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Clinical Application of CTVision Images-guided Precise Radiotherapy in Breast Cancer Patients with Postoperative

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Abstract: *By applying kilovolt (KV) level computerized tomography (CT) in Image-Guided Radiation Therapy system (IGRT) – CTVision, setup errors of postoperative breast cancer patients after breast bracket with thermoplastic molding in precise radiotherapy is studied, advantages and disadvantages of manual osseous registration and skin tag tumor bed area registration are compared, it is verified that breast bracket with thermoplastic phantom is the best fixing mode for postoperative breast cancer patients and then clinically possible extended value of CTV (Clinical Target Volume) and PRV (Planning Organ at Risk Volume) are discussed. Materials and methods: Siemens CTVision image-guided system is adopted for 10 cases of postoperative breast cancer patients, including 7 patients with modified radical mastectomy and 3 breast-conserving surgery patients which is using breast bracket with thermoplastic molding and scaned by Large aperture CT of CTVision image-guided system. Image guidance is respectively conducted 3 continuous times three days before treatment and once weekly during treatment, osseous manual registration and skin tag tumor bed area registration are conducted for verification image and planned image of postoperative breast cancer patients, setup error data of two different registration modes is measured, displacement error difference in direction of horizontal (X-axis), vertical (Y-axis) and longitudinal (Z-axis) is analyzed, and error effect on CTV and PRV extended boundary is explored. Results: 10 cases of postoperative breast cancer patients received 80 scans, average displacement errors in horizontal (X-axis) direction of osseous manual registration and skin tag tumor bed region registration are 0.7 ± 2.4 mm and -1.3 ± 5.6 mm respectively; displacement errors in vertical (Y-axis) direction are 0.5 ± 2.6 mm and -0.3 ± 4.4 mm respectively; displacement errors in longitudinal (Z-axis) direction are 0.7 ± 1.1 mm and 1.9 ± 2.0 mm respectively. Extended boundary of CTV of osseous manual registration and skin tag tumor bed area registration are 4.79 mm and 13.62 mm, 5.81 mm and 8.52 mm, 1.46 mm and 3.71 mm respectively in X-, Y-, Z-axis direction; extended boundary of organs at risk (PRV) are 2.62 mm and 7.28 mm, 3.13 mm and 4.50 mm, 0.80 mm and 2.04 mm respectively in X-, Y-, Z-axis direction. Re-setup or online mobile treatment couch calibration is conducted for the above osseous manual registration displacement error value over 5 mm in three-dimensional direction, and corrected* *displacement errors in X, Y, and Z directions are lower than those before correction, with re-setup or online correction rate at 3.8%. Discussion: (1) Setup error of intensity modulated radiotherapy of postoperative breast cancer patients with large aperture CT scan imaging of CTVsion image guided radiation therapy system is within an acceptable range, osseous manual registration is superior to skin tag tumor bed region registration, and therefore, intensity modulated radiotherapy of postoperative breast cancer patients with osseous manual registration to decide set-up errors is a more realistic option. (2) Fixing mode of breast bracket joint thermoplastic phantom is with good repeatability and stability, low positioning failure rate, and thermoplastic phantom can effectively control error caused by respiratory movement in longitudinal direction. Breast bracket joint thermoplastic phantom is one of the best fixing mode for postoperative breast cancer patients. (3) Based on the study on systemic error and random error in two registration modes of intensity modulated radiotherapy of postoperative breast cancer patients, CTV and PRV extended value obtained by setup errors of osseous manual registration mode is more realistic, extension of 5 mm of postoperative breast cancer plan is clinically feasible, and extension of organs at risk PRV should be decided by patients' tumor site and treatment plan design, etc.*

Keywords: *Image guidance, Siemens CTVision, Postoperative breast cancer, Intensity modulated radiotherapy, Setup errors, Extended boundary.*

