Percutaneous interstitial brachytherapy for adrenal metastasis: technical report

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We developed and evaluated the feasibility of a brachytherapy technique as a safe and effective treatment for adrenal metastasis. Adapting a paravertebral insertion technique in radiofrequency ablation of adrenal tumors, we developed an interstitial brachytherapy for adrenal metastasis achievable on an outpatient basis. Under local anesthesia and under X-ray CT guidance, brachytherapy applicator needles were percutaneously inserted into the target. A treatment plan was created to eradicate the tumor while preserving normal organs including the spinal cord and kidney. We applied this interstitial brachytherapy technique to two patients: one who developed adrenal metastasis as the third recurrence of uterine cervical cancer after reirradiation, and one who developed metachronous multiple metastases from malignant melanoma. The whole procedure was completed in 2.5 hours. There were no procedure-related or radiation-related early/late complications. FDG PET-CT images at two and three months after treatment showed absence of FDG uptake, and no recurrence of the adrenal tumor was observed for over seven months until expiration, and for six months until the present, respectively. This interventional interstitial brachytherapy procedure may be useful as a safe and eradicative treatment for adrenal metastasis.

Keywords: metastasis; adrenal gland; high-dose-rate brachytherapy (HDRBT); hyaluronate

INTRODUCTION

Adrenal metastasis develops in the course of aggressive or advanced cancer and is generally associated with a high incidence of synchronous or metachronous multiple distant metastases [1-3] by blood-borne dissemination. It is often asymptomatic but may cause unexpected life-threatening retroperitoneal hemorrhage [4, 5].

Because life expectancy is limited following diagnosis, less invasive treatment options such as radiotherapy [1, 2, 6], radiofrequency ablation [7], and laparoscopic adrenectomy [8, 9] have been favored. Radiofrequency ablation [10] provides a locally curative effect comparable with surgical adrenectomy [3, 8, 9]. Radiotherapy is used as palliative and/or curative treatment [6, 11]. Various local control rates are reported after stereotactic radiotherapy (SRT): 55% at 1 year after 40

Gy in 10 fractions (equivalent to 46.7 Gy in 2Gy fraction at $\alpha/\beta = 10$) (median: ranges from 16 Gy in 4 fractions to 50 Gy in 10 fractions) [1], and 90% at 1 year after 36 Gy in three fractions (equivalent to 83.1Gy) [2], and this may suggest a dose dependency of control rates that was reported with other metastatic tumors [12]. Although we may expect curative radiotherapy of adrenal metastasis, surrounding radiosensitive normal organs limit the availability of high-dose treatment, and this is stricter when the region has been previously irradiated or when the tumor is large. Interstitial brachytherapy [13], a type of targeted interventional radio-therapy [14], may provide a safe and accurate high-dose delivery. The reported technique of dose-intensive interstitial brachytherapy of 18–20 Gy in a single fraction delivered via the percutaneous paravertebral approach with curative results [15, 16] may be applicable in the treatment of adrenal metastasis, even in the case of reirradiation or a large tumor. We used a similar needle insertion technique used in RFA of adrenal metastasis [10].

We encountered two patients who developed adrenal metastasis: one who had a relapse of uterine cervical cancer following radiotherapy to the area, and one with pharyngeal malignant melanoma. We applied interventional brachytherapy to these patients.

MATERIALS AND METHODS

Indications
At the time of patient referral to the Department of Radiation Oncology, several or no tumors other than the adrenal metastasis had been detected by physical or imaging examinations including X-ray CT and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) study, and various treatment options were considered, including percutaneous interstitial brachytherapy. Following the patients' wishes for possible local cure and according to their choice, we planned brachytherapy treatment. The brachytherapy procedure generally followed the same procedure used for percutaneous adrenal interventions [17]. A written document of informed consent was obtained from each patient prior to treatment. The entire procedure was carried out at our outpatient clinic by staff qualified in radiation oncology, interventional radiology, and gynecological surgery. Thus the procedure was performed with standard institutional approvals.

