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BRIEF ARTICLE

Novel eradicative high-dose rate brachytherapy for internal mammary lymph node metastasis from breast cancer

Kazushi Kishi, Hirokazu Tanino, Tetsuo Sonomura, Shintaro Shirai, Yasutaka Noda, Morio Sato, Yoshitaka Okamura

Kazushi Kishi, Department of Radiation Oncology, Wakayama Medical University, Wakayama 641-8510, Japan
Hirokazu Tanino, Department of Surgery, Naga Hospital, Uchida 1282, Kinokawa City, Wakayama Prefecture 649-6414, Japan
Tetsuo Sonomura, Shintaro Shirai, Yasutaka Noda, Morio Sato, Department of Radiology, Wakayama Medical University, Wakayama 641-8510, Japan
Yoshitaka Okamura, 1st Department of Surgery, Wakayama Medical University, Wakayama 641-8510, Japan
Author contributions: Kishi K developed the methods, treated the patients and wrote the manuscript; Tanino H managed and treated the patients; Sonomura T, Shirai S, and Noda Y supported this clinical work; Sato M and Okamura Y approved the manuscript.
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Correspondence to: Kazushi Kishi, MD, PhD, Department of Radiation Oncology, Wakayama Medical University, Wakayama 641-8510, Japan. kazushi.kishi@gmail.com
Telephone: +81-73-441-0605 Fax: +81-73-441-0605
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Abstract

AIM: To develop a method of delivering an eradicative high radiotherapeutic dose safely preserving the surrounding skin in the treatment of internal mammary lymph node metastasis (IMLNM) of breast cancer.

METHODS: We report a 38-year-old female patient with a solo IMLNM showing no response to 60 Gy in 2.5 Gy fractions of external beam radiotherapy. To eradicate this tumor, a boost brachytherapy plan was created after percutaneous insertion of an applicator needle into the IMLNM lesion avoiding the pleura and vessels under ultrasound monitoring. According to the dose distribution, the required thickness of a spacer between the skin and the tumor was determined, and hyaluronic gel was injected up to this thickness under ultrasound monitoring. We evaluated skin doses, target doses and clinical outcome.

RESULTS: All procedures were performed easily. Sixteen Gy (34.7 Gy equivalent in 2 Gy fractions calculated by the linear quadratic model at $\alpha/\beta = 10$: $EQD2_{,\alpha/\beta = 10}$, cumulative total was 101.9 Gy EQD10) to 100% of the target volume was irradiated with cumulative maximum skin dose of 70 Gy $EQD2_{,\alpha/\beta = 3}$ which was 98.7 Gy $EQD2_{,\alpha/\beta = 3}$ without spacer. No procedure related- or late complications and no local recurrence at the treated site were observed for three years until expiration.

CONCLUSION: We consider that this procedure will provide an eradicative high-dose irradiation to IMLNM of breast cancer, preserving skin from overdose complications.

Key words: Brachytherapy; Hyaluronate; Internal mammary lymph node; Metastasis; Skin preservation; Breast cancer; Organ at risk

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INTRODUCTION

Metastasis to the internal mammary lymph nodes (IMLN) is one of the characteristic conditions in breast cancer. Although the incidence is rare in early stage[1], IMLNM

was found in 13.8% of patients with clinical N2 or N3 locally advanced disease[2], of which 27.9% were refractory to chemotherapy and 11% were refractory to both chemo- and radiotherapy of 50 Gy to 72 Gy. Dose escalation is a key to overcome radioresistance. However, high dose treatment is generally limited by low tolerability of the surrounding normal tissues. The calculated dose causing necrosis or ulceration in 5% of 10 cm^3 of irradiated skin in five years was reported to be 70 Gy[3]. This is recommended to ensure the safety of these tissues in high dose eradicative treatment to radioresistant tumors. One practical solution is to obtain a safe distance by using a spacer. Recently, high-dose eradicative radiotherapy using various spacers has been developed[4-9]. Of these spacers, high-molecular-weight hyaluronate is a safe intrinsic substance in the human body and when used as an injectable spacer is temporarily successful during high dose rate brachytherapy (HDRBT)[5,9,10-12]. HDRBT with a spacer may facilitate safe and effective dose delivery to IMLNM. We report a patient with an IMLNM as a sole recurrence.

