Subcutaneous Injection of Hyaluronic Acid to Decrease Acute Skin Toxicity After Adjuvant Interstitial Brachytherapy in Parotid Gland Cancer Patients: A Nonrandomized Controlled Trial

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Purpose: The aim was to evaluate the safety and efficacy of subcutaneous injection of hyaluronic acid in decreasing acute skin toxicity after adjuvant interstitial brachytherapy in parotid gland cancer patients.

Materials and Methods: Patients with histologically proven parotid gland cancer who would be treated with adjuvant interstitial brachytherapy were included in this nonrandomized controlled trial. Participants were nonrandomly divided into the experimental group and control group. Participants in the experimental group received an injection of hyaluronic acid subcutaneously immediately after interstitial brachytherapy during the operation. Acute toxicity was evaluated in the first 2 months.

Results: Thirty consecutive participants were included from April to September 2018. Twenty participants were in the experimental group, and 10 were in the control group. The median volume of hyaluronic acid was 8 mL (range, 4 to 11 mL). In total, the incidence of acute skin toxicity was 40% (8 of 20 patients) and 100% (10 of 10 patients) in the experimental group and control group, respectively. The difference in the dose delivered to 90% of the target volume of the affected skin was significant between the pre-plan (mean, 36.93 Gy) and the actuarial quality verification (mean, 27.70 Gy) in the experimental group (P = .004). The difference in scoring of acute skin toxicity was significant between the experimental and control groups (P = .001). No clear correlation was found between the dose delivered to 90% of the target volume of the affected skin and the scoring of acute skin toxicity (P = .266).

Conclusions: Subcutaneous injection of hyaluronic acid was safe and efficient in decreasing acute skin toxicity after adjuvant interstitial brachytherapy in parotid gland cancer patients according to the preliminary results.

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Surgery is the mainstay treatment for parotid gland cancer, whereas external beam radiotherapy is commonly recommended as adjunctive therapy for patients at high risk of local recurrence.[1,2] As another means of radiotherapy, iodine 125 interstitial brachytherapy has the advantage of being highly conformal, which results in high local control in patients with parotid gland cancer.[3,4] According to Zhang et al,[4] surgery that preserved the facial nerve and postoperative iodine 125 interstitial brachytherapy were successful in the treatment of parotid gland cancer in 12 patients. The most common acute toxicity was skin toxicity in parotid gland cancer patients treated with radiotherapy, which influenced the cosmetic appearance and function of patients. According to Chen et al,[5] 100% of patients experienced erythema with or without desquamation after radiotherapy for parotid-area metastasis. Similarly, Mao et al[6] reported that the incidence of acute radioepidermitis was 95% in a large group comprising 100 parotid gland cancer patients treated with adjuvant interstitial brachytherapy, in which grade 1 and grade 2 were found in the majority (82%). Several topical interventions are reported to prevent acute skin toxicity. As a mature product, hyaluronic acid is the most widely used filler substance by plastic surgeons. The aim of this nonrandomized controlled trial was to evaluate the safety and efficacy of subcutaneous injection of hyaluronic acid in decreasing acute skin toxicity after adjuvant interstitial brachytherapy in parotid gland cancer patients.

Materials and Methods

STUDY DESIGN

This prospective nonrandomized controlled trial was approved by the Ethics Committee of Peking University School Hospital of Stomatology (PKUSSIRB-201734047) and was conducted under the guidance of international ethical standards. Written informed consent was obtained from all participants. Patients with histologically proven parotid gland cancer after surgery who would be treated with adjuvant interstitial brachytherapy were included in this study. Patients with recent infection, connective tissue disease, or pregnancy were excluded. Participants were nonrandomly divided into the experimental group and control group. Those in the experimental group received an injection of hyaluronic acid subcutaneously immediately after interstitial brachytherapy during the operation. Those in the control group were treated by routine interstitial brachytherapy. The sample size designed was 20 in the experimental group and 10 in the control group. Before enrollment of the participants, the brachytherapy pre-plan had been completed to reduce bias. This study was a phase 2 trial with a small sample size and nonrandomized grouping.