Premedication
Treatment was performed in the outpatient clinic after subcutaneous local anesthesia with 10ml of 1% lidocaine and under awake-sedation with 25 mg of hydroxyzine pamoate and 5 mg of intravenous diazepam. The patient was able to report sensations during the procedure. Electrocardiography, arterial oxygen pressure, respiration, and blood pressure were monitored. Patient was kept in prone position throughout the procedure.

Needle deployment techniques
MicroSelectron system applicator steepled needles (1.3 mm in external diameter and 20 cm long Trocar needle, Nucletron, Catalog #110.113, Veenendaal, the Netherlands) were percutaneously inserted and deployed in the target under X-ray CT guidance (10). In the needle deployment plan, source energy, target size, nearby risk organs for radiotherapy and insertion procedures were taken into account. Fine-pitch (2 or 3 mm) X-ray CT images were then acquired and transferred to the treatment planning computer. A gel mixture containing contrast medium, hyaluronate, and saline was injected into the space surrounding the target [15, 16] to clearly delineate its margin when necessary, and to create a gel-filled intra-pleural route, forcing pulmonary tissue away from the needle route, with the aim of avoiding the pulmonary injury previously reported during adrenal intervention procedures [18].

Technical use of hyaluronate gel
We injected hyaluronate gel to create space between lung and pleura. The gel was prepared as a viscous mixture of 10 ml of hyaluronan (Suvenyl, Chugal, Tokyo, Japan: 1 mg/ml) and 0.8 ml of contrast media (Iopamiron, Bayer, Leverkusen, Germany: 300 mg Iodine/ml). We also used the gel injection to clearly visualize the target margin by filling the surrounding space with a contrast-enhanced gel. Details of similar techniques are described elsewhere [15, 19].

Treatment planning and irradiation
A CT-based 3D treatment plan was created using a graphical optimization tool (PLATO version 14, or, Oncentra-Brachy, Nucletron). For locally curative purposes, we aimed to prescribe 18–20 Gy to 100% of the target volume, and to minimize risk-organ doses by setting dose constraints in the treatment planning process [15, 16, 20].

We described the biological equivalent dose with the descriptive abbreviation of $GyE_{LQ2,\alpha/\beta=k}$ for a 2-Gy fraction schedule calculated using the linear quadratic (LQ) model at $\alpha/\beta = k$, instead of 'EQD' (equivalent dose), a widely used form, for our $GyE_{LQ2,\alpha/\beta=3}$, or $GyE_{LQ2,\alpha/\beta=10}$. According to the generally used description, $D_{p \text{ cc}}$ was the minimum dose to the most irradiated volume of p cc, and $D_{q\%}$ was the minimum dose to $q\%$ volume of the treatment planning volume of the target. Dose to the spinal cord and kidneys was calculated at $\alpha/\beta = 2$ and summated with the estimated previous dose. Our institutional risk-organ safety criteria stipulates the reirradiation dose under consideration: biological equivalent dose (BED) (calculated at $\alpha/\beta = 2$ for $D_{0.5cc \text{ spinal cord}}$) must be less than 135 when the interval from the initial radiotherapy to the time of reirradiation is not less than 6 months, or must be less than 90 when the

interval is less than 6 months, according to Nieder et al. [21]. $D_{20cc\ kidney}$ was kept at less than $25_{,\alpha/\beta=2}$.

The planned data were transferred to an Ir-192 remote after-loader system (Microselectron HDR Ir-192, Nucletron), and irradiation was started. We used a flexible arm to hold the transfer tube and to keep a smooth joint to the applicator needles.

After irradiation and follow-up
The needles were removed immediately after completion of the irradiation, and the patient was discharged when ready. Unlike radiofrequency ablation (RFA), no rest is required, and the patient was able to return to ordinary daily activities. The patient was then regularly followed up at our affiliated clinics.

