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Chapter XIII

Role of Brachytherapy Ablation in Management of Cancer Pain

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Abstract

In this chapter we describe a solution in reirradiation issue. Radiotherapy is an effective remedy for cancer pain, even if it is second treatment (reirradiation). A sufficient dose delivery may also promise a local cure. But re-irradiation treatment is very limited due to a tolerance level of the surrounding normal tissue.

To safely perform a high dose reirradiation treatment, we developed a novel procedure, by creating a safe distance with a gel injection: a native type high molecular hyaluronic acid, between the target under ultrasound or X-CT guidance. This material is thought to protect tissues from injury and inflammation, and, reportedly in recent studies, cell migration and proliferation mediated by surface receptors including CD44.

During the gel maintains the created distance, usually for a few hours, we perform a single session irradiation by high dose rate brachytherapy (HDRBT) with an CT-based 3D planning. This spearing procedure provided significant decrease of normal tissue complication probability.

In general, a prescribed dose was a result of individual trade-off of target dose and risk-organ dose to avoid serious complications. We can prescribe a single fraction dose of 15-18.0 Gy to the target volume in safe which dose is equivalent to 50.4-75.6Gy in conventional radiotherapy schedule (at $\alpha/\beta=3$), which provide an abrasive effect when we count and use the higher dose effect close to the brachytherapy source.

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In our previously published report with 30 patients with recurrent cancer after 60 Gy (median) of previous external beam treatment, distinct tumor shrinkage in 20 of 21 eligible patients including 6 disappearances, pain reduction in 18 of eligible 21, and no unexpected late toxicity greater than grade 2 were observed during the 19.5 months observation period.

This risk-organ sparing preservation procedure may provide a safe and efficient reirradiation treatment for painful recurrent cancer patient, providing not only pain reduction but also longstanding local cancer control without significant physical stress.

Introduction

Radiotherapy is an effective remedy for cancer pain, even if it is second treatment (reirradiation) A sufficient dose delivery may also promise a local cure[1,Hayashi, '02, 2,Okamoto, '02, 3,Wu, '07]. But re-irradiation treatment is very limited due to a tolerance level of the surrounding normal tissue [4,Emami, '91]. There reported significant incidences of late toxicities attributable to accumulated dose in each at-risk organs [3,Wu, '07, 5,Salama, '06]. In an attitude survey, only one-third (90 of 271) of radiation oncologists queried were positively responded about considering reirradiation for in-field failures after previous radical radiotherapy [6,Joseph, '08].

Recent advancement in external beam radiation technology added preciseness of beam setting-up by image guided radiotherapy (IGRT), accurate configuring of dose distribution by IMRT, and some track internal movements, however, none but surgical approach save the organ at risk closely attached to the target, or else such OAR can not be treated without significant involvement.

Modern high molecular polymer technology enabled us to utilize a safe hyaluronate gel in this purpose. The bioproductive hyaluronate is a much safer material than it, artificial counterpart [7,Prada, '07, 8,Arron, '07]. We invented and applied risk-organ sparing procedures with hyaluronate gel to separate risk organs from the target only during brachytherapy [9,Kishi, '04, 10,Kishi, '07, 11,Kishi, '07].

We devised a safe and practical solution to safely perform a high dose curative reirradiation treatment, which is creation of a planned distance by a minimally invasive procedure, by means of injection of a hyaluronic acid gel between the target under ultrasound or X-CT guidance [7,Prada, '07, 9,Kishi, '04, 10,Kishi, '07, 11,Kishi, '07, 12,Kishi, '06, 13,Kishi, '09, 14,Vordermark, '08, 15,Prada, '09]. The first stage of our strategy was spread against recurrent diseases requiring reirradiation with single session high dose rate brachytherapy (HDRBT). By this creation, estimated normal tissue complication probability (NTCP) was effectively decreased to a safe level.

This procedure provided not only an warrant of safeness in palliative irradiation but also local curative irradiation, because it provided a dose required for tumor control, a tumor ablation.