BRACHYTHERAPY PROCEDURE

The involved patients were treated by routine interstitial brachytherapy with iodine 125 seeds (type 6711; Beijing Atom and High Technique Industries, Beijing, China). Computed tomography scanning was performed before and after brachytherapy for preoperative planning and postoperative quality verification in a brachytherapy treatment planning system (BTPS; Beijing Atom and High Technique Industries). The clinical target volume (CTV) was defined as the gross target volume and its surrounding potential subclinical disease that was about 1 to 1.5 cm beyond the margins of the primary tumor. The prescription dose for CTV ranged from 8,000 to 13,000 cGy. The superficial fibroadipose connective layer had a mean thickness of 1.63 mm with a standard deviation of 0.2 mm according to Macchi et al.[7] Therefore, the skin corresponding to the target area was delineated as the organ at risk with a 2-mm thickness[6] (Fig 1A). The iodine 125 seeds were implanted into the target area with the patient under general anesthesia with an individual template made through a rapid prototyping technique or combined with computed tomography guidance, which was expounded in detail in our previous study.[8]

INTERVENTION

Immediately after iodine 125 seed implantation with the patient under general anesthesia, the skin field corresponding to the target area was delineated. The patient received an injection of Modified Sodium Hyaluronate Gel for Injection (Imeik Technology Development, Beijing, China) subcutaneously in the skin field. Withdrawal was performed to avoid the hyaluronic acid entering the vessels. Each product was attached with a sterile hypodermic needle for single use. The duration of the product chosen was at least 6 months, which was at least 3 half-lives of iodine 125. As a consequence, the skin was protected by hyaluronic acid.

FOLLOW-UP AND EVALUATION

The skin condition was recorded before brachytherapy using conventional and 3-dimensional photogrammetry; this was used for comparison with skin toxicity during follow-up. The follow-up intervals were 2 months and 6 months after therapy. About half of the radiation dose was delivered by the seeds in the first 2 months, and acute toxicity was evaluated. To evaluate skin toxicity, the criteria of the Radiation Therapy Oncology Group–European Organisation for Research and Treatment of Cancer[9] were used by 2

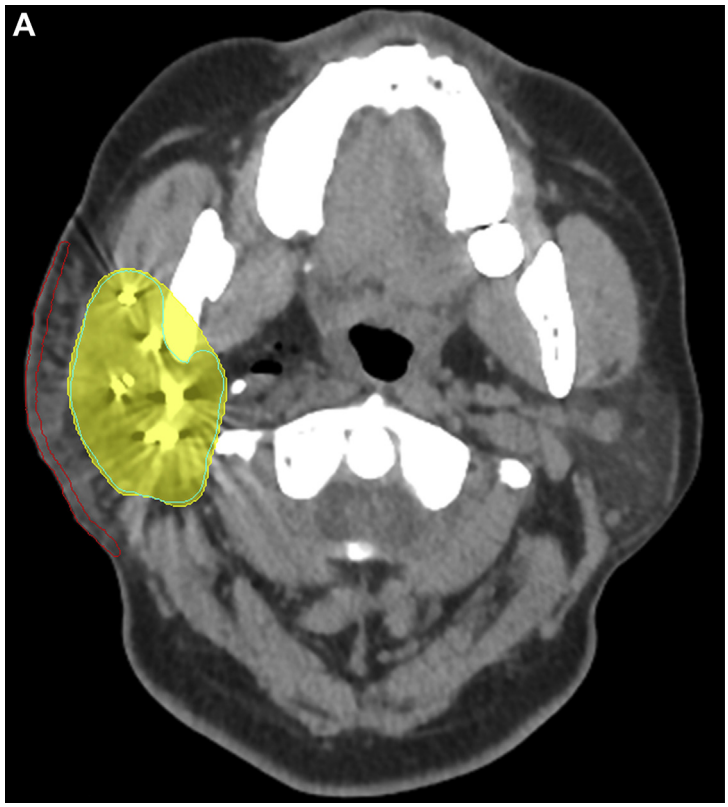

FIGURE 1. *A*, A computed tomography image for postoperative quality verification shows that the subcutaneous layer is filled with hyaluronic acid and the skin is away from the target area.**(Fig 1 continued on next page.)**

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experienced researchers blinded to the participants' groups during the follow-up. Acute radiotherapy-induced skin toxicity and other adverse events were recorded. Acute skin toxicity was scored using the following criteria: grade 0, no change over baseline; grade 1, follicular, faint or dull erythema, epilation, dry desquamation, and/or decreased sweating; grade 2, tender or bright erythema, patchy moist desquamation, and/or moderate edema; grade 3, confluent, moist desquamation other than skin folds and/or pitting edema; and grade 4, ulceration, hemorrhage, and/or necrosis.