Case presentation
Case one
A 47-year-old female patient with perfect performance status was referred for radiotherapy of a sole adrenal metastasis sized 4×2 cm. She was diagnosed 22 months earlier with stage IIb, pT2N1M0 uterine cervical squamous cell cancer. After two cycles of chemotherapy, each consisting of 60 mg/m^2 of irinotecan on day 1 and day 8, and 80 mg/m^2 of nedaplatin on day 1 [22], she underwent radical hysterectomy with bilateral salpingo-oophorectomies, where abdominal paraaortic lymph nodes (PALN) were positive but unresected. A total of 60 Gy of radiotherapy was administrated to the PALN, and 40 Gy to the pelvic field (Fig. 1a). Thirteen months before, the patient developed multiple lymph nodal chain relapse. She received 54 Gy in 3-Gy fractions of image-guided intensity-modified radiotherapy (IG-IMRT) (Fig. 1b–d) to relapsed PALN, and 62.5 Gy in 2.5-Gy fractions of conformal radiotherapy to thoracic and supraclavicular nodal metastases. She underwent six cycles of chemotherapy, each with 50 mg/m^2 of cisplatin. Four months before, two small relapses at PALN were detected, which were treated with interstitial brachytherapy [15, 16]; 2 weeks before, left adrenal metastasis was detected on FDG-PET and MRI (Fig. 2a, b).

According to the patient's wish for local cure, we prescribed 20 Gy in one fraction (50 $GyE_{LQ,2,\alpha/\beta=10}$, 92 $GyE_{LQ,2,\alpha/\beta=3}$) to the 100% volume of the PTV (Figs. 3 and 4), with $D_{0.5cc\ spinal\ cord} = 1.95$ Gy (1.93 $GyE_{LQ,2,\alpha/\beta=2}$), $D_{10cc\ left\ kidney} = 6.4$ Gy (13.44 $GyE_{LQ,2,\alpha/\beta=2}$), and $D_{20cc\ left\ kidney} = 5.3$ Gy (9.67 $GyE_{LQ,2,\alpha/\beta=2}$). Accumulated spinal cord dose was estimated as approximately 40 Gy (BED = 80 at $\alpha/\beta = 2$). These doses met the institutional safety criteria.

Case two
An 82-year-old female, who was almost bedridden, was admitted for treatment of adrenal metastasis from malignant melanoma. The metastasis measured 4.5 cm in maximum diameter (Fig. 5). She had been diagnosed 12 years before with malignant melanoma in the nasal cavity, staged at pT4b0M0, and underwent tumor excision followed by chemotherapy consisting of 10 cycles of cisplatin, vinblastine, dacarbazine, and tamoxifen. Six and four years before, she developed tumor relapse at the right and the left Eustachian orifices, respectively, which were treated successfully with conformal radiotherapy (62.6 Gy/2.5 Gy × 25 fractions to each, for 5 weeks). Two years before, she developed multiple metastases in the submandibular lymph node, right maxillary sinus, and left femoral bone. The former and latter were treated with single-session brachytherapy of 20 Gy and 48 Gy of conformal radiotherapy of 48 Gy in 6 Gy/8 fractions for 10 days, while that in the right maxillary sinus disappeared spontaneously and was left untreated. In the previous year she had tumor relapses in the left nasal cavity and right deep cervical lymph node, both of which were treated with conformal radiotherapy of 62.5 Gy. This time, she chose single-session brachytherapy because she considered that her poor physical condition would not enable daily treatment, and because it was thought that external beam irradiation would involve a significant volume of her liver and kidney.

We prescribed 20 Gy in one fraction to the 100% volume of the PTV (Figs. 5 and 6), with $D_{0.5cc\ spinal\ cord} = 9.5$ Gy (BED = 55 Gy, 27.31 $GyE_{LQ2,\ \alpha/\beta=2}$), $D_{10cc\ right\ kidney} = 10.3$ Gy (31.67 $GyE_{LQ2,\alpha/\beta=2}$), and $D_{20cc\ right\ kidney} = 5.7$ Gy (10.97 $GyE_{LQ2,\alpha/\beta=2}$). These doses met the institutional safety criteria.

RESULTS

Technical outcome
The average time required for the interventional procedure, irradiation, and the entire treatment procedure were 1 hour, 11 minutes, and 2.5 hours, respectively. Both patients were discharged at noon. There were no procedure-related complications, and no additional medication was required.