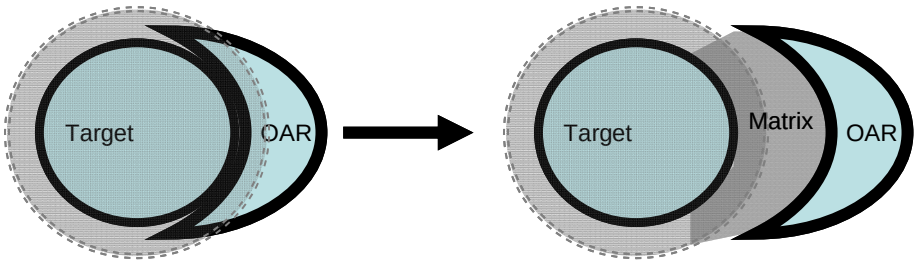

Figure 1. Organ at risk (OAR) is displaced away from a zone of intensive irradiation (dotted circle) by space creation with matrix injection.

Basic Concepts

The primitive basic concept of this procedure is liberating the organ at risk (OAR) by injecting a space between the critical organ and the target (Figure 1).

Materials and Methods

High Molecular Weight Native-type Hyaluronate

Since 2004 we applied injectable spacers for risk-organ preservation during brachytherapy [9,Kishi, '04, 10,Kishi, '07, 11,Kishi, '07]. Including historical materials, autologous blood, saline, hyaluronate (hyaluronic acid: HA), dextrose and others have been used for various purposes. Gel dissection is a kind of blunt dissection and unlike a hydrodissection. Besides the target tissue character, the viscosity, biological inertness, and biodegradability of the material are important keys to select an injectable spacer.

Hyaluronate (also called hyaluronic acid or hyaluronan) is a anionic, nonsulfated macromolecular glycosaminoglycan, composed of repeated disaccharide units of glucuronic acid and N-acetylglucosamine (Figure 2), and has a wide molecular weight variation. *Native-type is* a single straight chain, widely consists in creatures and in the extracellular space of human and animal tissue, which is degraded by our innate hyaluronidase to lower molecular hyaluronate and for further biodegradation. Hyaluronate plays a lot of roles in our body, structuring, lubrication, tissue protection, and wound healing.

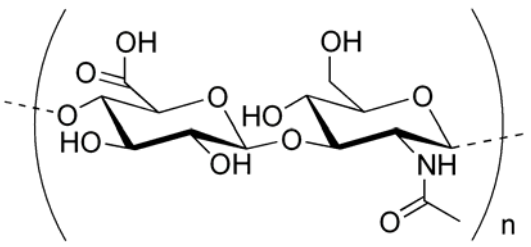

Figure 2. Hyaluronate.

Cellular surface receptors, CD44, RHAMM (Receptor for hyaluronic acid-mediated motility) and ICAM-1 (Intercellular adhesion molecule-1) has hyaluronate biding site, which regulates cellular migration, proliferation and inflammatory responses. These biding activity is partially regulated by molecular size of the hyaluronate: *High molecular weight hyaluronate* (HMW-HA) acts almost inhibitory of above responses, and low one promotes. In recent reports, HMW-HA inhibits MMP production[16,Hashizume, '10] as well as vascular leakiness[17,Singleton], and there is a size function of hyaluronate[18,Wolny]. It is supposedly a self-inefficient- until-degraded mechanism of an aggregated mass made of ligand.

In medical use, effectiveness of native-type hyaluronate has been reported in management of radiation dermatitis [41] [19,Primavera, '06], in prevention of postoperative adhesion in pelvis [20,Kusunoki, '05], and as antioxidant scavenger inhibiting inductions of NFkB, caspase and apoptosis [21,Campo, '08], and which depends on its molecular weight and concentration[22,Krasiтrki, '09].