MATERIALS AND METHODS

Patient

A 38-year-old female patient was referred for radiotherapy of a sole IMLNM of 2 cm in diameter. Eight years before, she underwent right mastectomy for stage Ⅱ breast cancer of 5 cm in size, histologically proved as invasive ductal carcinoma with estrogen receptor overexpression. She received postoperative intravenous chemotherapy consisting of Cyclophosphamide 500 mg/body weight (1.5 m^2), Adriamycin 50 mg/body and 5-fluorouracil 500 mg/body on day 1, repeated every 3 wk for a total of eight courses (six courses and an additional two courses); and per oral treatment with tamoxifen, 20 mg/body daily for 5 years. The patient was followed up regularly for 3 years. No postoperative radiotherapy was performed.

In August of the 6th year after surgery, the patient began to feel occasional pain in her anterior chest wall. X-ray computed tomography (CT) examination revealed a parasternal spherical mass, and this was histologically confirmed as ductal carcinoma with estrogen receptor overexpression. Progesterone receptor and HER2 receptor were negative. Under the diagnosis of metachronous IMLNM, exemestane as hormonal treatment was started and was found to be temporarily effective, but the symptoms recurred after 5 mo and the tumor size increased. The CEA level increased to 18.6 μg/mL. She was referred to our clinic.

As first radiotherapy to the IMLNM, a three-dimensional plan of 60 Gy in 2.5 Gy fractions (67.2 Gy-$EQD2_{,\alpha/\beta=10}$) by external beam radiotherapy (EBRT) was prescribed (Figure 1). Doses in the skin were 36 Gy (32.4 Gy $EQD2_{,\alpha/\beta=3}$) at 0.1 mm depth as an epidermis reference point (RP), 48 Gy (48 Gy-$EQD2_{,\alpha/\beta=3}$) at 2.5 mm depth as a dermis RP, and 54 Gy (57.1 Gy-$EQD2_{,\alpha/\beta=3}$) at 5 mm depth as a subdermis RP. Pulmonary V_{20} (the volume of lung receiving at least 20 Gy) was 6.3%.

Table 1 Calculated skin dose

Skin		Epidermis	Dermis	Subdermis
Reference point	Depth from the skin surface (mm)	0.1	2.5	5
EBRT	Dose (cGy)	36	48	54
	Equivalent dose* - a	40	48	57.1
BT without spacer	Dose (cGy)	9.3	8	12.5
	Equivalent dose* - b	22.9	17.6	41.6
	Cumulative dose of a + b	62.9	65.6	98.7
BT with spacer	Dose (cGy)	1.8	4.4	6.7
	Equivalent dose* - c	1.73	6.51	12.9
	Cumulative dose of a + c	41.73	54.51	70
Ratio of dose reduction in equivalent dose*: c/b	$EQD2_{,\alpha/\beta=3}$ (cGy)	1/13.2	1/2.7	1/3.22

EBRT: External beam radiotherapy; BT: Brachytherapy.

However, the tumor showed no significant reduction in size at 1 mo after radiotherapy (Figure 2). It was the only lesion. Following the patient's desire for local cure by radiotherapy, we planned an immediate boost brachytherapy. Informed consent was obtained from the patient prior to treatment, which was performed with standard institutional approval. The entire procedure was performed at our outpatient clinic.

Preparation and needle deployment

Hyaluronic gel mixture was prepared by mixing 50 mg sodium hyaluronate with a median molecular weight of 3.4 million Daltons (Suvenyl, Chugai/Roche, Tokyo, Japan) with saline, to produce a volume of 50 mL. The patient was sedated but awake. Under monitoring with ECG, PaO_2, respiration, and blood pressure, and under ultrasound and X-ray CT (SCT-7000, Shimadzu, Kyoto, Japan) guidance, a brachytherapy applicator needle (1.1 mm outer diameter; 16 cm length) was inserted in the target, avoiding vascular and pulmonary injury (Figure 2A and B). Then, 3 mm-pitch CT images were acquired and transferred to the treatment planning computer (PLATO, Nucletron, Veenendaal, Netherlands).

