Journal of Radiation Research, 2013, 54, 748–754
doi: 10.1093/jrr/rrs137 Advance Access Publication 21 February 2013

Esophageal gel-shifting technique facilitating eradicative boost or reirradiation to upper mediastinal targets of recurrent nerve lymph node without damaging esophagus

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(Received 19 August 2012; revised 20 December 2012; accepted 21 December 2012)

We developed a new technique using hyaluronic gel injection as a spacer to safely move the esophagus away from the high-dose area during interstitial brachytherapy of a mediastinal target close to the esophagus. We percutaneously injected a high-molecular-weight hyaluronic gel mixed with contrast medium to create a space between the esophagus and the target during interstitial brachytherapy. We applied this technique to two cases of relapsed recurrent nerve lymph node metastasis from esophageal cancer: one refractory tumor after 50 Gy of radiotherapy, and one recurrence after mediastinal radiotherapy of total 64 Gy. We prescribed 20 Gy and 18 Gy in one fraction to each target, with calculated esophageal D_{2cc} (the minimum dose to the most irradiated volume of 2 cc) of 4.0 Gy and 6.8 Gy, respectively. Calculated enhancement factor by gel shifting in equivalent dose was 2.69 and 2.34, respectively. In each patient, accumulated esophageal D_{1cc} (minimum dose to the most irradiated volume of p cc. minimum dose to the most irradiated volume of 1 cc) was 74.4 Gy and 85.6 Gy without shifting, and 59.1 Gy and 37.6 Gy with shifting, respectively. There were no procedure-related complications. Four months after the brachytherapy, each tumor was remarkably diminished. No evidence of recurrences or late complications were observed 8 months and 9 months after the procedure, respectively. The esophageal gel-shifting technique may facilitate eradicative brachytherapy to upper mediastinal targets without damaging the esophagus, and can be used in conjunction with boost irradiation or reirradiation to overcome the problem of salvage failure.

Keywords: hyaluronate; spacer, brachytherapy; reirradiation; boost; esophageal cancer; recurrent nerve lymph node, risk organ, toxicity

INTRODUCTION

Reirradiation or boost irradiation to a mediastinal target is frequently limited by the surrounding structures. The recurrent nerve lymph node (RNLN) is one of the most common sites of lymph node metastasis from thoracic esophageal cancer [1]. RNLN exists along the recurrent nerve [2], and is the most common site of exclusive involvement [3] and of micrometastasis [4]. Prophylactic dissection of RNLN recently became considered as essential for curative esophagectomy [5] but is not yet a well-established standard practice for unapparent nodal enlargement.

Salvage treatments for RNLN relapse include chemotherapy, radiotherapy [6] and a second surgery [4]. Recent reports show better results for high-dose salvage radiotherapy [7], but because the dose is often limited by surrounding at-risk organs [8], re-salvage for radiotherapy failure is problematic. Solo RNLN relapse after radiotherapy or refractory RNLN may be best treated with salvage surgery [4], but this can only be performed in a limited number of patients [9]. Although it is reported that reirradiation can be as effective as the initial treatment in other parts of the body [10], this method is commonly limited by the presence of surrounding normal tissue, including the esophagus

[11]. When the esophagus is postoperative, tolerance to radiation injury may be less than intact. In summary, postoperative RNLN metastasis relapse after radiotherapy or refractory to radiotherapy is a difficult problem.

The radiotherapeutic techniques of image-guided radiation therapy – intensity-modulated radiation therapy (IGRT-IMRT) [12] and/or brachytherapy [13] provide advantages for preserving risk organs. In previous studies, we incorporated interventional techniques into high-dose-rate interstitial brachytherapy to enhance the preservation capacity for at-risk organs including the skin [13, 14], pharyngeal mucosa [13], small intestines [15, 16] and rectum [17, 18]. The risk organs were separated from the target by a space created by injection of hyaluronate gel. Here, we describe the application of this spacing technique to move the esophagus away from the mediastinal target in cases of relapsed and refractory RNLN metastasis. We treated two cases of relapsed RNLN from esophageal cancer: one with refractory left RNLN that continued to expand even after 50 Gy of salvage radiotherapy, and one with infield recurrence of the right RNLN after 64 Gy of salvage radiotherapy.