Introduction

Conventional radiation therapy in combination with other treatment technologies are mature for postoperative breast cancer patients, which can effectively reduce the rate of local recurrence and mortality of breast cancer [6]. Image-Guided Radiation Therapy (IGRT) is one of the latest imaging technologies combining imaging and precise radiotherapy as one. Compared to conventional radiotherapy, it can obtain real-time tumor target, outer contour of surrounding organs and spatial location, which well improves quality guarantee of precise radiotherapy. In precise radiotherapy of breast cancer, image-guided radiotherapy equipment obtains good monitoring target and displacement change of normal tissues and organs through registration techniques in line with tumor characteristics, which guarantees more implementation of precise radiotherapy [3].

Since the breast is located in the thorax, consisting of fat, soft tissue and other components, it is prone to elastic deformation caused by arm, wrinkled skin and other stretch. Modified radical mastectomy patients have chest surface position changes due to traction of surgery scar and other effects. Osseous registration mode, similar to a rigid structure registration, has relatively fixed anatomical structure, while skin tag tumor bed area registration can change correspondingly with change in position of the body surface. In this paper, Siemens CTVision image guided radiation therapy system is adopted, and by attaching metal markers to corresponding area of breast tumor bed area of skin, displacement change of markers is monitored during patients' treatment, so the setup errors of osseous manual registration and skin tag registration is measured, and the different effects of registration and relationship between the two is preliminarily investigated. Moreover, statistics difference is compared based on setup error of two registration modes, to find out the best registration mode, obtain systemic error and random error of positioning, and then guide actual external expansion of Clinical Target Volume (CTV) and Planning Organ at Risk Volume (PRV). By comparison of setup error difference of osseous manual registration and skin tag registration, value of two combined registration modes of breast bracket joint thermoplastic molding in setup guidance for postoperative breast cancer patients is discussed, in order to better perform precise radiotherapy.

Materials and methods

Case selection

Ten postoperative breast cancer patients during April 2013 and December 2013 are selected, inclusion criteria: (1) Diagnosed as breast cancer; (2) patients needing tumor resection or mastectomy and/or lymph node dissection or sentinel lymph node dissection due to invasive carcinoma; (3) patients without chemotherapy severe osseous marrow suppression caused cannot be radiotherapy; (4) patients with good upper extremity function and can receive breast bracket molding; (5) patients without undesirable healing of operation area or severe operation area inflammation or lymph edema or armpit dropsy; (6) previously without radiotherapy of the breast area. Exclusion criteria: (1) Karnofsky Performance Status (KPS) < 70 points; (2) patients who cannot cooperate with CT scan or treatment; (3) no indication of radiotherapy; (4) fail to have radiotherapy due to other reasons. All patients in this study obtained informed consent.

Case features: All patients are female with median age at 48.5 years (41 to 53 years), including 7 cases of breast cancer on the left, 2 cases of breast cancer on the right, and 1 case of bilateral breast cancer, there into 7 cases of modified radical mastectomy (1 case with postoperative local chest recurrence), and 3 cases of breast conserving surgery. All patients are pathologically confirmed with breast infiltrating ductal carcinoma.

According to clinical stage in Fourth Edition of "Cancer Radiation Therapy", staging of patients with modified radical mastectomy belongs to IIb (2 cases), IIIa-IIIc (5 cases), patients with breast conserving surgery belong to I-IIb. All patients underwent 4-8 cycles of chemotherapy, and radiotherapy began after 2-4 weeks of chemotherapy. Among then, according to hormone levels, there are 7 patients with endocrine therapy or receiving endocrine therapy during radiotherapy (see Table 1 for clinical data of included patients).