Treatment planning, gel injection and irradiation

We created a 3D brachytherapy treatment plan prescribing 16 Gy (34.67 Gy-$EQD2_{,\alpha/\beta=10}$) to 100% of the planned target volume. Calculated skin dose to the epidermis RP at 0.1 mm depth was 9.3 Gy (22.9 Gy-$EQD2_{,\alpha/\beta=3}$), the dermis RP at 2.5 mm depth was 8 Gy (17.6Gy-$EQD2_{,\alpha/\beta=3}$) and to the subdermal RP at 5 mm depth was 12.5 Gy (41.6 Gy $EQD2_{,\alpha/\beta=3}$) (Figure 2C, Table 1); each cumulative dose was 62.9, 65.6 and 98.7 Gy $EQD2_{,\alpha/\beta=3}$, respectively. Tentatively we tried to keep the maximal skin dose below 70 Gy $EQD2_{,\alpha/\beta=3}$[3], and the maximal dose to subdermal tissue was calculated below 6.7 Gy (12.9 Gy-$EQD2_{,\alpha/\beta=3}$). Thus, the calculated minimum spacer thickness was 6.9 mm (total skin

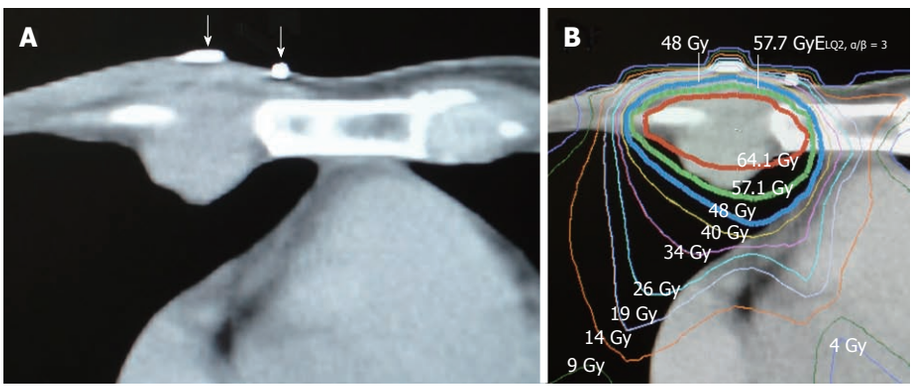

Figure 1 X-ray computed tomography images before radiotherapy and external beam radiotherapy treatment plan. A: A lesion typical of internal mammary lymph node metastasis is observed, with no skin involvement; B: External beam therapy plan on the same slice. Subdermal dose at depth of 5 mm, epidermal dose, and dermal dose at depth of 2.5 mm was 57.1 Gy, 40 Gy and 48 Gy EQD2, α/β = 3, respectively, and 8-9.3 Gy (17.6-22.9 Gy-EQD2, α/β = 3). Isodose curves are 98% and 90% to 10% at intervals of 10% of 60 Gy, from innermost to outermost. White arrows: Positional markers for external beam radiotherapy simulation.

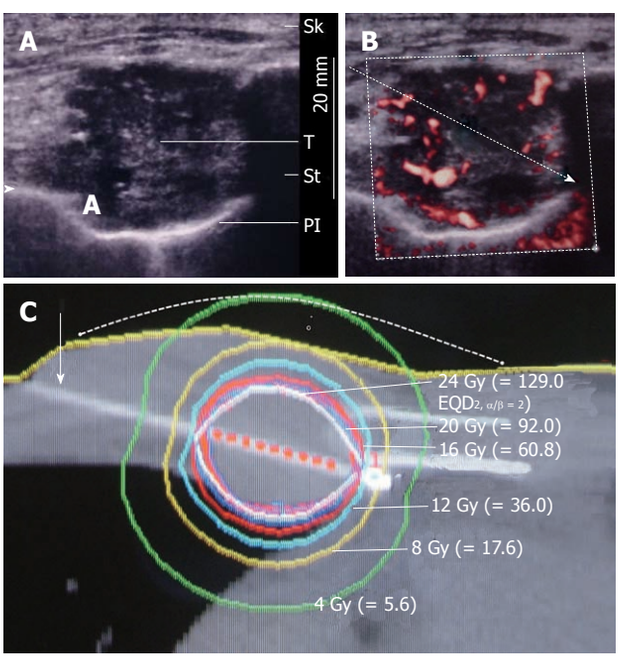

Figure 2 Plain ultrasound image (A) and power Doppler image showing the planned route for needle insertion to avoid vessels, pleura and lung (B): Brachytherapy dose distribution and inserted brachytherapy needle (white arrow) with nine red points (interval: 2.5 mm) for source activation. The dashed line shows a supposed skin surface line raised by 7.0 mm and a single dot and a circle show the shifted dermal and subdermal reference point, respectively (C). The skin density is increased by subcutaneous injection of lidocaine, not by skin invasion. Dotted circle indicates planning target volume contour. Isodose curves are 150% (white), 125% (blue), 100% (red), 75% (light blue), 50% (yellow) and 25% (green) of 16 Gy, from innermost to outermost. Sk: Skin; T: Tumor; St: Sternum; PI: Pleura.