MATERIALS AND METHODS

Indications

The indications for treatment were single exclusive refractory RNLN, and infield recurrence of RNLN after radiotherapy for initial postsurgical recurrence, in two patients for whom chemotherapy or surgery were no longer indicated. The feasibility of the treatment was evaluated after finding a safe route for percutaneous needle insertion for each patient's particular anatomical condition, as assessed by X-ray computed tomography (CT) and magnetic resonance imaging (MRI), and confirmed by ultrasound examination. The risks and merits of the treatment were explained to the patients. Following confirmation of the patients' wishes for possible local control and according to their choice, we obtained consent from each patient prior to treatment. Standard institutional approval was given for the procedure. The entire procedure was performed at our outpatient clinic by physicians qualified in the fields of radiation oncology, interventional radiology and gastrointestinal surgery.

Definition of RNLN

RNLNs are defined as the lymph nodes that lie along the recurrent nerve in the thorax, which is between the upper border of the sternum and the upper border of the subclavian artery. They are further subdivided into the right, middle and left nodes (Japanese Classification of Esophageal Cancer) [2].

Gel preparation

A gel was prepared as a viscous mixture of 10 ml of hyaluronan (1 mg/ml; Suvenyl, Chugai/Roche, Tokyo, Japan) and 0.8 ml of contrast media (300 mg iodine/ml; Iopamiron, Bayer, Leverkusen, Germany) [15, 17]. This volume was roughly estimated for an effective esophageal shifting from a target point.

Monitoring, premedication and patient setup

The patients were monitored with electrocardiography and for P_aO_2, respiration and blood pressure throughout the procedure. To enable them to report any abnormal sensation, they underwent awake sedation with 25 mg of hydroxyzine pamoate until completion of needle deployment and gel injection. The patients were positioned supine on the CT couch.

Percutaneous needle insertion and gel injection

Following local anesthesia of subcutaneous tissue with lidocaine and under ultrasound and CT guidance, a 21-gauge needle was inserted at a puncture point lateral to the trachea at the level of the upper edge of the sternum and advanced to the location for gel injection, with regard to the anatomic structure (Fig. 1) [19]. The needle penetrated the skin first; second, subcutaneous tissue (superficial cervical fascia, SCF) between both edges of the platysma in SCF; third, the relatively hard investing layer of deep cervical fascia (DCF) containing the suprasternal space (space of Burns) filled with adipose connective tissue and the transverse cervical vein (which is commonly kinked and plexiform, and should thus be avoided), and adipose tissue below this fascia; and fourth, the pretracheal layer of DCF over the peritracheal space continuous with paraesophageal adipose tissue. To advance the needle safely, we shifted the trachea

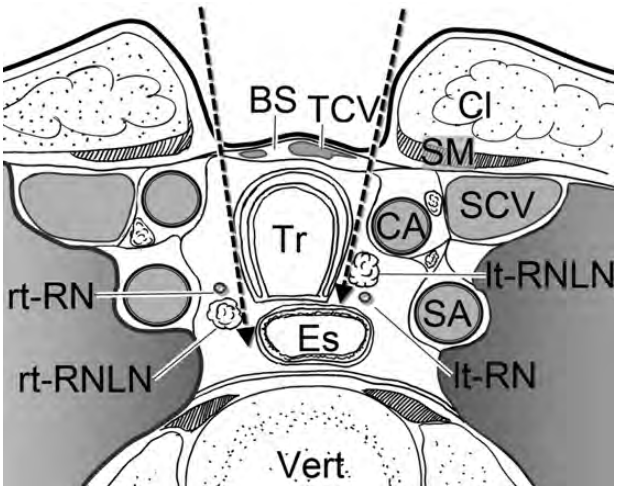

Fig. 1. Neck anatomy and needle access plan. The needle routes (dotted arrows) are at the level of the cervicothoracic junction, immediately superior to the upper sternum. The needle paths avoid the transverse cervical veins (TCV) to reach the gel injection point. BS, space of Burns; CA, common carotid artery; Cl, clavicle, Es, esophagus; Tr, trachea, lt, left; rt right; RN, recurrent nerve; RNLN, recurrent nerve lymph node; SA, subclavian artery; SM, strap muscles; Vert, vertebra [28].

by about 5–10 mm manually to the right or left when necessary. Using this route, the needle passes medial to the sternohyoid and sternothyroid strap muscles to avoid the influence of muscle contraction on the needle. When the needle tip reached the predetermined injection point, we gently injected the gel to create a space, forcing the esophagus away from the target [16]. We confirmed the created space and shifting effect by CT. When the effect became sufficient, the gel injection was terminated.

