Case Report

Reirradiation of paraaortic lymph node metastasis by brachytherapy with hyaluronate injection via paravertebral approach: With DVH comparison to IMRT

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ABSTRACT

PURPOSE/INTRODUCTION: To safely irradiate retroperitoneal targets as paraaortic lymph node by separating abdominal at-risk organs from the target during irradiation, we created a percutaneous paravertebral approach of high-dose-rate brachytherapy with hyaluronate gel injection (HGI). We report a case treated with this technique.

METHODS AND MATERIALS: We encountered a patient with symptomatic regrowth of paraaortic lymph node metastasis from prostatic cancer. He had previously received 58.4 Gy of radiotherapy to the same region 12 months prior. Brachytherapy needles and a HGI needle were deployed via the paravertebral approach under local anesthesia at our outpatient clinic.

RESULTS: A single dose of 22.5 Gy (equivalent to 60.94 Gy in 2 Gy per fraction schedule calculated at $\alpha/\beta = 10$) was delivered to the target, with preservation of the surrounding small intestine by HGI with $D_{2cc}$ (minimum dose to the most irradiated volume of 2 mL) of 5.05 Gy. Therapeutic ratio was 3.64 times higher for this brachytherapy plan compared with an intensity-modulated radiation therapy plan. At followup at 1 year after brachytherapy, the symptoms had disappeared, tumor size had reduced with no fluorodeoxyglucose accumulation, and prostate-specific antigen level had decreased.

CONCLUSION: We consider that high-dose-rate brachytherapy with the HGI procedure offers effective treatment even in this type of reirradiation situation. © 2013 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Reirradiation; Paraortic lymph node; High-dose-rate brachytherapy; Hyaluronate; Risk organ; Prostate cancer; Bowel

Introduction

Reirradiation is an effective treatment option in many clinical situations. It is reported to have similar effectiveness for local tumor control and pain reduction compared with the initial irradiation (1–3), but it has also been associated with significant incidence of late toxicity attributable to accumulated dose in at-risk organs, such as the small intestine (3, 4). New technologies, such as intensity-modulated radiation therapy and intensity-guided radiation therapy (IMRT-IGRT) that facilitate accurate and selective dose delivery still have limitations when the target is closely surrounded by risk organs. In this context, we propose a liquid spacing technique using hyaluronate gel injection (HGI) with high-dose-rate brachytherapy (HDRBT) (5–10).

We encountered a patient with recurrent paraaortic lymph node metastasis (PALNM) from prostate cancer that relapsed 12 months after radiotherapy of 58.4 Gy. We created both IMRT-IGRT and HDRBT-HGI plans and compared the therapeutic ratio of target dose and at-risk organs between the two plans. The patient was treated and followed up for more than 1 year; followup is ongoing. We discuss the
feasibility, safety, and effectiveness of HGI-HDRBT in this situation.

**Patient**

We encountered a 72-year-old patient with relapsed PALNM after initial radiotherapy (Fig. 1) complaining of stiffness in the left leg. Three years before admitting to our clinic, he visited a vicinity clinic with urinary difficulty lasting for a few weeks. He was diagnosed with prostate cancer (T3N1M1; Gleason score, 5 + 4; serum prostate-specific antigen [PSA] level, 20.3 ng/mL); MRI revealed seminal vesicle invasion and metastatic left iliac and paraaortic nodal swelling. Hormonal therapy with 100 mg of chlormadinone acetate (progesterone analog) daily was immediately started and continued at the same dosage. Luteinizing hormone-releasing hormone therapy caused allergic responses and was not used. After 1 year, the patient noticed macroscopic hematuria. His PSA level had reelevated (4.8 ng/mL), and X-ray CT examination revealed an increase in the prostatic tumor size. The patient underwent initial radiotherapy by external beam: a total of 70.4 Gy in 1.8–2.0 Gy fractions for the prostate and seminal vesicles and a total of 58.4 Gy for the metastatic left iliac node and paraaortic lymph nodes. These totals were a summation of a wide-field treatment of 50.4 Gy in 1.8 Gy fractions covering the whole pelvis and paraaortic area and boost treatments (Fig. 1b). One year later, his PSA level had reelevated (1.13 ng/mL), and recurrent PALNM of 9.75 mL in volume was detected. The patient was referred to our clinic for reirradiation and chose to undergo IMRT-IGRT but changed his mind before treatment and requested brachytherapy instead.