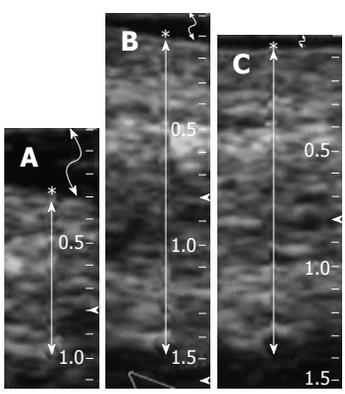

Figure 3 Measurement of skin thickness: The skin thickness from the epidermis to the bottom of the subdermis was approximately 7 mm before the gel injection (A), approx. Fourteen mm after gel injection (B) and the thickness almost remained the same after irradiation (C). Slight decrease in the thickness might be due to compression by the probe. A low echogenic gel area is seen in the mid zone of the subcutaneous tissue including bright spots of air bubbles (B and C). Asterisk: Skin surface (epidermis); While arrow: Range of skin including epidermis, dermis and subdermis; Curved arrow: A gel layer between the surface of the skin and the ultrasonography probe (top), which surface gel was for a precise measurement avoiding compression.

thickness: 13 mm). Before irradiation, hyaluronic gel was injected into the subcutaneous tissue using a 21-gauge needle. The created thickness of the skin was confirmed by ultrasonography with a 10 MHz transducer before and immediately after irradiation (Figure 3). The planning data were sent to an I-192 remote after-loader system (Microselectron HDR Ir-192, Nucletron) and irradiation was started. After irradiation, the needles were promptly removed and the patient was allowed to rest; she left the clinic, when ready, on foot. The patient was followed-up regularly at our clinics.

RESULTS

Procedural results

Figures 2C and 4 show irradiation of 100% volume of the planning target volume by 16 Gy in one fraction (32.4 Gy-EQD2, α/β = 10). Pulmonary tissue volume receiving more than 20 Gy-EQD2, α/β = 3.07[13] was 7.8 cc. The thickness of the gel injected skin did not show significant change before and after the irradiation which took 11 min (Figure 3). The calculated equivalent dose in the subdermis RP was 12.5 Gy-EQD2, α/β = 3, which without spacing was 41.6 Gy-EQD2, α/β = 3 (Table 1). The reference point dose at the epidermis, dermis, and subdermis was decreased to 1/13.2, 1/2.7 and 1/3.22, respectively. The time required for the gel injection procedure and

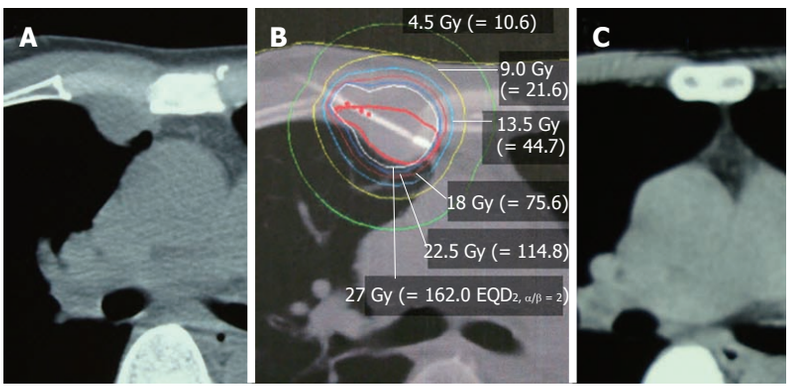

Figure 4 X-ray computed tomography (A) and brachytherapy dose distribution (B) images of the second lesion. Computed tomography image shows no tumor recurrence at 1 year after treatment (C). The attachment pattern of the anterior mediastinum changed with breath holding. In images (A) and (B), slices were obtained at the maximal cross-section of the tumor. Isodose curves are 150%, 125% (thin line), 100% (18 Gy), 75%, 50% and 25%, from innermost to outermost.