Needle deployment

Under CT guidance, interstitial brachytherapy applicator steepled needles (Microselectron system; 1.3 mm in external diameter and 12 cm long) were inserted percutaneously and deployed in the target [20]. Thin-slice (2 or 3 mm) CT images were acquired and transferred to the treatment planning computer.

CT-based treatment planning

In order to determine contours of the target and at-risk organs on the planning CT images, we referred raw CT images taken before, during, and after gel injection, and reconstructed contours containing interpolated lines.

A CT-based 3D treatment plan was created using a graphic optimization tool (PLATO version 14 or Oncentra Brachy; Nucletron, Veenendaal, the Netherlands). We aimed to prescribe 18–20 Gy to 90% of the planning target volume (PTV). The PTV was equal to clinical target volume (CTV) as usual in interstitial brachytherapy, and the CTV was set equal to gross tumor volume (GTV) in the present solitary recurrent lesions of RNLN metastasis. We tentatively set our criteria for accumulated esophageal dose as D_{1cc} less than 70 $GyE_{LQ2,\ \alpha/\beta=3}$, taking into account published tolerance dose [8].

Plan evaluation and irradiation

We described biological equivalent dose as $GyE_{LQ2,\ \alpha/\beta=k}$ for a 2-Gy fraction schedule calculated using the linear quadratic (LQ) model at $\alpha/\beta = k$ (instead of equivalent dose), in the widely used forms of $GyE_{LQ2,\ \alpha/\beta=3}$ and $GyE_{LQ2,\ \alpha/\beta=10}$. $D_{p\ cc}$ was defined as the minimum dose to the most irradiated volume of p cc. The planning data were transferred to an I-192 remote after-loader system (Microselectron HDR Ir-192, Nucletron), and irradiation was started.

Postirradiation care and follow-up

The needles were removed immediately after completion of the irradiation, and the patient was discharged when ready. Each patient was regularly followed up at clinics.

Case 1

A 54-year-old male patient was referred for radiotherapy for a sole left RNLN metastasis. He had been diagnosed 1 year earlier with stage II, pT2N0M0 intrathoracic esophageal squamous cell cancer. He underwent thoracoscopic esophageal resection with lymph node dissection up to the second region, laparoscopic gastric tube creation and esophagogastric anastomosis in the posterior mediastinum followed by two cycles of chemotherapy, each consisting of 750 mg/m^2 5-fluorouracil on Days 1–5 and 80 mg/m^2 cisplatin on Day 1 (FP) [21]. He developed sepsis with *Pseudomonas fluorescens*, *Clostridium glabrata*, *Acinetobacter baumannii* and *Staphylococcus epidermis*, which was treated with antibiotics (ciproxan 400 mg/day and micafungin 100 mg/day for 4 weeks). One month prior to referral, follow-up CT revealed a RNLN recurrence that was treated with 50 Gy of external beam radiotherapy delivered in 2-Gy fractions for 5 weeks (Fig. 2A) and concomitant administration of one course of FP chemotherapy. However, fluoro-deoxy-glucose (FDG) positron emission

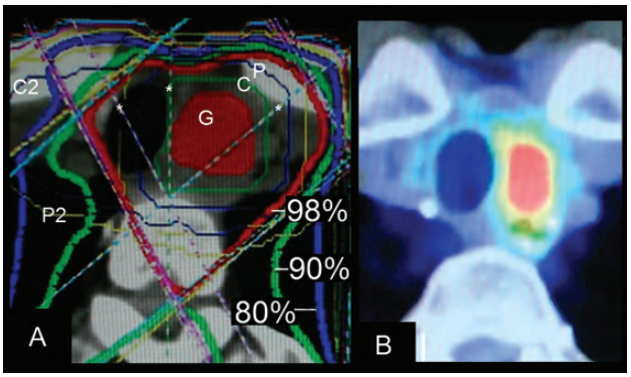

Fig. 2. (**A**) Dose distribution in external beam radiotherapy of 50 Gy to the target. Isodose lines are 98%, 90%, 80%, 70%, 60% and 50% from innermost to outermost. G, gross RNLN tumor; C, clinical tumor volume; P, planning target volume; C2, clinical tumor volume for mediastinal nodes; P2, planning target volume to C2. Asterisks are beam center lines. (**B**) FDG-PET CT image obtained 1 month after EBRT reveals persistent high FDG accumulation in the tumor. Note the proximity of the esophagus to the tumor. Images A and B show maximal tumor area.