Clinical outcome
No immediate complications arose related to the procedure or treatment, and no fever, appetite loss, abdominal pain or discomfort, renal dysfunction or neural symptoms have been observed so far in either patient. Imaging studies obtained two and three months after brachytherapy showed disappearance of the FDG accumulation in the adrenal lesion and a remarkable reduction in tumor size (Figs. 2c, d and 5b). However, the first patient developed multiple mesenteric lymph node recurrence in the previously irradiated region, and this led to bile duct obstruction. Though it was successfully managed by stenting, the patient then decided to discontinue intensive medical support and returned to her home city six months after treatment. She expired at home one month later. The second patient regained
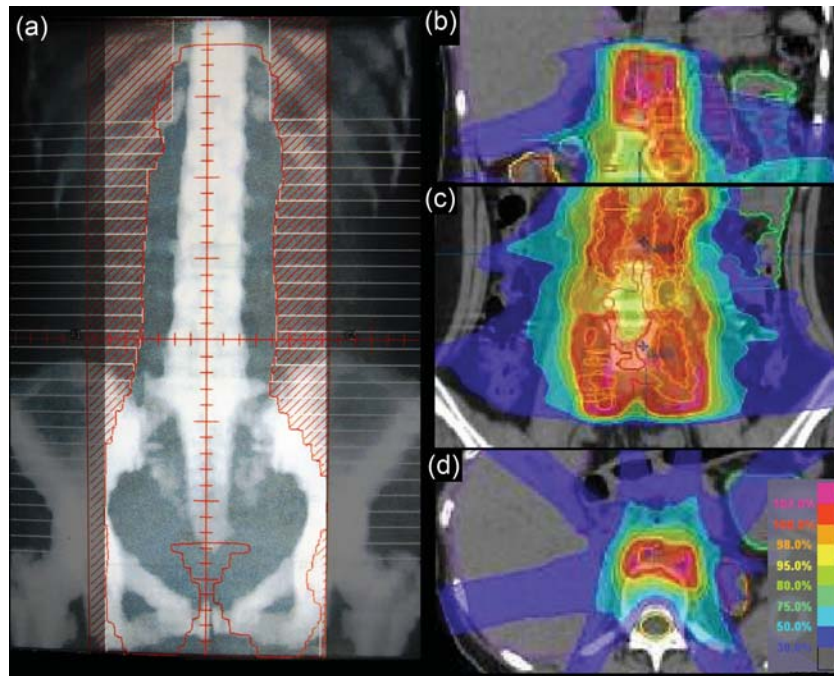