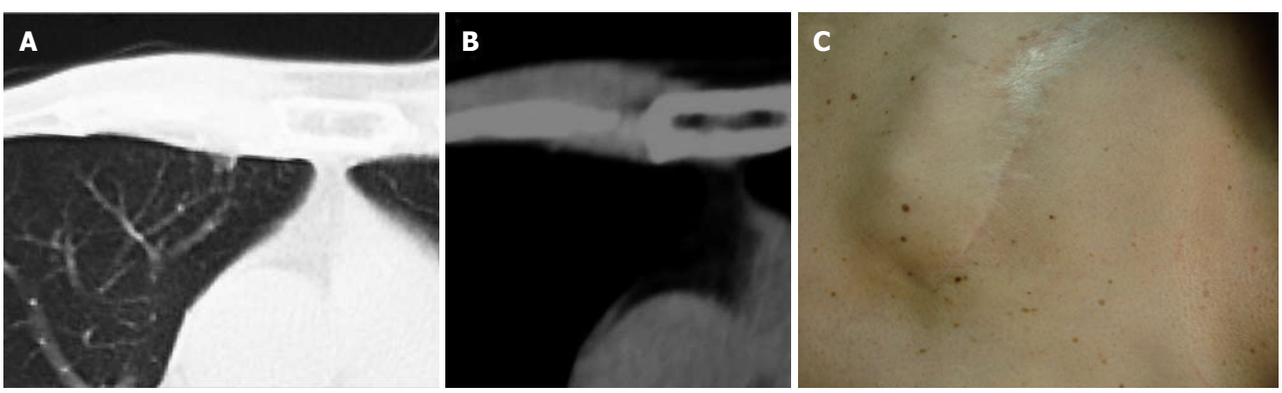

Figure 5 X-ray computed tomography images obtained 2 years after the first treatment show no tumor recurrence (A, B) and no pulmonary injury except a tiny fleck (A), no skin damage is observed except for slight pigmentation due to EBRT (C).

the total treatment time was 10 min and 2.5 h, respectively. There were no procedure-related complications, and no additional medication was required.

Clinical outcome

Four weeks later, a marked reduction in tumor size was observed and the CEA level decreased from 18.6 μg/mL to 10.0 μg/mL. One year later, the patient developed another IMLNM 7 cm cranial to the previous one. This second lesion was treated with a single brachytherapy dose of 20 Gy (92 Gy $EQD2_{,\alpha/\beta=3}$) with the maximal skin dose of 5 Gy (Figure 4). The needle was inserted passing through the cartilage. The subdermal dose was decreased to 1/3.25 by gel injection. Two years after this treatment there was no evidence of the tumor on X-ray CT imaging, and no pulmonary or skin damage (Figure 5). Both local lesions were cured without complications. The patient died 3 years later due to liver metastasis.

DISCUSSION

IMLNM and radiotherapy

Treatment of IMLNM has long been a delicate balance as there are tradeoffs between elective surgery for metastatic tumors and survival benefit[14], and between prophylaxis to relapse and radiation toxicity to the lungs and heart[15,16]. Increased non-breast-cancer mortality including cardiac events in post-surgically irradiated women[17,18] is thought to be related to involvement of these normal organs. The incidence of adverse radiation effects is higher in meta-analyses on older trials with larger fields[15,19]. Thus, older radiation techniques with deep tangents or direct fields on IMLN have been abandoned from the current standard. However, there is still a need for prophylaxis of IMLNM. Recent studies with electron boost to IMLN[20], and even with tangential field irradiation[15], found no increase in these risks. It is necessary to balance the cost, risk and benefit of these prophylaxes. The present approach may provide a countermeasure to prophylaxis failure.

Adjuvant brachytherapy in breast cancer treatment

In adjuvant radiotherapy, surgical margin-intensive treatments including IMRT or brachytherapy[21] such as 5-d treatment with MammoSite[22] were developed based on an incidence map of ipsilateral breast recurrence[23,24]. This type of accelerated partial breast irradiation (APBI) is time-saving, has cosmetic advantages, and enables preservation of normal organs such as heart and lungs. The use of APBI brachytherapy is consistently increasing. In contrast, a retrospective study on Medicare beneficiaries found an association between APBI brachytherapy and a higher rate of later mastectomy (4.0% *vs* 2.2%), increased toxicities, and post-operative complications, compared to traditional radiation therapy[25]. Large randomized trials comparing APBI brachytherapy to whole breast irradiation are ongoing.

Reirradiation brachytherapy

In general, reirradiation or boost irradiation is increasing in importance for the treatment of relapsed and/or refractory cancer[26,27]. The clinical rationale of local eradicative treatment is thought to be high for oligometastasis[28]. Brachytherapy has advantages for selective intensive treatment of a small target[29], and its usefulness is reported in the treatment of ipsilateral recurrence[30]. However, reirradiation is often limited by normal organs, especially closely surrounding organs such as skin. Skin protection during intensive brachytherapy was achieved by injectable spacers such as hyaluronate[4,5]. This spacing technique can be used to protect the intestines[12,31], and rectum[11,32], as well as other organs[33]. The present report is an extension of these critical organ preservation procedures to eradicative reirradiation of IMLNM by brachytherapy.