STATISTICAL ANALYSIS

The Mann-Whitney *U* test was used to compare the dose delivered to 90% of the target volume (D_{90}) of the CTV, the D_{90} of the affected skin, and the scoring of acute skin toxicity between the experimental and control groups. The paired-samples *t* test was used to compare the mean D_{90} values of the affected skin between the pre-plan and the actuarial quality verification in the experimental group. The bivariate correlation procedure with the Spearman ρ was used to analyze the relationship between the D_{90} of the affected skin and the scoring of acute skin toxicity. $P < .05$ was considered statistically significant, and all *P* values presented were 2-sided. Statistical analysis was performed using IBM SPSS Statistics software (version 20; IBM, Armonk, NY).

Results

PATIENT CHARACTERISTICS

In this nonrandomized controlled trial, 30 consecutive participants with parotid gland cancer who would be treated with adjuvant interstitial brachytherapy were included from April to September 2018. Twenty participants were in the experimental group, and 10 were in the control group. Of the 30 participants, 10 were men and 20 were women. According to the staging criteria of the Union for International Cancer Control (seventh edition), all patients had N0M0 disease. Detailed information on patient characteristics is shown in Table 1.

BRACHYTHERAPY PARAMETERS

Radioactive seeds with activity of 18.5 to 22.2 MBq per seed were used. The median D_{90} of the CTV was 115.88 Gy (range, 87.80 to 133.79 Gy), and the median V_{100} (percentage of the target volume receiving ≥100% of the prescription dose) was 93.6% (range,

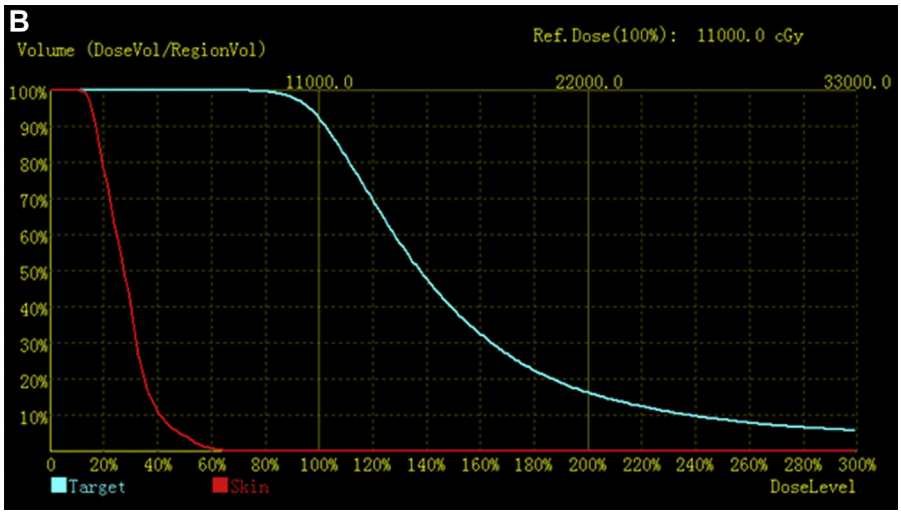

FIGURE 1 (cont'd). *B*, Dose-volume histogram of target area and affected skin. *Yellow area* indicates the target area of the quality verification, *green line* indicates the planned target area, and *red line* indicates the affected skin as organ at risk.

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90.3 to 98.6%), whereas the V_{150} (percentage of the target volume receiving ≥150% of the prescription dose) was less than 50% for all patients. The median volume of hyaluronic acid was 8 mL (range, 4 to 11 mL) according to the size of the target area, and the D_{90} of the affected skin was 27.32 Gy (range, 10.49 to 57.33 Gy) (Fig 1B).