We use a commercially available gel of high molecular hyaluronate for articular space injection (3.4 million Daltons of median molecular weight, 2.2 million of viscosity molecular size; Suvenyl, Chugai/Roche, Tokyo, Japan), which is a non-animated native-type produced by genetically-engineered bacterial fermentation. The spacing effect usually lasted for a few to several hours depend on its concentration and anatomic factors of the injected site. Frequently, 5% of contrast medium (Iopamiron 300mgI/ml, Bayer, Germany) is added to saline mixture for visualization in X-ray CT images. Because the durability is concentration dependent, an enriched gel is prepared by purpose.

Image Guided Interventions and Radiation

A. Preparation

Premedication: Because the procedure is minimally invasive, no sedative premedication is mandatory, and ordinary meal before the treatment in the morning is recommended to perform it in a relaxed mode of the patient in most cases. An anxiolytic use of hydroxyzine pamoate or else is recommended. However, carefully well considered individual medial management is required throughout the procedure in some flail patients.

Keeping the patient awake: It is helpful to ask the patient's sensation during a crucial needling maneuver to safely and effectively perform it precisely. To know the sensation related to the needle position, and extension of the injected gel, therefore deep sedation is not recommendable.

A use of sedatives: After completion of the deployment, use of benzodiazepam is recommendable, which effectively decreases post traumatic psychological process from the pain, anxiety or fear. Unexpected motion during irradiation must be cautioned.

Monitors: Patients are brought into the operating room and prepared with ECG, respiration, oxygen saturation, blood pressure monitors, and sterile drapes on the X-ray CT couch.

B. Needle Deployment

1. Process

CT landmark and local anesthesia: After the first set of plain CT images over the target are acquired, the puncture points are determined. 10 or 20 ml of 1% lidocaine solution is injected into the subcutaneous space at expected puncture site. Besides superficial marking on the skin, two to five 23G needles may be inserted to 2 to 6 cm in depth around the target as internal landmarks.

Microselectron system applicator needles of 1.1 mm in external diameter and 8-20 cm in length are used. We inserted and deployed the applicator needles in addition to the landmark needles under CT or real-time ultrasound guidance. Then the needles are advanced into the tumor and deployed as indicated. Fine pitch (2mm or 3mm) X-ray CT images are then acquired and transferred to the treatment planning computer.

After deployment of applicator needles, fine pitch X-ray CT images were acquired for radiation treatment planning process.

2. Special Technical Remarks in Needle Deployment

a. Bone and perivertebral intervention: Bone is one of the most involved and frequently cause cancer pain of either sensory and neuropathic. Usually, the involved bone is not difficult to pierce through a window in which a healthy bony structure is lost, irrespective with an existence of calcified zone. A drill as that of 13-gauge bone biopsy needle (Osteosite Bone Biopsy Needle; Cook, Canada) may be required to make an access through a hard bone surface. A subpleural gel injection produces a safe space for needle insertion without the lung tissue injury.

b. Needle-eye's view: To find and step-in a safe path to a deep target, we built a scenario of what needle-tip encounters as ; skin, subcutaneous adipose tissue, muscle fascia, muscle, a fascia, and inter-fascial adipose tissue and possible nerve plexus, and the target.

c. Superficial lesions: A high-precision ultrasound system is used to examine the following superficial structures including the dermis, epidermis, subcutaneous tissue, muscle, peritoneum, sub-fascial soft tissues, intestines, intestinal peristalsis, eyes, vessels, as well as the tumors and to determine the infiltration range.

d: Nerve plexus: Sensation of pain may increase when pressure of inserting the needle further stimulation. A swelling and pressing tumor may be covered with a layer of irritated of nerves to which additional local anesthesia with lidocaine is usually very effective. Use of denervative anesthesia with phenol glycerol may be chosen here but it masks future signals of local tumor recurrence.

C. Gel Injection

1. Preparation: Appropriate volume, concentration, and timing of injection of hyaluronic acid gel is depend on the anatomical structure of the site and required duration of the spacing. Most often, 50 to 150 mL of 1mg/ml hyaluronic acid saline solution is prepared. This concentration of 1mg/mL is enough for injection immediately before starting irradiation and usually durable for over 30 minutes to 4 hours depend on the injected sites.