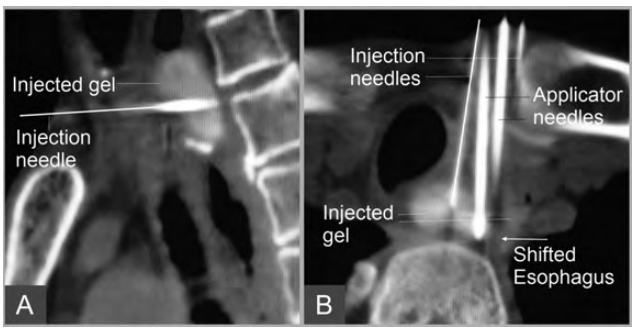

Fig. 3. Sagittal (**A**) and axial (**B**) X-CT images show the space created by the injected gel, and shifting of a portion of the esophagus.

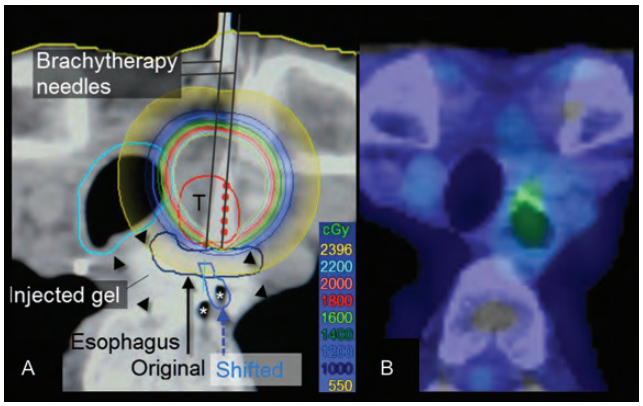

Fig. 4. (**A**) Dose distribution in boost brachytherapy. Both the shifted and approximate original positions of the esophagus are contoured. T, gross tumor volume; asterisks, air space in the shifted esophagus (right) and injected air (left); arrowheads, extent of injected gel. (**B**) PET-CT image obtained 3 months after the boost brachytherapy shows disappearance of the tumor mass and no uptake.

tomography (PET) with X-ray CT study imaging 1 month after EBRT revealed persistent high FDG accumulation in the tumor (Fig. 2B). The patient desired boost treatment as soon as possible, and boost brachytherapy assisted by esophageal shifting was considered.

After injection of the prepared gel, pooling of the gel and its shifting effect were confirmed on CT (Fig. 3A, B). We prescribed 20.0 Gy in one fraction (50.0 $GyE_{LQ2,\ \alpha/\beta=10}$) to 90% of the PTV (Figs 4C, 5A), with D_{2cc} of the shifted esophagus of 4.0 Gy (5.6 $GyE_{LQ2,\ \alpha/\beta=3}$) (Fig. 5B). In a simulation without gel shifting, D_{2cc} of the esophagus was calculated to be 7.3 Gy (15.0 $GyE_{LQ2,\ \alpha/\beta=3}$). The enhancement factor due to gel shifting was 2.69 (15.0/5.6) for D_{2cc} and 2.69 (24.4/9.07) for D_{1cc}. The previous dose to the involved esophagus for the D_{2cc} area was 20 Gy. (The area involved for D_{2cc} was estimated at the time of brachytherapy planning after gel injection. The previously irradiated dose was not identical to the previously prescribed dose to the original target.) Thus, the accumulated esophageal D_{2cc} and D_{1cc} values were 65.0 Gy and 74.4 Gy without gel shifting, which decreased to 55.6 Gy and 59.1 Gy, respectively, with gel injection.