The difference in the D_{90} of the CTV and the affected skin was not significant between the experimental and control groups (P = .173), which precluded the bias of pre-plan parameters. The difference in the D_{90} of the affected skin was significant between the pre-plan (mean, 36.93 Gy) and the actuarial quality verification (mean, 27.70 Gy) in the experimental group (P = .004).

Table 1. PATIENT CHARACTERISTICS

Characteristic	Experimental Group	Control Group
No. of patients	20	10
Age, median (range), yr	38.5 (19-75)	47.5 (32-67)
T classification		
T1	5	2
T2	7	6
T3	3	1
T4	5	1
Histologic grade		
High grade	11	3
Low grade	9	7
Primary or recurrent tumor		
Primary tumor	18	8
Recurrent tumor	2	2
Sunken-in parotid region before brachytherapy	15	9

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TOXICITIES

In comparison with the skin condition before brachytherapy, 8 patients experienced acute skin toxicity of grade 1 and 12 patients had grade 0 in the experimental group (Fig 2). In the control group, 8 patients experienced acute skin toxicity of grade 1, 1 patient had grade 2, and 1 patient had grade 3. Of the 16 patients with grade 1, 13 had erythema and 3 had dry desquamation. One patient with grade 2 experienced erythema and desquamation. One patient with grade 3 had moist desquamation. In total, the incidence of acute skin toxicity was 40% (8 of 20 patients) and 100% (10 of 10 patients) in the experimental group and control group, respectively.

The difference in scoring of acute skin toxicity was significant between the experimental and control groups (P = .001). No clear correlation was found between the D_{90} of the affected skin and the scoring of acute skin toxicity (P = .266). The sunken skin due to parotidectomy in the parotid region recovered to some extent in the experimental group. No patient experienced other toxicity during the follow-up. No adverse event related to hyaluronic acid occurred.

Discussion

The skin is relatively sensitive to radiation damage. With cumulative radiation doses, acute skin toxicities including erythema, epilation, and desquamation become apparent. Moreover, these acute skin toxicities may have a significant impact on the patient's