Fig. 1. Previous irradiation in Case 1. Anterior–posterior field in the first irradiation to the paraaortic area and pelvis (a) with spinal dose of 20 Gy. Reirradiation by IG-IMRT to the relapsed lymph node, performed with estimated spinal dose of 18–20 Gy at the level of the left adrenal gland (b–d).
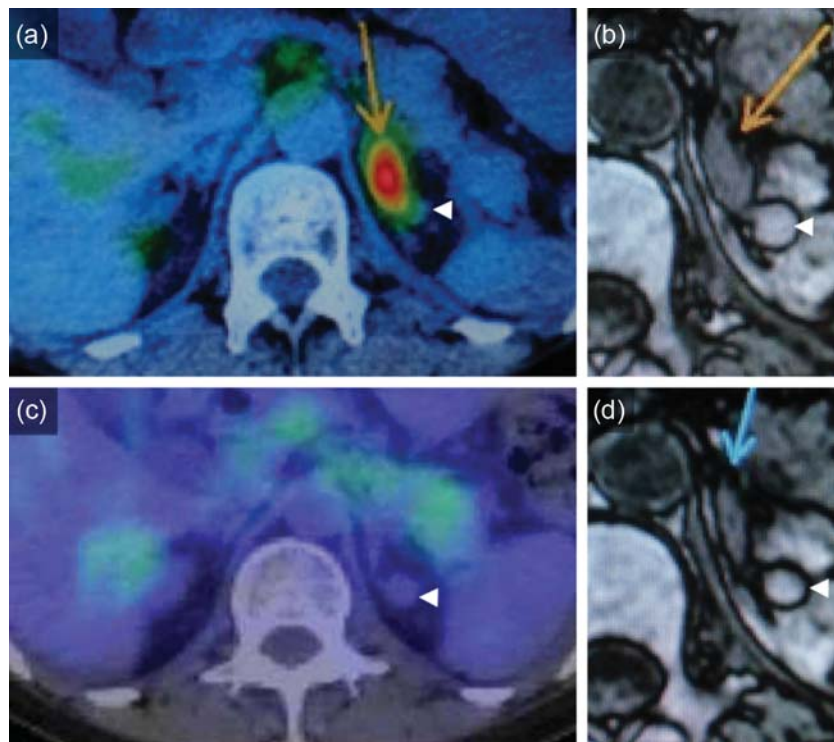
Fig. 2. Overlaid FDG-PET and MRI images before and after treatment in Case 1. The prominent FDG accumulation (a) and adrenal mass (b) observed before treatment are shown to have diminished after treatment (c, d). Arrows indicate the left adrenal gland; arrowheads indicate an apical renal cyst.
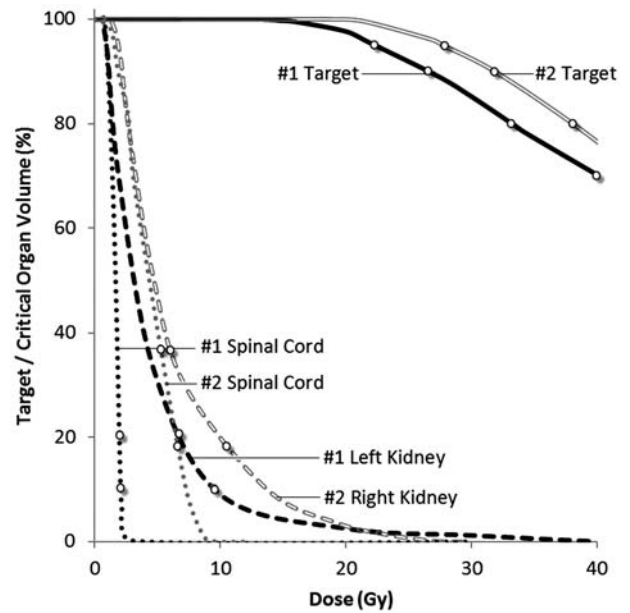
Fig. 3. Brachytherapy ablation treatment in Case 1. Applicator needles (short arrows 1, 2, and 3) are percutaneously inserted into the target (long dashed arrow) through the paravertebral muscles. Target was margined by the contrast-enhanced gel (asterisk). Dose distribution curves are from 25% to 300% (from outermost to innermost). Abbreviations: Spl, spleen; Sc, spinal cord.