Case 2

A 73-year-old male patient with chronic cardiac dysfunction was referred for radiotherapy of a single metastasis to right RNLN. He had been diagnosed 3 years earlier with intrathoracic lower esophageal squamous cell cancer, and underwent esophagectomy with lower mediastinal and abdominal lymph nodal dissection under thoraco-laparotomy with left-sided intra-thoracic gastric tube reconstruction for stage IV, pT3N4M0. Lymph nodal dissection was not performed in the upper mediastinum because of underlying cardiac failure. Six months after the surgery, FDG-PET revealed lymph node relapse in the paraaortic and subcarinal region, and he received 64 Gy of external beam irradiation in 2-Gy fractions for 6 weeks and 4 days. Three months before the referral, right RNLN metastasis was detected close to the esophagus (Fig. 6A). Because this area had been involved in the previous prescribed field of 42 Gy, external beam retreatment was not considered.

The size of the tumor had continued to increase during the period until brachytherapy (Fig. 6B). The prepared gel was injected, and pooling of the gel and the shifting effect were confirmed on X-ray CT imaging (Fig. 6C). We prescribed 18 Gy in one fraction (42.0 $GyE_{LQ2,\ \alpha/\beta=10}$) to 80% of the PTV volume (Fig. 6D), with 16 Gy (60.8 $GyE_{LQ2,\ \alpha/\beta=3}$) of tracheal D_{2cc} and 6.8 Gy (13.3 $GyE_{LQ2,\ \alpha/\beta=3}$) of esophageal D_{2cc} (Fig. 5A). The previous irradiated dose to the corresponding area was 20 Gy. In a simulation without gel shifting, D_{2cc} of the esophagus was calculated as 15 Gy (31.3 $GyE_{LQ2,\ \alpha/\beta=3}$). The enhancement factor for gel shifting was calculated as 2.34 (31.3 $GyE_{LQ2,\ \alpha/\beta=3}$/13.3 $GyE_{LQ2,\ \alpha/\beta=3}$) for D_{2cc}, and 3.72 (65.6 $GyE_{LQ2,\ \alpha/\beta=3}$/17.6 $GyE_{LQ2,\ \alpha/\beta=3}$) for D_{1cc}. Thus, accumulated esophageal D_{2cc} and D_{1cc} were 51.3 Gy and 85.6 Gy without gel shifting, which decreased to 33.3 Gy and 37.6 Gy, respectively, after gel injection (Fig. 5B).

RESULTS

Technical outcome

The average times required for the interventional procedure, irradiation and the entire treatment procedure were 1 h, 11 min, and 2.5 h, respectively. Both patients were discharged at noon. There were no procedure-related complications, and no additional medication was required.

Clinical outcome

Eight and 9 months have elapsed since the brachytherapy in Cases one and two, respectively. There were no immediate complications related to the procedure or treatment. No fever, appetite loss, abdominal pain or discomfort, renal dysfunction or neural symptoms have been observed so far in either patient. Imaging studies obtained 3 months (Case 1) and 4 months (Case 2) after brachytherapy treatment showed a remarkable reduction in tumor volume of the reirradiated target lesions in both cases (Figs 4B, 6E). Follow-up imaging studies at 8 months (Case 1) and 6 months (Case 2) showed no changes. There were no apparent relapses in other areas of the body; however, Case 2 suffered 2 months of pneumonia without the obvious symptoms usually seen in infectious pneumonia, and possibly caused by the external beam radiation therapy given 7–8 months prior. The pneumonia jeopardized evaluation of the treatment effect on FDG-PET. The patients are still being followed up at the outpatient clinic and have perfect performance status.