Table 1. The clinical data of postoperative patients with breast cancer

No.	Gender	Age	Position	Surgery options	Stage	Method
01	female	44	left	Modified	T2N0M0	IMRT (6 fields)
02		51	right	Modified	T2N2M0	IMRT (5 fields)
03		53	right	Modified	T3N1M0	IMRT (5 fields)
04		47	left	Modified	T3N1M0	IMRT (5 fields)
05		48	left	Modified	T4N1M0	IMRT (5 fields)
06		44	left	Modified	T2N2M0	IMRT (5 fields)
07		50	left	Modified	T2N3M0	IMRT (7 fields)
08		41	left	Conserving	T2N1M0	IMRT (5 fields)
09		50	left	Conserving	T2N0M0	IMRT (7 fields)
10		49	left	Conserving	T2N1M0	IMRT (5 fields)

Equipment

Image-guided radiation therapy system: Siemens ONCOR Impression Linear Accelerator and Siemens 82 cm large aperture SOMATOM OPEN CT with sliding rail in the same room sharing Siemens 550TXT treatment couch, consist of the CTVision image-guided radiation therapy system. It includes: (1) OPTIFOCUS multi-leaf collimator of accelerator, with the only built-in, two-focus type, and all wild multi-leaf collimator, which has 41 pairs, and 40 cm x 40 cm maximum light field; (2) large aperture CT scan with high resolution for soft tissue and clear picture; (3) CTVision laser positioning system; (4) adaptive targeting software planning system; (5) On centra Master Plan physical planning system (TPS); (6) R303-1 LOT: 206143 breast thermoplastic phantom; (7) R610-CF B09092 breast bracket; (8) homemade skin tag markers (oval metal in 5 mm diameter) and the like.

Position immobilization and CT simulated positioning

Patients lie in the supine position on a special breast bracket, with head deviating to the uninjured side, ipsilateral arm extending and placing on arm support, and ipsilateral hand fully rising to grip handle on the top, thereby reducing exposure dose to the lung. Ask the patients to place uninjured arm naturally on one side of the body, adjust inclination of headrest, arm support, holding rod, breast bracket baseboard according to patients' position, and adjust wedge shaped plate at buttocks to prevent body slipping. Through appropriate adjustment, it makes patients' chest wall parallel with breast bracket baseboard, so patients position is in the best comfortable position, which is in favor of repeatability of body position. Relevant parameters of breast bracket are recorded. It is necessary to ask patients to breathe calmly, and then fix thermoplastic phantom previously softened in constant temperature water tank to patients' chest. At last, fastening breast bracket baseboard, and waiting phantom to cool and turn into hard molding would be done.

Utilizing the 82 cm large aperture CT to scan the patients plan CT was obtained. It has to do that correctly adjusting patients position on breast bracket, marking circularly with a red oily pen on patients' breast area, setting a "cross-shaped" mark on breast tumor bed area, affixing homemade skin tag markers (developable on CT), affixing plastic phantom to patients' chest that is fastened it to breast bracket, making corresponding skin positioning mark, and then duplicating the same circular mark on thermoplastic molding with black marker pen in accordance with the circular marks on the skin. Moreover, it should be to determine anchor point on phantom with CTVision laser system, make positioning marks at body midline or bilateral middle axillary line with artifact-free metal particles and mark margo inferior of first rib, 2 cm lower than contralateral breast folds, surgical scar and drainage port, which is in favor of target delineation identification. Then, it turns to 82 cm large aperture CT to scan, with scan parameters including 120 KV, Eff mas 200, CTDIvol 17.92 mGy. Delay 4 s in scanning, scanning slice is 5 mm in thickness, scanning ranges from lower edge of the thyroid cartilage to1cm under lower breast mark. At last, scanned CT image is transmitted to On centra Master Plan planning system through area network.