Before processing each treatment, informed consent was obtained from the patient. Treatments were performed with standard institutional approval.

**IMRT planning**

Using thin slice X-ray CT images (LightSpeed 16; GE Healthcare, Buckinghamshire, UK) and Brainscan (version 5.2; Brainlab AG, Feldkirchen, Germany), an IMRT plan was created to deliver 60 Gy in 3 Gy per fraction for 4 weeks. The spinal cord and kidneys were the critical organs previously involved in the 50.4-Gy field.

**Brachytherapy preparation and planning**

**Preparation of hyaluronate gel**

Forty milliliters of 0.16% sodium hyaluronate was prepared with saline in advance, using a commercially available high-molecular hyaluronate (3.4 million daltons of median molecular weight, 2.2 million of viscosity molecular size; Suvenyl; Chugai/Roche, Tokyo, Japan). This hyaluronate is a native-type bioproduct. Contrast medium (2 mL of iopamiron 300 mg I/mL; Bayer Healthcare, Leverkusen, Germany) was added to the gel.

**Premedication**

Treatment was performed at the outpatient clinic under awake sedation with 25 mg of hydroxyzine pamoate and 5 mg of intravenous diazepam. The patient was able to report his sensations during the procedure. Electrocardiogram, arterial pressure of oxygen, respiration, and blood pressure were monitored.

![Fig. 1. Course of (a) serum prostate-specific antigen (PSA) level and (b) previous irradiation fields: a wider field (arrows) for pelvis and paraaortic lymph node area and a narrow field (arrowheads) for selective boost treatment are shown. EBRT = external beam radiotherapy; PALNM = paraaortic lymph node metastasis.](image)
Needle deployment and planning

A 21-gauge steepled needle with side holes (improved shape for straight-line insertion) was used for minimally invasive gel injection. Microselectron system applicator needles (1.1 mm in external diameter and 20 cm in length) were inserted to the target under X-ray CT guidance. The CT-guided HGI procedure took approximately 30 min. The space created by the gel injection was observed as an area of contrast enhancement around the target (Fig. 2). Injection of the gel created a spacer approximately 10-mm thick.

Fine-pitch (2 or 3 mm) X-ray CT images were then acquired and transferred to the treatment planning computer. A CT-based three-dimensional treatment plan was created using a graphic optimization tool (PLATO version 14; Nucletron, Veenendaal, The Netherlands) (Figs. 3 and 4).

Dose—volume histogram analysis

In the brachytherapy plan, 22.5 Gy was prescribed to 100% of the target volume, and $D_{2cc}$ (minimum dose to the most irradiated volume of 2 mL) of the small intestine was 5.05 Gy (Fig. 5a). In the IMRT plan, 60 Gy in 3 Gy per fraction was prescribed to the target, and $D_{2cc}$ to the small intestine was 38 Gy in 1.8 Gy per fraction (Fig. 5b). The equivalent dose for a 2 Gy fraction schedule was calculated using the linear–quadratic (LQ) model, at $\alpha/\beta = 2$ (GyELQ2,α/β=2) for the small intestine and $\alpha/\beta = 10$ (GyELQ2,α/β=10) for the target. $D_{2cc}$ was 8.87 GyELQ2,α/β=2 in the brachytherapy plan and 34.5 GyELQ2,α/β=2 in the IMRT plan (Fig. 5c). $D_{cc}$ was 12 GyELQ2,α/β=2 in the brachytherapy plan and 38.9 GyELQ2,α/β=2 in the IMRT plan. Therapeutic of 100% planning target volume dose/$D_{2cc}$ to the small intestine was 60.94 GyELQ2,α/β=10/8.87 GyELQ2,α/β=2 = 6.87 for brachytherapy and 65 GyELQ2,α/β=10/34.5 GyELQ2,α/β=2 = 1.88 for IMRT, yielding an enhancement factor of 3.64.

Irradiation

After transporting the planning data to an iodine-192 remote afterloader system (Microselectron HDR Ir-192; Nucletron, Veenendaal, The Netherlands), irradiation was started. The irradiation took approximately 10 min.

