gy (range, 70.66-213.02 Gy). There were no significant differences in V_{100} and D_{90} of tumor before and after HA injection (p = 0.50, p = 0.39, respectively). The mean OAR-Max (skin) and

Table 4. Dosimetric parameters before and after hyaluronic acid injection

Patient	PD (Gy)	Activity ($\times 10^7$ Bq)	Numbers	CTV (cc)		D_{90} (Gy)		V_{100} (%)		OAR-Max (Gy)		OAR-Mean (Gy)	
				Before	After	Before	After	Before	After	Before	After	Before	After
1	140	2.22	21	6.20	6.20	159.77	165.57	96.3	96.7	110.43	55.62	164.50	11.80
2	140	2.96	26	10.90	11.00	185.70	184.07	98.9	98.8	62.11	50.35	13.29	11.90
3	120	2.96	15	13.00	12.70	77.21	78.49	72.5	70.7	106.01	77.90	27.27	19.81
4	120	2.22	27	14.60	14.30	137.39	132.08	94.6	95.5	102.92	63.76	24.17	15.79
5	120	2.22	10	1.60	1.60	143.31	164.47	95.0	91.9	94.47	70.98	36.65	24.58
6	120	2.96	55	43.10	42.00	191.47	163.06	91.7	98.0	91.11	66.34	37.30	28.53
7	120	2.22	68	101.20	97.00	65.96	70.66	69.6	71.0	65.89	57.72	23.56	19.99
8	120	2.22	13	2.00	2.00	184.90	184.17	99.9	100.0	72.35	54.71	18.06	14.08
9	100	2.22	22	10.20	10.20	102.26	102.26	91.3	91.3	36.72	33.99	150.02	13.87
10	120	2.22	15	2.80	2.30	208.52	213.02	100.0	100.0	228.70	69.67	11.87	6.12
11	100	2.22	10	4.30	5.00	110.69	98.00	93.2	89.0	136.60	72.13	34.54	23.48
Average	120	2.42	26	19.08	18.57	142.47	141.44	91.18	91.17	100.66	61.20	49.20	17.27
p value					0.11		0.39		0.50		0.01		0.04

PD – prescription dose, CTV – clinical target volume

Fig. 2. Dose-volume histogram curve of the tumor target and skin before and after hyaluronic acid (HA) injection. The green curves represent the doses at the target tumor, and the purple curves represent the doses at the skin (solid line: before HA injection; dashed line: after HA injection). Compared to the doses measured before HA injection, the post-injection doses were not significantly different for tumor, while the mean OAR-Max and OAR-Mean were significantly lower after HA injection

OAR-Max – the maximum dose to relatively small volume (0.1 cc) at the skin; OAR-Mean – the maximum dose

OAR-Mean (skin) prior to HA injection were 100.66 Gy and 49.20 Gy, respectively, while the mean skin OAR-Max and OAR-Mean post-HA injection were 61.20 Gy and 17.27 Gy, respectively. The post-HA injection values were both significantly lower than the pre-HA injection values ($p = 0.01$, $p = 0.04$, respectively). Table 4 presents dosimetric parameters of the target tumor and skin before and after HA injection. Figure 2 shows the DVH curve for Patient 1.

Follow-up

By the end of April 2018, the follow-up time was 1-6 months, and the average time was 3.36 months. Side effects related to the injection or the compound itself were not observed. Upon follow-up imaging, the substance could hold its shape and position stably and lasted for 6 months (Figure 3).