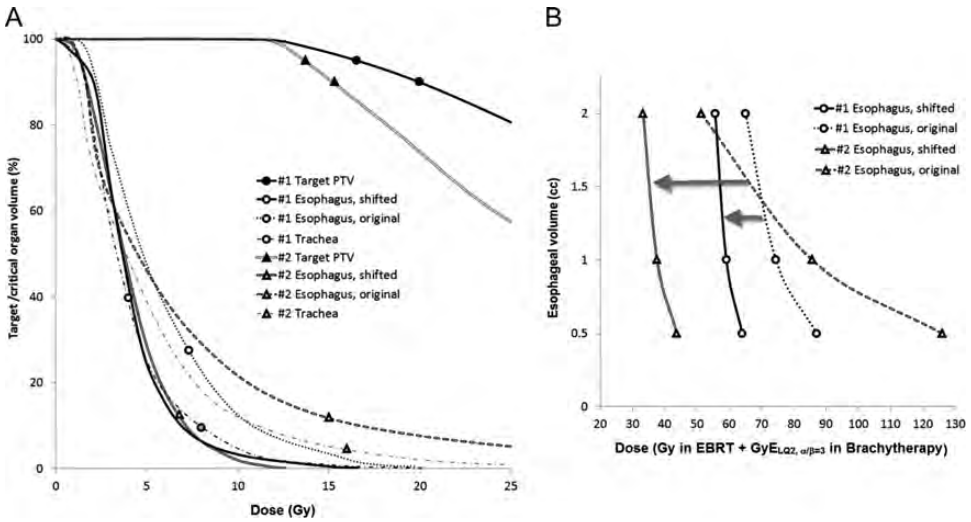

Fig. 5. (**A**) Dose–volume histograms of brachytherapy treatments for Case 1 (#1) and Case 2 (#2) show high target coverage and low involvement of critical organs in terms of actual dose (Gy). Circles indicate $D_{95\%}$, $D_{90\%}$ of the targets; triangles indicate D_{2cc} of critical organs. (**B**) Total dose with previous irradiation of 50 Gy in Case 1, and of 20 Gy in Case 2, calculated as equivalent dose in a 2-Gy fraction schedule at $\alpha/\beta = 3$. The total equivalent doses are reduced by gel shifting.

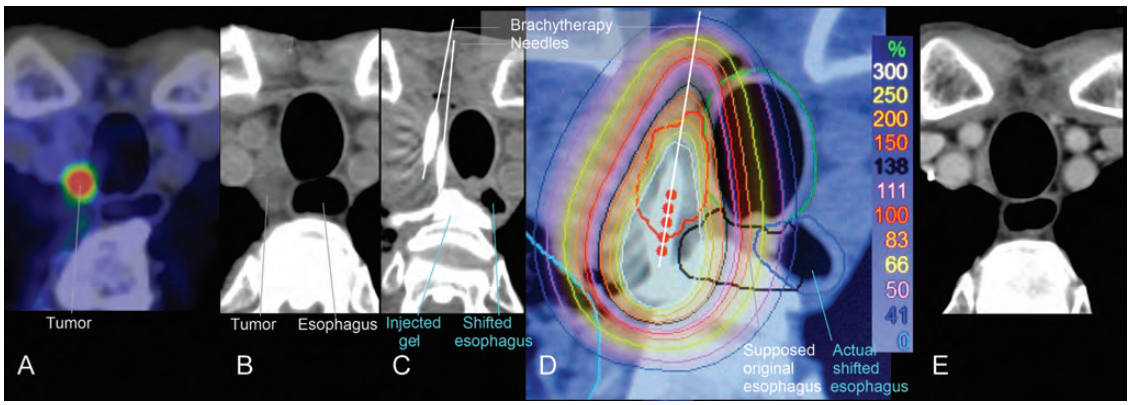

Fig. 6. Case 2 with right RNLN recurrence. (**A**) FDG-PET image obtained 2 months prior to referral shows high FDG uptake in the metastatic RNLN. (**B**) Unenhanced CT image obtained at the time of referral shows further tumor enlargement during this 2-month period. (**C**) The esophagus is shifted to the left after gel injection. (**D**) Dose distribution in the brachytherapy plan. The approximate original position of the esophagus is shown superimposed. Radiation pneumonia is evident in the right lung. (**E**) CT image obtained 4 months after brachytherapy shows a significant reduction in tumor mass size compared with that shown in (B).

DISCUSSION

Reirradiation to a mediastinal target

Reirradiation is becoming increasingly important in treatment of relapsed cancer [10]. The clinical rationale for local eradicative treatment is thought to be high for oligometastasis [22]. Zang *et al.* reported that chemoradiotherapy with dose ≥60 Gy improved survival rates in loco-recurrent esophageal cancer [7]. Reirradiation to a mediastinal target, however, is commonly limited by the poor radiotolerance of at-risk organs such as the esophagus and spinal cord [11].

Feasibility of the present procedure in terms of possible patterns of RNLN metastasis

Patterns in the management of RNLN are as follows: location on the left (Case one), right (Case two) or centrally (pretracheal); boost (Case 1) or reirradiation (Case two); after surgical nodal dissection (Case one) or intact (Case two). We treated only two patients, but most of the above possible patterns were encountered.

Patients with RNLN relapse may have widespread nodal disease. Mizutani *et al.* reported abundant collateral routes in right RNLN by inspection of over 20 cadavers [23]. It is

thought to be important to treat a wider area and to maintain monitoring.