Fig. 4. Dose–volume histogram of brachytherapy treatments in Case 1 (#1) and Case 2 (#2). The dots on each curve show the points for $D_{95\%}$, $D_{90\%}$, $D_{80\%}$, and $D_{70\%}$ of the target, $D_{0.5cc}$ and D_{1cc} of the spinal cord, and D_{10cc} and D_{20cc} of the closer kidney.

previous physical status and is currently being followed up at our outpatient clinic over 6 months after the treatment. We had observed no recurrence of the treated adrenal glands.

DISCUSSION

Treatment benefits

In choosing treatment for adrenal metastasis, the high probability of distant metastasis must be considered. Though local treatment may reduce a risk of life-threatening retroperitoneal hemorrhage [4, 5], their life expectancy may be limited. Time-saving and less invasive treatment would be preferred if patients have a short life expectancy. A previous study reported the one-year overall survival rate (1y-OS) and disease-free survival rate after surgery for clinically-isolated adrenal metastasis was 74% and 42%, respectively [3]. After stereotactic radiotherapy in various patients with adrenal metastasis, the one-year local control rate, overall survival rate, and distant control rate were reported as 55%, 44%, and 13%, respectively [1], and as 90%, 39.7%, and 13%, respectively [2] The former was
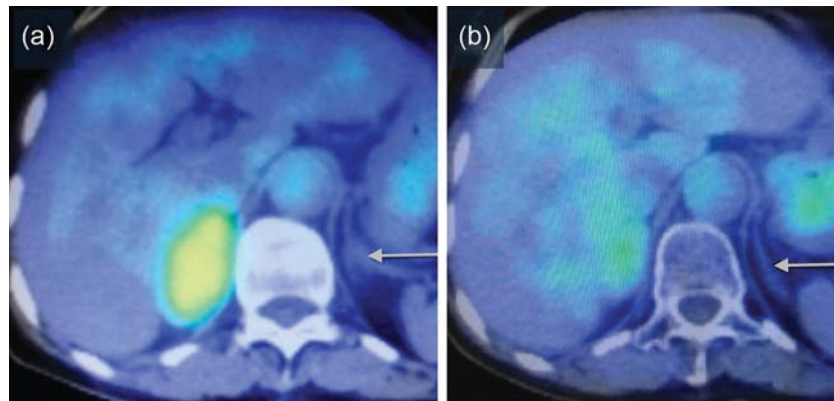
Fig. 5. Overlaid FDG-PET images before and after treatment in Case 2. The right adrenal gland shows prominent FDG accumulation and is much larger than the left adrenal gland (black arrow) (a). These features are diminished after treatment (b).
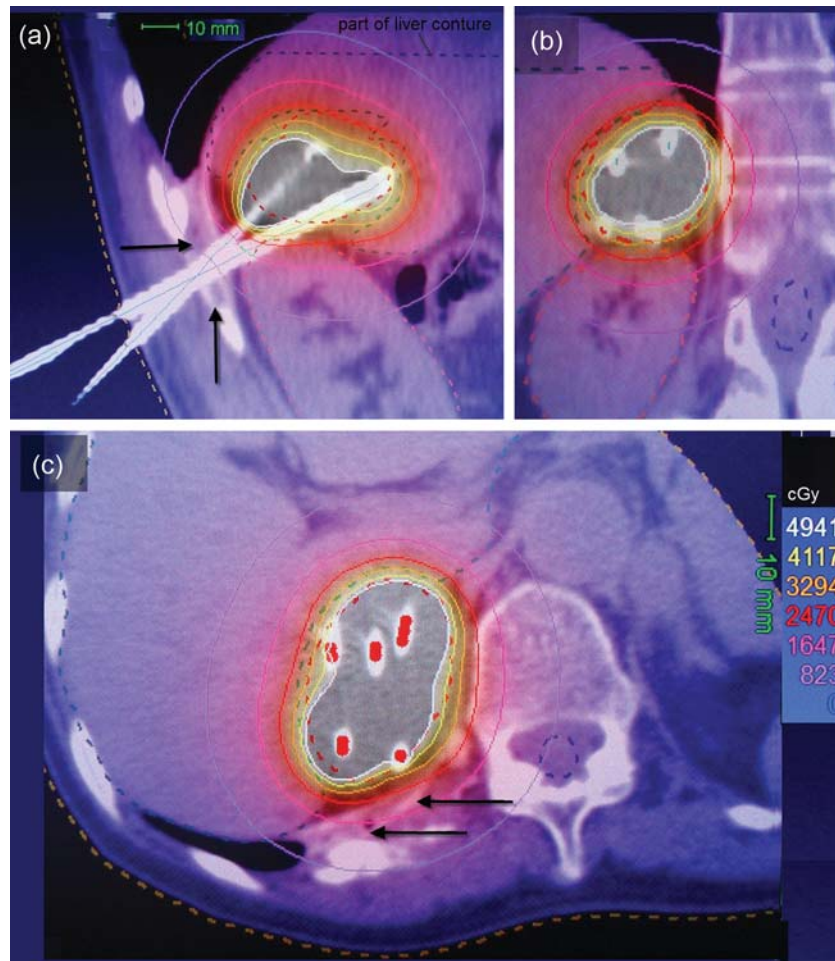
Fig. 6. Interventional brachytherapy in Case 2. Applicator needles are percutaneously inserted into the target through a created gel-filled intra-pleural route (black arrows) that enables the pleural space to be navigated without causing a pneumothorax. Because the space is narrow, the needles cross in the intra-pleural route. (a) Dose distribution curves are 8.23 Gy to 49.41 Gy from outermost to innermost (a–c).

after a mean dose of 25.7 $GyE_{LQ,\alpha/\beta=2}$, and the latter after 83.1 $GyE_{LQ,\alpha/\beta=2}$. Taken together, the overall survival rate appears more related to the distant control rate than the local control rate. Oshiro *et al.* (2011) reported that a more favorable prognosis was observed in patients with metachronous metastasis (1y-OS, 83%) compared to those with synchronous metastasis (1y-OS, 55.6%) [23]. Patients with isolated and/or metachronous adrenal metastasis may benefit more from local treatments.