Rationale of the present technique

Although local eradication may be expected with combined chemotherapy and EBRT to breast cancer-IMLNM, some are refractory[2]. Dose escalation may be effective for overcoming radioresistance, but is generally associated with an increased likelihood of normal tissue complications[3]. Even when recently developed technologies are employed, the inability to avoid risk organs close to the target remains a weak point. In combination with HDRBT, the creation of an artificial space between the target and risk organs in a minimally invasive procedure may provide an effective solution.

Advantage of the subvolume effect in brachytherapy

Unlike EBRT, by its nature interstitial brachytherapy delivers an additional dose to the tumor subvolume. Kim *et al*[34] 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 portion of the tumor volume (60%-80%) could be boosted up to 130%. In the present case, the dose distribution and dose-volume histograms show that the tumor subvolume received significant intensive doses. Further research should be performed to examine the subvolume effect in brachytherapy.

Gain in therapeutic ratio

To date, there are no generally accepted safety limits for small skin areas based on dose volume relationship, except for the area based data for 10 cm^3 and larger[3]. Though a small degree of skin necrosis may not be a serious matter, it should be avoided if possible. Using gel injection, the therapeutic ratio of the target dose and skin dose in the present case was improved by 3.25-4.17. It may be said that the gel spacing procedure can provide a significant improvement in the therapeutic ratio that safely promotes high dose radiotherapy required for local eradication.

Feasibility and safe practice

The percutaneous intercostal needle approach can be performed safely by ultrasound and/or X-ray CT guidance, even penetrating the cartilage as in the second lesion, avoiding injury to arteries or high flow veins. Because this method with gel injection is a short-time single session therapy, this may also be useful in treating multiple lesions at the same time on an outpatient basis.

Skin dose estimation in the future

Even in the case of reirradiation, it is necessary to avoid skin perforation by radiotherapy. Of the three layers of the skin (epidermis, dermis and subdermis), the thickness of each differs widely according to site and species. We can observe these delicate structures by high frequency ultrasound imaging[35]. Although the biological response to radiation differs by skin layer, available dose-complication probabilities are calculated for the whole skin[3]. We have complied with the published recommendations.

In the clinical situation, these considerations cause difficulties in accurate dose calculation and in measurement of thin layers, especially in EBRT. The use of explicit setup, irradiation techniques, Monte-Carlo calculation, and detailed skin information using high-precision ultrasound examination will promote more accurate estimations.

We think that brachytherapy with the hyaluronate gel injection procedure, *via* the percutaneous intercostal approach, can provide safe and eradicative high-dose irradiation with skin preservation for IMLN metastasis from breast cancer.

ACKNOWLEDGMENTS

The patient's consent for publication (http://www.wjgnet.com/1949-8470office/eximage/2sign.jpg) of the results was obtained before submission of the manuscript.

COMMENTS

Background

Recent progress in radiation technology has facilitated safer targeted reirradiation. However, the target is often so closely surrounded by previously irradiated critical normal structures that curative reirradiation cannot be safely performed.

Research frontiers

The creation of a safe distance during radiotherapy using injectable spacers can be applied in various sites of the body. These studies are creating new horizons in radiotherapy: critical organ-preserving radiotherapy with spacers, and safe and curative reirradiation.

Innovations and breakthroughs

The authors added two radiotherapy innovations in this study. They focused on skin preservation with detailed dose analysis in the epidermis, dermis and subdermis. Detailed dose analysis in the skin layers has not been well discussed in conventional external beam treatment due to the uncertainty of measurement and calculation (excluding Monte Carlo algorithm). It is necessary to precisely estimate safe spacer thickness. The other innovation was the boost or reirradiation of IMLN relapse.

Applications

The hyaluronate gel spacer will be applicable in all areas of the body for initial radiotherapy or reirradiation. It will protect skin from radiation damage. This study may facilitate the further application and development of interventional procedures and materials in the field of therapeutic radiation oncology.

Peer review

This paper is a clinical report on using high-dose rate brachytherapy to treat internal mammary lymph node metastasis of breast cancer. Using the authors' reported technique (spacer and EQD calculations), they concluded that their procedure can provide the breast cancer treatment with good skin sparing and therapeutic ratio. This paper is well organized and comprehensive.

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