2. Injection: Injection into the space between the tumor and the risk organs is continued until the thickness gains a large enough margin of safety for the risk organ. Further injection is performed to maintain the space if necessary. Patency of the distance is reconfirmed after the irradiation.

2. Confirmation: The space created by the injected gel is monitored by ultrasound sonography or X-ray CT to watch for unexpected gel immigration and to measure the thickness of the gel space.

D. Radiotherapy

1. Planning: After contouring the target and surrounding critical organs and recognizing the needle positions from the imported X-ray CT images in the planning computer, a treatment plan is created using 3D-inverse and graphic optimization method (PLATO version 13.7, Nucletron, Veenendaal, Netherlands).

2. Plan assessment: We assessed desirable separation distances between the target and the risk organs, according to the calculated total dose of the risk organs [23,Burman, '91]. At this point, target dose, risk organ dose and separation distance are individual trade-off problems according to each patient's condition. When it is difficult to prescribe a desirable dose due to low allowance of the risk organ dose or due to encountered difficulty to create sufficient separation distance the prescribed dose must be decreased and distance recalculated step by step. Equivalent dose in conventional 2 Gy fractions schedule is calculated with linear-quadratic (LQ) model and linear-quadratic-Linear (LQL) model [24,Astrahan, '08] and expressed as $GyE_{LQ.3}$ and $GyE_{LQ.3,6}$, respectively, where $\alpha/\beta = 3$ and transition dose：DT = 6 for late effects of tumor and normal tissue.

3: Special remarks in Equivalent dose calculation and expressed as $GyE_{LQ.3}$ and $GyE_{LQ.3,6}$, respectively, where $\alpha/\beta = 3$ and transition dose: DT = 6 for late effects of tumor and normal tissue.

It should be noted that the LQ model may not provide precise estimation for single shot irradiations [25,Brenner, '08, 26,Kirkpatrick, '08]. In this setting ($\alpha/\beta=3$), each single fraction dose of 20, 18, and 16 Gy was calculated to be an equivalent total dose of 92.0, 75.6, and 60.6Gy in conventional 2Gy fractions schedule.

4. Irradiation: After an optimal set of prescribed dose and separation distance parameters is determined, the planning data were then transported to a Remote After-Loader System (Microselectron HDR Ir-192 version 2, Nucletron). In this case series a median dose of 18 Gy (range, 16-20 Gy) for GTV and a separating distance of not less than 1cm is prescribed. Patient is moved to a shielded brachytherapy room. During the irradiation the patients are monitored by video-camera and vital data are recorded. The irradiation requires usually 10 to fifty minutes depending to the target size and dose.

E. Recovery to Dismissal

After the irradiation staffs enter the room to release the patient from monitors and dwelling needles. Usually hemostasis is easy. Patients are moved to resting couch and then discharged.

Evaluation and Follow-up

They are followed up at our out patient clinic at the first week, and the first month. Follow-up includes individual surveillance and management on adverse effect of radiotherapy and development of recurrent or metastatic diseases. Tumor status and general conditions are evaluated regularly. The first tumor evaluation is usually done two to three months after the treatment. Sign and symptom of radiation induced late toxicity is recorded and graded according to the latest CTCAE[27,Trotti, '03]. Pregabalin is effective for neuropathic pain[28,O'Connor, '09] due to residual symptoms and radiation induced.

Summary of Clinical Effects

In our report on thirty patients with reirradiation [13,Kishi, '09].

They had previous irradiation with a median dose of 60 Gy (range, 44-70 Gy) in 2-Gy fractions. All patients had subjective symptoms: 25 had pain, of which 21 was refractory to analgesics, 25 complained of local mass of which three were ulcerated. By location there were 13 head and neck lesions, three breast, abdominal wall lesions, two each bone, perineum, chest wall, intramuscular, lymph nodal lesions, and one pelvic wall.