Anatomical advantage and safety concerns

The present procedure takes advantage of the anatomical nature of this part of the esophagus, i.e., that it is generally unfixed and is not encased, which makes it an ideal candidate for shifting by gel injection. In each case presented here, the esophagus was easily shifted away from the target RNLN, resulting in a doubling of radiation safety parameters.

In this technique, the needle follows a short and narrow path through the space of Burns, which contains the kinked transverse cervical vein. Although care must be taken to avoid bleeding during insertion, the needle is not affected by muscle tension. When surgical lymph node dissection has been performed, as in Case 1, this vein is commonly removed.

Another risk is injury to the recurrent nerve. We minimized this risk by using awake sedation so that voice function could be checked throughout the procedure, and by avoiding the use of local anesthesia near the nerve.

Treatment dose

As yet there are no dedicated reports regarding desirable reirradiation dose for metastatic lymph nodes from esophageal cancer. Dose–response relationships in reirradiation are generally thought to be similar to (or not inferior to) those in the first radiotherapy, for various tumors [10]. Thus, 60 Gy equivalent or more may be preferable if this is safely applicable. When such a high target dose cannot be prescribed safely, there is the possible advantage of subvolume effect in the center of the tumor if interstitial brachytherapy is performed [24]. Moreover, Ruggieri *et al.* reported that severely hypofractionated radiotherapy may overcome hypoxic resistance [25]; we would expect this advantage to also apply to boost brachytherapy. Further accumulation of data is required to explore this subtheme.

Dose to at-risk organ

There are no common criteria for safe and effective reirradiation. In brachytherapy reirradiation (and also in similar types of spot reirradiation), only a part of the critical organ is reirradiated nonuniformly. Although we tentatively set a criterion with D_{1cc} for the esophagus, this was highly speculative; in addition, we have little clinical experience of our own in this regard. The information we used for reference was TD5/5 (dose for 5% esophageal stricture/perforation event in 5 years) for irradiation involving one-third of the esophagus of 60 Gy, and TD50/5 of 68–72 Gy [8]; it is also hypothesized that less partial involvement appears to cause fewer adverse events [26]. Based on our clinical experience, in which we used and observed tentative safety criteria with D_{2cc} for surgically intact small intestine [15, 16], rectum [17, 18] and skin [13], we did not see overt late damage; however, these findings require continued assessment, and those for tracheal and anastomotic sites require further discussion.

Material safety

Native-type hyaluronan exists widely in the body as an innate substance and is metabolized promptly. Hyaluronan is a ligand to cluster of differentiation 44 (CD44), intercellular adhesion molecule-1 (ICAM-1), and a receptor for hyaluronan-mediated motility to facilitate cellular migration, proliferation and invasion. This may induce enhancement effects on some tumors and may not be beneficial if it is mixed with tumor cells. For this reason, the injection should be limited to the surrounding space and not penetrate the tumor. Our *in vivo* research found that initiation of migration takes more than 8 h (unpublished data); therefore, the presently described procedure will have no negative effect on tumor control because single-session eradicative brachytherapy is completed within a few hours. Also worthy of consideration is that CD44 is a potent stimulant of T-cell development [27]. Immune-potentiation by this method may merit further investigation.

Weaknesses of the study

The observation periods in the present study were too short to enable a discussion of late toxicity; the present study is a technical report of a novel method. It can be difficult to obtain sufficiently long follow-up periods in patients who require immediate salvage treatment for recurrent esophageal cancer.

SUMMARY AND CONCLUSION

We aimed to establish a basic methodology for safe salvage boost radiation or reirradiation procedure to mediastinal lymph nodes, which are typically RNLN, using hyaluronate gel injection to shift the esophagus away from the target. In two clinical cases of reirradiation to PNLN metastasis, gel shifting was performed via the space of Burns, resulting in a successful decrease in esophageal D_{1cc} and no procedural complications. Follow-up imaging studies obtained 4 months after the procedure showed a reduction in the size of the irradiated tumor.

We consider that the esophageal gel-shifting technique facilitates safe and eradicative reirradiation or boost irradiation to PNLN recurrence.

ACKNOWLEDGEMENTS

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT Grant), grant

number 23659595. The patients consented to publication prior to submission of the manuscript.

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