Definitions of target and organs at risk

Modified radical mastectomy patients

Target delineation standard refers to the latest Radiation Therapy Oncology Group (RTOG): CTV about chest wall and supraclavicular and subclavicular region, is delineated that lymphatic-drainage area including supraclavicular and subclavicular region, chest wall under the breast, I-II axillary lymph nodes, pectoralis major fascia, interpectoral lymph nodes. Chest CTV: front boundary is 2 mm from skin recovery, rear boundary is between ribs and pleura, outer boundary is midaxillary line, inner boundary is sternocostal joints, upper boundary is next tier of clavicular head, lower boundary is 2 cm under contra lateral breast folds, surgical scars and drainage port are included in the target area; supraclavicular and subclavicular region CTV: front boundary, rear boundary, outer boundary, inner boundary, upper boundary, lower boundary are respectively: posterior border of sternocleidomastoid, frontal edge of scalene muscle, side edge of sternocleidomastoids, except thyroid and trachea, lower end of cricoid cartilage, lower end of clavicular head. Furthermore, based on CTV, expand 5 mm in inner, outer, rear boundary, expand 1 cm in upper and lower boundary, expansion in direction of lung tissue depends on specific circumstance and is determined to be Planning Target Volume (PTV), while front boundary can coincide with CTV. PTV of upper chest wall and supraclavicular and subclavicular lymph node naturally fuses to lower bottom of clavicular head as a whole through external expansion. Meanwhile, it is defined that, heart, ipsilateral lung and contralateral lung, contralateral breast, liver of right-sided breast cancer patients are organs at risk (OAR).

Breast conserving surgery patients

Take breast cancer treatment guidelines and specifications (2013 edition) of Chinese Anti-Cancer Association as a guide: (1) GTV (tumor gross target volume): tumor bed area of patients; (2) CTV: all breast tissue of affected side inter pectoral lymph nodes and chest wall lymphatic drainage area under the breast. Front boundary, rear boundary, outer boundary, inner boundary are respectively 5mm under the breast skin, pleurasymphyses, midaxillary line (including surgical scars and drainage port), sternocostal joints; (3) PTV: with lung tissue not included in basis of CTV, respectively expand 5 mm in the direction of inner boundary and outer boundary, front boundary PTV can be appropriately extended to the skin surface but not over the skin, upper boundary and lower boundary expand 1 cm, decide whether to apply lymphatic drainage area irradiation of axilla, supraclavicular and subclavicular region according to patients' high risk factors; (4) OAR (organs at risk): patients' lung and contralateral lung, heart (including pericardium and coronary arteries), contralateral breast glands based on the contour of lung, delineation of upper boundary, lower boundary, inner boundary, outer boundary, front boundary, rear boundary is respectively at thoracic entrance, fold under the breast, body midline, midaxillary line, 5 mm under the skin, junction of mammary gland and the chest wall. Delineation of target and organs at risk is jointly reviewed by a physician and a doctor above deputy director.

Planning design and evaluation limitation

IMRT treatment plan after modified radical mastectomy

7 cases of modified radical mastectomy patients were treated with IMRT. Plans are designed by On centra Master Plan planning system. Siemens CTVision system is 6 MV energy is adopted. The IMRT plans are including six cases of radiotherapy with 5 fields, and one case with 6 fields. With chest wall tangent field as the main tangent angle, adding two or more irradiation angle in the inside or outside, its aim to try to avoid lung tissue and to control contralateral lung and contralateral breast which are in a low dose irradiation region. The prescription dose of CTV is: 50 Gy/25 times, 2 Gy each time, 5 times a week. Treatment plan is jointly completed by two physicists, and two senior radiologists jointly review plans and select the best plan to implement treatment.

IMRT Treatment plan after breast conserving surgery

IGRT mode and treatment planning system of three cases of breast conserving surgery patients are the same as those of modified radical mastectomy patients. The IMRT plans are including one case of radiotherapy with 5 fields, and two case 2 with 7 fields. Irradiation angle is arranged according to target prescription dose and limit requirement of organs at risk. The prescription dose of GTV is: 60-66 Gy, 2-3 Gy/time, 5 times/week, and CTV is: 50 Gy, 2 Gy/time, 5 times/week. Completion and quality audit requirement of treatment plan accord with that of patients with modified radical mastectomy.