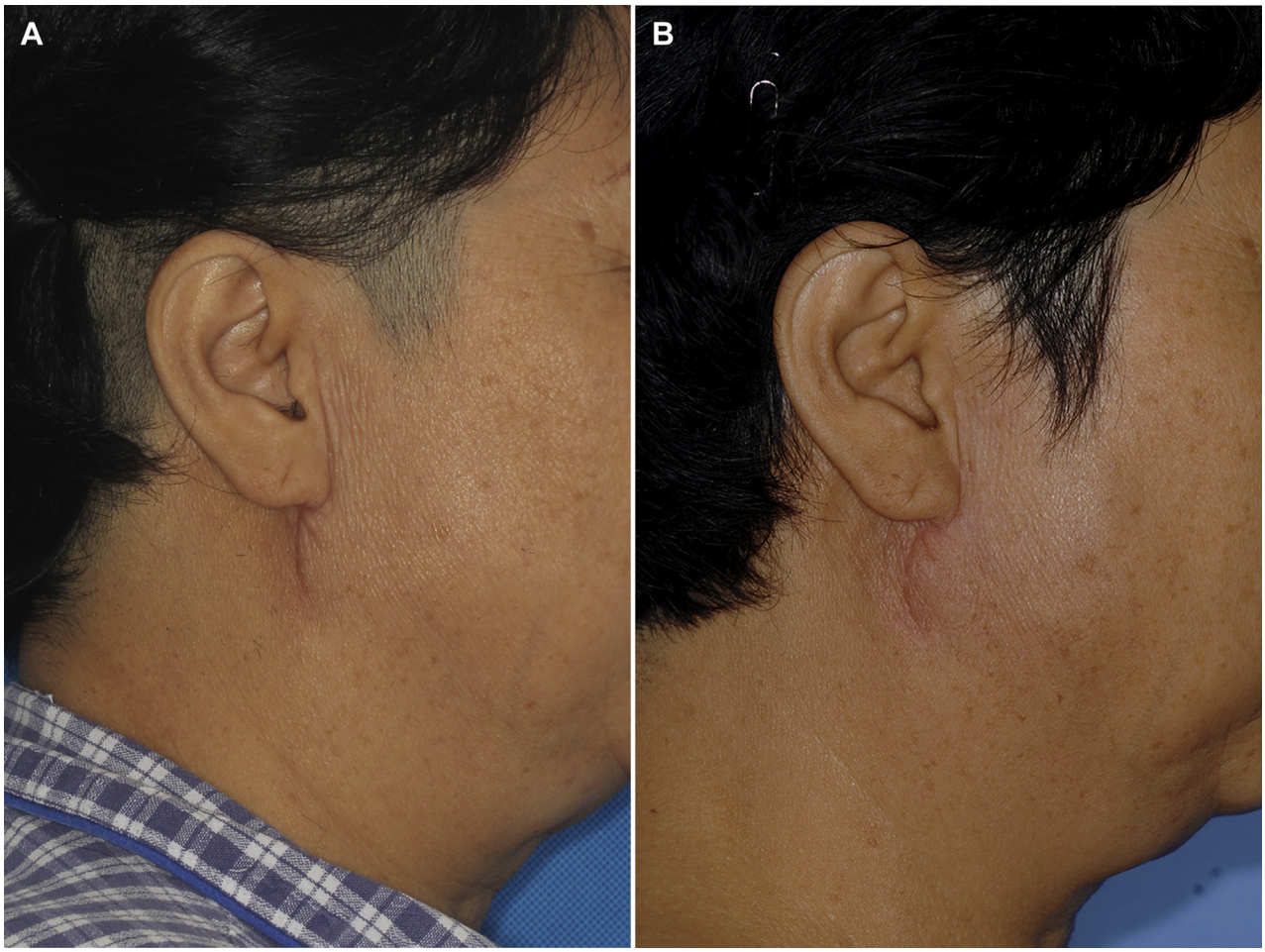

FIGURE 2. Compared with the skin condition before brachytherapy *(A)*, the facial profile 2 months after brachytherapy showed grade 0 skin toxicity in the experimental group *(B)*.

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quality of life. Several topical interventions have been reported to prevent acute skin toxicity[10,11]; nevertheless, there is no strong evidence indicating differences between topical pharmacologic interventions and nonpharmacologic topical controls.

As an invasive method,[12-14] injection of hyaluronic acid was reported to decrease vital organ toxicity in genitourinary cancer patients. In another area of oncology, Prada et al[12] found that rectal toxicity from radiation delivered with low-dose-rate brachytherapy was decreased by transperineal injection of hyaluronic acid in the anterior perirectal fat in prostate cancer patients. The hyaluronic acid group had a lower incidence of mucosal damage than the non–hyaluronic acid group and no macroscopic rectal bleeding. Similarly, in a multicenter phase 2 trial, prostate hypofractionated radiotherapy was combined with an injection of hyaluronic acid to preserve the rectal wall and reduce acute toxicity rates.[13] Moreover, the incidence of acute vesical toxicity was lower in the hyaluronic acid group with vesical instillations of hyaluronic acid in cervical and endometrial cancer patients according to Samper Ots et al.[14] The technique for injection of hyaluronic acid was safe. No severe related adverse effects were reported.[12,14] However, few studies concerning the injection of hyaluronic acid to decrease skin toxicity after radiotherapy have been performed. In our study, subcutaneous injection of hyaluronic acid was performed immediately after iodine 125 seed implantation with the patient under general anesthesia without pain. The hyaluronic acid increased the distance between the skin and the radioactive source, which provided a significant radiation dose reduction from brachytherapy. Moreover, the hyaluronic acid filled the subcutaneous tissue and recovered the sunken appearance due to parotidectomy.