Immediately before reirradiation, the median tumor (target) size was 4.0cm (range 2-13 cm), and median tumor volume was 18.8 cm3 (2.4-646.7 cm3).

Of these 30, 15 were locoregional recurrence of the primary disease, 10 were distant metastasis where three were incision disseminations, and 5 were regional nodal relapse. By number of lesions at the time of reirradiation, 13 patients had one, eight had two, six had three, and three had four. The at-risk organs involved 29 skin areas, four intestinal, three each mucosal and three retinal parts. The median dose to these *at risk organs* in the previous radiotherapy was 50Gy (range: 40-70) in these 22-35 fractions. Single-fraction dose of 18.0 Gy (median, equivalent to 75.6 Gy at an alpha/beta value of 3; range, 16-20 Gy) was prescribed to the tumor. The median created distance was 10 mm (range, 10 – 15). Irradiation required approximately 10 to fifty minutes depending to the target size and dose. By the gel injection the at-risk organ dose decreased from 9.1 +/- 0.9 Gy to 4.4 +/- 0.4 Gy (mean +/- standard deviation, $p < 0.01$), and the normal tissue complication probability decreased from 60.8% +/- 12.6% to 16.1% +/- 19.8% ($p < 0.01$). Distinct tumor shrinkage in 20 of 21 eligible patients, including tumor disappearance in 6 patients, pain reduction in 18 of 21 eligible patients, and no unexpected late toxicity greater than grade 2 were observed.

The median observation period was 19.5 months (range, 3 - 43). At the second month, a distinct decrease in tumor volume was observed in 20 (95%) of eligible 21 patients including 6 (24%) disappearances out of eligible 25.

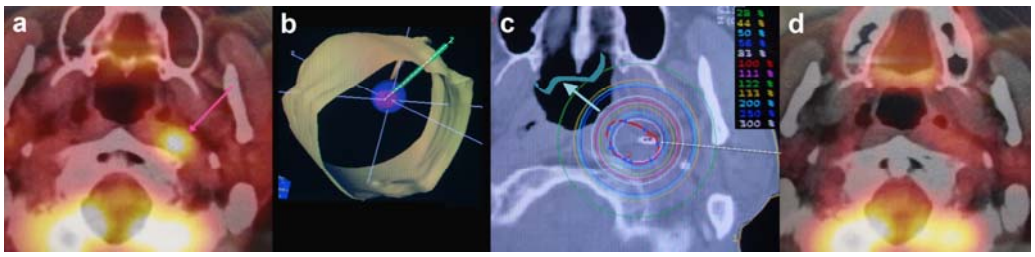

Figure 3. Case 1.

Clinical Cases

Case 1

A-50-years old man who complained abnormal sensation on the neck one year after left neck surgery of pharyngeal pouch cancer followed by 50Gy of external beam radiotherapy was found developed a left retropharyngeal lymph node (Rouviere's node) metastasis. In spite of chemotherapy the tumor and the symptom increased. Accumulation of FDG in PET study (a). An applicator needle (dotted line) was inserted from the left side of the neck (b) and single dose 20Gy (100% line) was prescribed (c). Part of the needle is seen in the target. Note higher dose area in the target. Pharyngeal mucosa was shifted to low dose area by injected hyaluronate during irradiation (thick arrow and ribbon). FDG accumulation was remarkably decreased two months after the brachytherapy (d). The patient has been healthy without any evidence of relapses over three years.

Case 2

A-67-years old man intubated at the emergency room because of severe dyspnea due to tracheal tumor obstruction was referred to our division. We treated the peritracheal and trachea-obstructing tumor (a, arrow) with interstitial brachytherapy (in figure a, five needle parts are seen on the left side of the tube) with more than 16Gy (b). One month later trachea was clearly open and free from tumor (c). No tumor regrowth was observed in the trachea thereafter.