After irradiation and followup

The needles were removed after irradiation was complete, and the patient was discharged after 2 h under observation. There were no procedure-related complications. The patient is regularly followed up at our affiliated clinics.

Outcome

One week after the treatment, he reported disappearance of the leg stiffness. No complications were found in follow-up over 12 months after reirradiation.

Followup positron emission tomography-CT and MRI studies taken 7 months after the brachytherapy showed negative fluorodeoxyglucose accumulation and reduction of the tumor size to 1 cm (Fig. 2b). The serum PSA level of carbohydrate antigen 19-9 showed a remarkable decrease to 0.5 ng/mL at 10 months after reirradiation. At the present 13 months after reirradiation, there are no signs or symptoms of abdominal complications and no evidence of recurrence at the site of reirradiation.

Discussion

Reirradiation of PALNM

Relapse of previously irradiated paraaortic lymph nodes surrounded by small intestine is not a rare clinical situation, but reirradiation in this situation is strictly limited because

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Fig. 2. (a) X-ray CT image at the time of paraaortic node relapse (arrow). (b) Overlaid fluorodeoxyglucose-positron emission tomography image 9 months after reirradiation shows no accumulation in the shrunken tumor (arrow). Images show the maximal cut surface of the tumor.
of accumulated intestinal radiation toxicity. In the present case, HGI-HDRBT provided a superior therapeutic ratio compared with IG-IMRT and enabled curative dose treatment with prominent therapeutic enhancement.

Intestinal tolerance

To date, no definitive consensus or guidelines exist regarding the tolerance level of the small intestines both in reirradiation and brachytherapy. In external beam reirradiation, a cumulative bowel dose of 90 Gy was proposed as a tolerance level (11). The small intestines are generally thought to be more sensitive than the large bowel and which tolerance level may be rather close to that of stomach. In brachytherapy, Streitparth et al. (12) proposed $D_{1cc}$ thresholds of 11 Gy for general gastric toxicity and 15 Gy for ulceration, which were equivalent to 35.75 and 63.75 Gy in 2 Gy fraction schedule, respectively. We could choose a safer option by comparing the dose–volume histogram, as in Fig. 5c.

Procedural safety

The present technique of paravertebral insertion of applicator needles and HGI to the subperitoneal space enabled HDRBT to be achieved safely without significant radiation to the small intestine. The paravertebral access route is a safe percutaneous interventional maneuver that is also used in retroperitoneal biopsies (13) and neurolysis.

Hyaluronate

Hyaluronate is a biosafe substance that is naturally present in the extracellular space of human and animal tissues and is degraded by our innate hyaluronidase. High-molecular-weight native-type hyaluronate has been previously used...
for risk organ preservation during HDRBT (5, 7–9), where the spacing effect generally lasted for a few to several hours depending on its concentration and anatomic factors of the injected site. The radioprotective and anti-inflammatory effects of hyaluronate are described previously (14–16). Artificially cross-linked hyaluronate is a biodegradation-resistant time-proof variant (Restylane SubQ; Q-Med, Uppsala, Sweden) (17) that is used as a filler in cosmetic augmentation. Prada et al. (18, 19) reported using this type of hyaluronate for creating and maintaining space during IMRT, HDRBT, and low-dose-rate brachytherapy for prostate cancer. In addition, Vordermark et al. (20) commented that a material with faster resolution would be suitable for application to high-dose-rate intraluminal brachytherapy. Although adverse reactions have been reported in these time-proof variants (21–27), adverse events appear to be much less common after recent advances in purification technology.

**Time and cost-effectiveness of the procedure**

Native-type hyaluronate is a commercially available product that is inexpensive compared with the cross-linked type, which costs 60 times more. Injection of the gel takes only a few minutes.

**Advantage of brachytherapy in reirradiation**

Because of the steep dose attenuation with distance, interstitial brachytherapy is advantageous over IMRT. In IMRT and most other types of external beam radiotherapy, the size of surrounding high-dose area is generally proportional to the size of the target; in addition, the available angle range is often strictly limited to avoid previously irradiated critical organs, such as the spinal cord and kidney as in the present case.

**Conclusion**

We consider that the HGI procedure is helpful for improving the therapeutic ratio of HDRBT in curative dose reirradiation of PALNM.

**References**