There is a dose-effect relationship for acute skin toxicity to some extent. As for high-dose-rate brachytherapy for early breast cancer, the thermoluminescent dosimetry skin dose was significantly related to acute skin reaction, pigmentation, and telangiectasia according to Perera et al.[15] Mao et al[6] reported that

grade 0 to 2 acute skin toxicity increased when the dose delivered to skin was higher than 110 Gy and that skin toxicity above grade 2 increased when the dose delivered to skin was higher than 140 Gy. According to the results of our trial, the dose delivered to the affected skin was significantly reduced in the experimental group. In addition, acute skin toxicity was decreased despite no clear dose-effect relationship. Moreover, the results showed that erythema was the most common acute skin toxicity, which could turn into pigmentation in the future. Subcutaneous injection of hyaluronic acid was effective in decreasing toxicity, which reduces the accompanying cosmetic and wound-healing problems.

In conclusion, subcutaneous injection of hyaluronic acid was safe and efficient in decreasing acute skin toxicity after adjuvant interstitial brachytherapy in parotid gland cancer patients according to the preliminary results. Despite the satisfactory results, the limitation of the nonrandomized controlled trial should be noted. More high-level evidence is needed to support the conclusions.

References

1. Orlandi E, Iacovelli NA, Bonora M, et al: Salivary gland. Photon beam and particle radiotherapy: Present and future. Oral Oncol 60:146, 2016
2. Adelstein DJ, Koyfman SA, El-Naggar AK, et al: Biology and management of salivary gland cancers. Semin Radiat Oncol 22:245, 2012
3. Mao MH, Zhang JG, Zhang J, et al: Postoperative [(1)(2)(5)I] seed brachytherapy in the treatment of acinic cell carcinoma of the parotid gland: With associated risk factors. Strahlenther Onkol 190:1008, 2014
4. Zhang J, Zhang JG, Song TL, et al: 125I seed implant brachytherapy-assisted surgery with preservation of the facial nerve for treatment of malignant parotid gland tumors. Int J Oral Maxillofac Surg 37:515, 2008
5. Chen AM, Grekin RC, Garcia J, et al: Radiation therapy for cutaneous squamous cell carcinoma involving the parotid area lymph nodes: Dose and volume considerations. Int J Radiat Oncol Biol Phys 69:1377, 2007
6. Mao MH, Zhang JG, Zheng L, et al: The incidence of radioepidermitis and the dose-response relationship in parotid gland cancer patients treated with 125I seed brachytherapy: Incidence of radioepidermitis and the dose-response relationship. Strahlenther Onkol 191:26, 2015
7. Macchi V, Tiengo C, Porzionato A, et al: Histotopographic study of the fibroadipose connective cheek system. Cells Tissues Organs 191:47, 2010
8. Huang MW, Zhang JG, Zheng L, et al: Accuracy evaluation of a 3D-printed individual template for needle guidance in head and neck brachytherapy. J Radiat Res 57:662, 2016
9. Cox JD, Stetz J, Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31:1341, 1995
10. Ferreira EB, Vasques CI, Gadia R, et al: Topical interventions to prevent acute radiation dermatitis in head and neck cancer patients: A systematic review. Support Care Cancer 25: 1001, 2017
11. Chan RJ, Webster J, Chung B, et al: Prevention and treatment of acute radiation-induced skin reactions: A systematic review and meta-analysis of randomized controlled trials. BMC Cancer 14: 53, 2014
12. Prada PJ, Gonzalez H, Menendez C, et al: Transperineal injection of hyaluronic acid in the anterior perirectal fat to decrease rectal toxicity from radiation delivered with low-dose-rate brachytherapy for prostate cancer patients. Brachytherapy 8:210, 2009
13. Chapet O, Decullier E, Bin S, et al: Prostate hypofractionated radiation therapy with injection of hyaluronic acid: Acute toxicities in a phase 2 study. Int J Radiat Oncol Biol Phys 91:730, 2015
14. Samper Ots PM, Lopez Carrizosa C, Rodriguez A, et al: Vesical instillations of hyaluronic acid to reduce the acute vesical toxicity caused by high-dose brachytherapy do not affect the survival: A five-year follow-up study. Clin Transl Oncol 11:828, 2009
15. Perera F, Chisela F, Stitt L, et al: TLD skin dose measurements and acute and late effects after lumpectomy and high-dose-rate brachytherapy only for early breast cancer. Int J Radiat Oncol Biol Phys 62:1283, 2005