Comparison of the merits of brachytherapy and radiofrequency ablation

RFA is a recently developed interventional procedure that can be performed in a one session treatment, and holds topological merit in the treatment of adrenal metastasis. The technique of needle insertion through the back muscles is a well-established safe method because the needles are held stable by the thick layers of fasciae and muscles, and

are reported with a perfect procedural success rate [10, 17]. In a new technique, but using a similar procedure, we introduced dose-intensive interventional brachytherapy to adrenal tumors. This was also performed in a single session on an outpatient basis.

Although interventional needle insertion techniques are used for both brachytherapy and RFA, there are physical and biological differences between the treatments. In brachytherapy, dose distribution is precisely calculable according to the laws of physics, whereas RFA utilizes the degenerative effect of a single application of heat ablation and is commonly followed by fever, depending on the magnitude of induced tissue damage. Another difference between the two procedures includes the needle sizes (representatively 15 Fr (1.81 mm) for RFA and 1.3 mm for brachytherapy).

Major complications reportedly occur in 2.2% of RFA procedures [24], due to the insertion of thicker needle(s),

and to the thermal diffusion that cannot be predicted precisely [25–26]. On the other hand, brachytherapy is a radiotherapy that provides gradual tumor shrinkage by apoptosis and cellular necrosis. Brachytherapy induces no pain during and after irradiation, and there is no unexpected dose distribution. Patients are not required to restrict their daily activities after brachytherapy ablation, as is generally necessary for fragile RFA-induced necrotized lesions. Unlike heat ablation, brachytherapy ablation is suitable for outpatient-based management.

Previous applications of brachytherapy for adrenal metastasis

To the best of our knowledge, the first two cases of adrenal metastasis treated by brachytherapy were reported by Wiener et al. [27]. Among their 19 serial palliative brachytherapy cases, one case of adrenal metastasis from renal cell carcinoma treated with 11 Gy (19.25 $GyE_{LQ,2, \alpha/\beta=10}$) showed a partial remission for six months, and the other from non-small cell lung cancer treated with 12 Gy (22 $GyE_{LQ,2, \alpha/\beta=10}$) died at three months, before follow-up evaluation. The doses used were much smaller than those employed with eradicative intent for other metastatic tumors [13].

Required dose

There can be no generally recommendable dose for treating adrenal metastases because of the heterogeneity of their origin. However, as mentioned in the Introduction, intensive dose delivery is generally considered to promise local control. Single-fraction external-beam treatment for various extracranial metastases, with doses ranging from 18 Gy (55.4 $GyE_{LQ,2,\alpha/\beta=10}$) to 24 Gy (68 $GyE_{LQ,2,\alpha/\beta=10}$) [12], showed a significant dose-dependency of tumor control rate. These data suggest that the doses of 11 and 12 Gy used in the previously published brachytherapy attempt [27] might be too small for tumor eradication. Further study is required to determine a recommended dose.

Advantage of subvolume effect in brachytherapy

Unlike external beam radiotherapy, interstitial brachytherapy by its very nature delivers an additional dose to the tumor subvolume. Tome et al. calculated that significant increases in tumor control probability, from 50% to 75%, would be achieved for a small increase in the risk of necrosis, when a substantial proportion of tumor volume (60%–80%) could be boosted up to 130% [28]. In the present cases, the dose distribution and dose–volume histograms (Fig. 4) showed that the tumor subvolume received significantly intensive doses. Further study is required to investigate the subvolume effect in brachytherapy.

Limitation and applicability

This is a relatively new interventional oncology solution combining therapeutic radiation oncology and interventional radiology; therefore skills in each field are needed for it to be safely performed. A large adrenal metastasis may be better prophylactically treated with a hemostatic embolization in advance, though embolization itself has not been considered curative. In a weakened patient, in whom a pneumothorax may be induced by this procedure, or when use of sedatives are contraindicated, this may no longer be practicable. The life expectancy of the patient must be considered throughout the management. However, this procedure may be worth considering before RFA, even in case of reirradiation.

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