Case 3

A 84 year-old male patient with hemi-paralysis after brain infarction developed a postoperative submandibular lymphnode metastasis from oral floor cancer(a). Because unavailability of repeated or long term treatment, he desired to be treated by single session brachytherapy. We injected sub mucosal and subcutaneous space surrounding the tumor to make safe distance then delivered 18Gy (76.5GyELQ) (b). No tumor was detectable after six months (c).

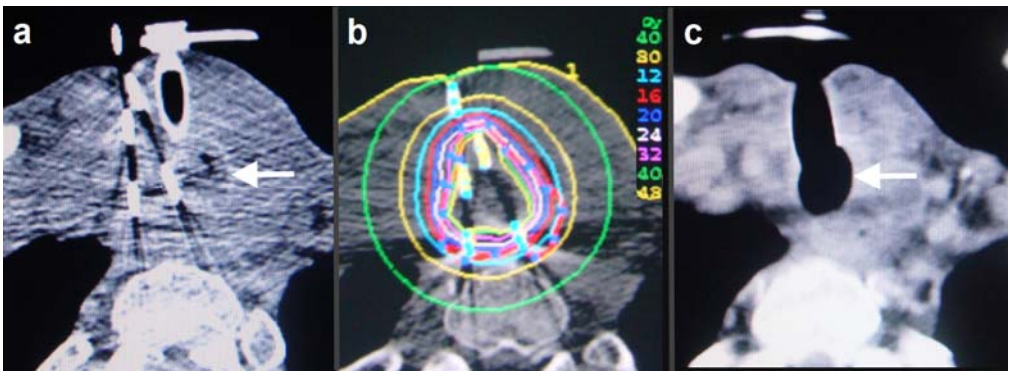

Figure 4 . Case 2.

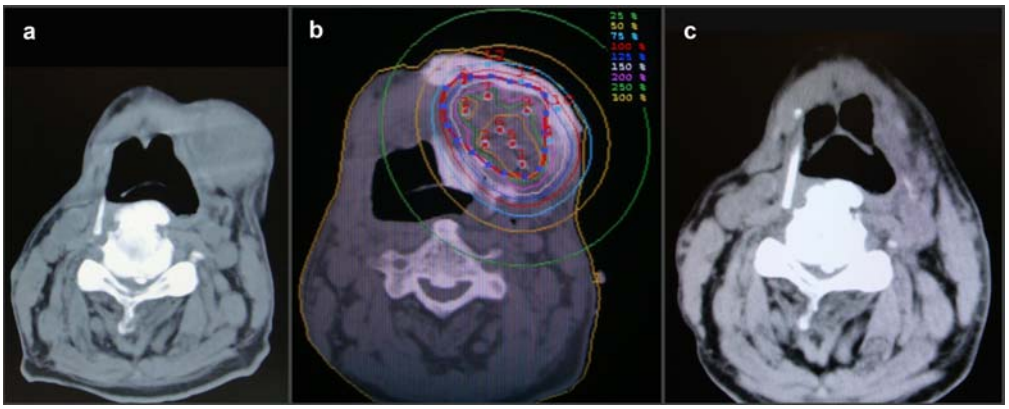

Figure 5. Case 3.