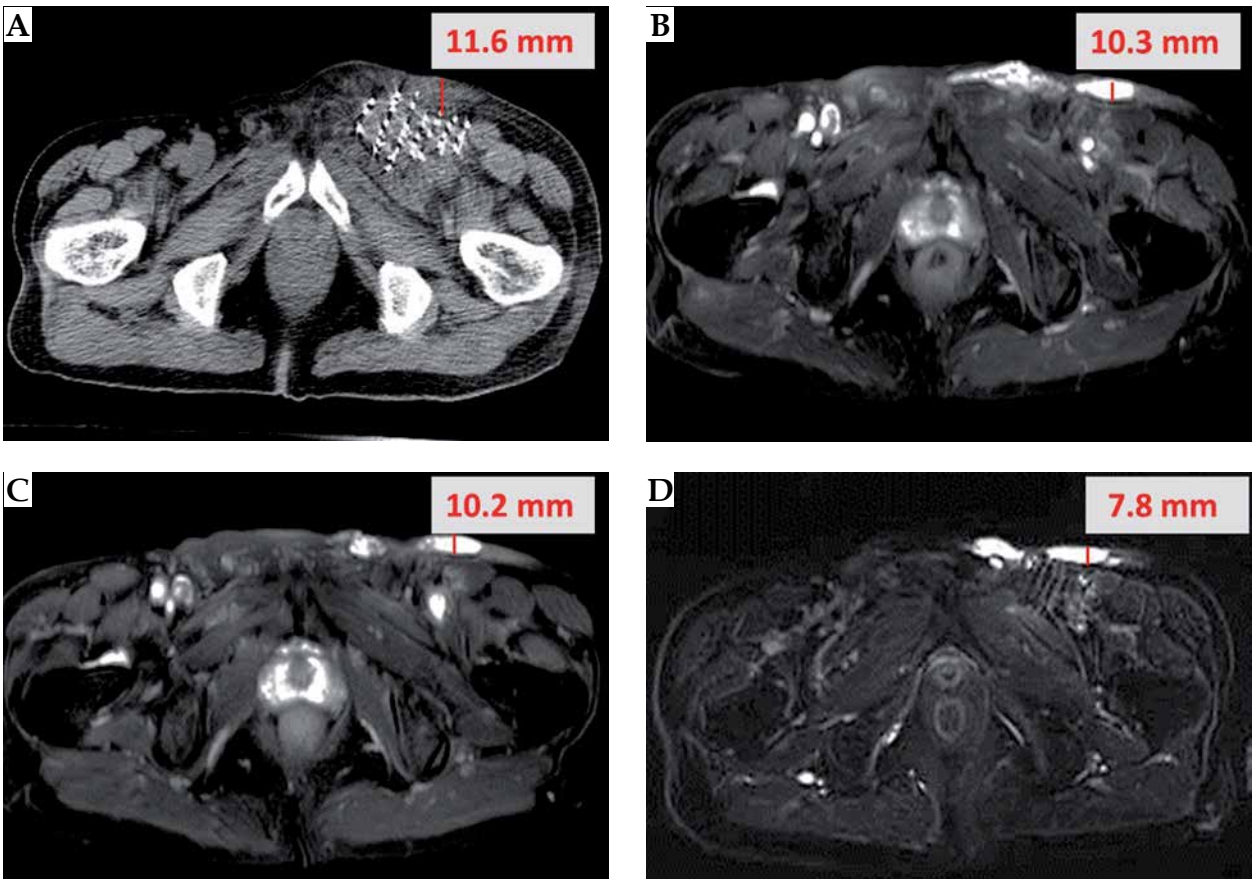

Fig. 3. Images of hyaluronic acid (HA) for Patient 7. **A**) Point of injection on CT; **B**) 1 month after the injection on MRI; **C**) 2 months after the injection on MRI; **D**) 3 months after the injection on MRI

Discussion

Brachytherapy is an important treatment modality for many malignant tumors. The advantages of brachytherapy include the enhancement of irradiation at the tumor target and the reduction of irradiation of normal peritumor tissues. Previous studies [18,19] demonstrated improved results with increasing radiation doses in malignant tumors treated with brachytherapy; however, dose increase at the tumor target could also lead to a higher probability of side effects at adjacent normal tissues and organs.

Recent work has aimed to decrease OARs irradiation doses in patients treated with radiation therapy. These studies [20,21,22,23] showed that HA injection formed a new space between the tumor target and OARs, which could reduce radiation doses to OARs (such as the rectum) during brachytherapy. In this study, we showed that with HA injection, the new space between tumor and skin (a mean size of 1.0 cm) could be created in patients treated with LDR brachytherapy.

We further assessed the effect of the new space resulting from HA injection on the dose coverage of the tumor and skin. Our results showed that the D_{90} and V_{100} of the tumor target were not significantly different; however, OAR-Max and OAR-Mean of skin decreased significantly when compared with the pre-HA injection parameters. A previous study [24] obtained data from thermoluminescent dosimeter (TLD) measurements and demonstrated a statistically significant decrease after HA injection in the mean D_{max} and mean D_{mean} to the rectum in HDR brachytherapy. Our results were in line with these results and showed that the dose coverage to the OAR (skin) was significantly decreased due to the new space resulting from HA injection, while the dose on the tumor target has not significantly changed.

The side effects of hyaluronic acid injection were evaluated during follow-up; side effects related to either the injection or the compound itself were not observed. This procedure does not cause more pain, but it does increase the needle passages and operating time, which increases the risk of punctures and medical costs.

There are several limitations to this study, including relatively small number of patients and short time of follow-up. In addition, the volume of HA used to create the space was not defined.

Further study is needed to fully assess the benefit gained by decreased skin toxicity. This technique also offers a possible method of protection for adjacent normal organs or tissues, while delivering high treatment doses with LDR brachytherapy to obtain better tumor control.

Conclusions

Our results demonstrated that a new space between tumor and skin could be obtained with hyaluronic acid injection in patients with a subdermal tumor, and this

new space could significantly decrease the skin dose in LDR brachytherapy. This method offers the possibility of preventing the delivery of high-dose radiation to adjacent normal tissues during cancer treatment.

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Disclosure

Authors report no conflict of interest.

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