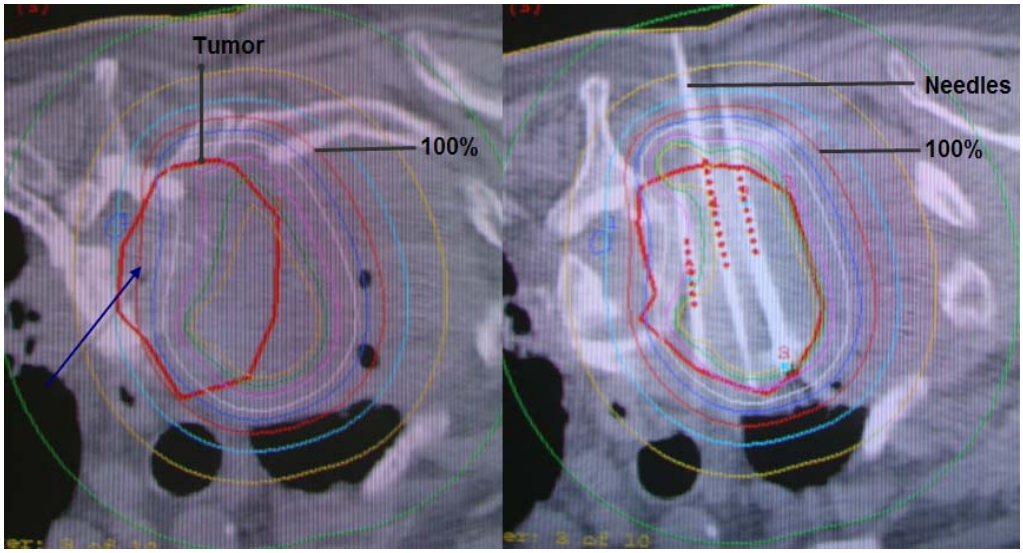

Figure 6. Case 4.

Case 4

An elderly female patient with severe pain due to advanced lung cancer. No narcotics was effective. The tumor is invading into the vertebral bone and perivertebral tissues causing neuropathic pain around the chest wall. External beam radiotherapy was not indicated due to interstitial pneumonia. We performed interstitial brachytherapy of single 15Gy ($54GyE_{LQ,3}$), and the local pain was thereafter mitigated and controlled. Dose lines: to outer, 25% step: to inner, 50% step. Dots: active source points. Spinal $D_{0.5cc}$ (■) was 10Gy (■$54GyE_{LQ,3}$).

Discussion

Goal and Mission

Our purpose is relieve cancer related pain, fear and anxiety, by providing a good local control with a curative radiation dose using minimally invasive procedures even in patient with previously irradiated recurrent tumor that is one of the most difficult situation in cancer treatment. In recent years, the numbers of reports on reirradiation treatment had been increasing[13,Kishi, '09, 29,Rades, '08, 30,Watkins, '09]. We reported several clinical results, and our approach is still growing.

Biological Rationale

Strong hypoxia in recurrent tumor after irradiation: In general tumors larger than a certain size (>0.1 mm) develops hypoxic areas due to insufficient vascular supply. These hypoxic area is also a sanctuary from hydrophilic chemotherapeutic agents, though launching waves of attacks may work. Cellular adaption to hypoxia includes cell cycle arrest and prolongation of repair deadline, increased capability of anaerobic glycolysis which results lactic acid pooling, and moving programs to produce actins and lose cadherins. Previously irradiated tissue tends to be more hypoxic and therefore frequently more radioresistant. Popovtzer et al. reported 92% was in-field third recurrence which occurred in 77% of median 68Gy-reirradiated patients in relapsed 154 squamous head and neck cancer patients [31,Popovtzer, '09]. To this HDRBT has an adequateness of having high dose areas around position of the source inserted in the tumor.

Diagnostic Jeopardy

Diagnosis of recurrence: Because the radiotherapy itself induce the tissue hypoxia, biological responses occurs in and around the irradiated area making precise judge difficult. Imaging evidences for the tumor recurrence are, in stronger order, 1) increase in tumor size (especially new nodule protrusion), 2) revascularization in the tumor (not static revascularization around the tumor), 3) strong increase in FDG-PET accumulation.

Symptomatic worsening, emergence of ring enhancement zone, weak or moderate appearance of FDG-PET accumulation, are frequently reporting reactive phenomenon. Recommendable approach is to rationally integrate and interpret time course of the findings of PET-CT, Enhancement study of MRI, and diffusion images in MRI.

Low Occurrence Rate of Complication

In our previous report of reirradiation with total accumulated dose of 125.6 Gy (median), actual incidence was lower (0% directly related to the radiotherapy) than expected (16.1%) in 19.5months observation period. It might be because we had created a sufficient safety margin in the gel spacing procedure, and because of time interval from the previous radiation effect.

Radiobiologic Factors

1. LQ model may overestimation single high dose effect: The LQ model is well validated, experimentally and theoretically, allegedly up to about 10 Gy/fraction, and reasonable for clinical use up to a large dose of about 18 Gy per fraction in fractionated schedules [25,Brenner, '08]. Recent studies revealed significant over estimation of large single dose treatment effect calculated by LQ model both in clinical and experimental data [24,Astrahan, '08, 26,Kirkpatrick, '08, 32,Iwata, '84]. *Overestimation of single high dose effect* tends to increase in a larger dose than Dt = 2 x (alpha/beta ratio) [24,Astrahan, '08]. In LQL model, a linear function works over Dt Gy. The LQL model seems to be under evaluation.

2. Interval effect : Interval more than 6 months significantly increased spinal tolerance level[33,Nieder, '06, 34,Nieder, '05]. Several authors reported effectiveness of reirradiation by external beam [2,Okamoto, '02, 3,Wu, '07, 35,Sulman, '08, 36,Wurschmidt, '08, 37,Oksuz, '04] with relatively small incidence of grade 3-4 toxicity for the cumulative dose of 110 – 117Gy, where these median interval ranged 13 – 92 months.

Dose Required for Tumor Control in Reirradiation

Previously irradiated tumor may increase its radioresistance. Popovtzer et al. reported 92% was in-field third recurrence which occurred in 77% of median 68Gy-reirradiated patients in relapsed 154 squamous head and neck cancer patients [31,Popovtzer, '09]. Further data accumulation is required.

Remarks on other Injective Materials

Several other materials have been reported as spacers.

1.Artificial cross-linked hyaluronate: There is a time proof variant of hyaluronate which is artificially cross-linked and resistant to biodegration. and some are durable for months

(Restylane SubQ, Q-med, Uppsala, SWEDEN)[38,Restylane®-International] and are used as a filler for cosmetic augmentations by subcutaneous injection. Unlike native type hyaluronate, no biological researches including receptor mediated process was available on this variant. Use of this type of hyaluronate were reported by Prada et al. to create and maintain a space during IMRT, HDRBT and LDRBT of prostate cancer [7,Prada, '07, 15,Prada, '09]. To these Vordermark et al. commented that a material with a faster resolution would be suitable for an application in HDRIBT[14,Vordermark, '08]. These timeproof hyaluronate implants may cause immune[39,Hamilton, '07] or inflammatory reactions[8,Arron, '07] or infections[40,Christensen, '09] [8,Arron, '07, 41,Ghislanzoni, '06, 42,Wolfram, '06, 43,Wiest, '09, 44,Edwards, '07] and some of these were surgically removed [8,Arron, '07, 41,Ghislanzoni, '06, 42,Wolfram, '06, 43,Wiest, '09, 44,Edwards, '07].

2. Dextrose solution: Dextrose solution has been one of frequently used spacer. This is a low viscosity fluid rather difficult to create effective durable space and so usually requires large dose. In a report 625ml (range, 250–1,200 mL) of 5% dextrose in water was required to separate organs (for approximately 1cm seen in their figures) during radiofrequency ablation [45,Arellano, '10]. Electrolyte imbalance and fluid overlord must be cautiously monitored.

Time and Cost-effectiveness

The cost of the native-type high molecular hyaluronate approximately $10-15 for a 2.5ml (2.5mg) vial, and is much less than that of the artificially cross-linked durable type (by approximately 1/60) and the time required to complete the procedure is 10 to 15 minutes in most cases; thus, HGI is highly time and cost-effective.

Extending Further Possibilities

Not only creating a safe distance, or allowing curative radiotherapy what have been impossible for long time, our creation will provide further developments. This spacing will safely guide a landing of larger machines and/or organs without intensive surgical procedure. All what has been obliged to the ancient idea that given anatomic constellation is unchangeable would be now liberated. We, biologically a human, in the process of development had been changing our fetal anatomical constellation to the present.

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