Dose limitation

Intensity modulated radiation therapy of modified radical mastectomy and breast conserving surgery patients require that 95% of prescription dose covers 100% PTV volume, 110% of prescription dose does not exceed 10% PTV volume. Ipsilateral lung, contralateral lung, heart, contralateral breast doses are limited within certain range, ipsilateral lung: $V30 < 20\%$, V20 < 30%, D_{mean} < 20 Gy, contralateral lung V20 < 15%, V10 < 30%, heart (left): V30 < 10%, V40 < 5%, average dose of contralateral breast < 5 Gy.

Monitoring of setup errors

Image registration method

Sending fabricated IMRT plan to CTVision treatment planning system workstation through area network is the first step. In position verification before and during radiotherapy, two technicians who work more than five years proceed with isocenter setup operation. In first-time treatment, image-guided verification is done for three consecutive days, then once a week, and every patient receives 8 image-guided verification on average.

Setup follows positioning. The patient lies down on the breast bracket, then is adjusted with the relevant parameters of breast bracket and markers corresponding to the body surface. It adjusts the patient to a comfortable position, while the patient breathes quietly, pasted homemade marker to 'cross-shaped' marker line for skin positioning of tumor bed area, and fix patient's chest with thermoplastic phantom molded during patient positioning, referred to red "circular" marker on body surface and replicated black „circular" marker on phantom. Then aligning to locating point with CTVision laser system, and pasting artifact-free metal particles. After completion of setup, conduct large aperture CT scan by rotating treatment couch 180°, with scanning thickness at 5 mm.Transmit the CT image to Syngo operating system platforms and rebuild. Through planning CT image registration, reconstructed CT images can obtain sagittal, coronal and axial images. Image registration is performed by the same physicist, while image registration during the entire radiation receives joint participation of physicists, researchers to identify scanning parameters and scope, methods and area of registration.

Principle of image registration

Image registration is realized mainly through maximized overlap of key anatomical mark by large aperture KVCT scanned images during planning image and verification. Currently, there is no gold standard in clinical application of image registration technology. In clinics, anatomical structure registration mode with better stability is adopted to verify location error according to characteristics of different parts of tumor. This study focuses on registration mode of osseous anatomical structure and skin tag tumor bed region for image-guided verification setup error. Verification image scan range is: from acromial high of collarbone to sternum xiphoid, scanned CT images can well display anatomical structure of registration area and target CTV region. By automatic registration of verified scanned CT reconstruction image and plan image, which proceeds with registration based on maximized overlap of anatomical structures and with manual fine-tune registration when automatic registration is not desirable, image coincides with plan image at sagittal, coronal and axial anatomical position. Since image acquired by large aperture KVCT of CTVision image- guided radiation therapy device is clear, with high resolution of soft tissue, registration process can be quick and accurate. Skin tag tumor bed area registration is conducted by overlap of tumor bed area skin marker on CT scan images and skin marker on planning image tumor bed area. To adjust sagittal, coronal and axial coincidence of two image development markers is of visual observation, simple and easy.

Building of three-dimensional coordinates of isocenter

In CTVision image-guided system, a three-dimensional coordinate system is created with isocenter of linear accelerator as the origin (mechanical center). Using Syngo graphical operation system, it represents deviation value of isocenter formed by positioning 3 metal particles at the same level of planning image during positioning and CT scanned image data verification center in three-dimensional coordinate, with positioning isocentre as the origin and with patient's horizontal direction, vertical direction, longitudinal direction as X-, Y-, Z-axis of three-dimensional coordinate system. Isocenter displacement that favors the right side in horizontal direction is expressed as negative value, that favors the left side is expressed as positive value; favors top (head side) in vertical (head-foot) direction is negative, favors bottom (foot) is positive; favors (front) abdomen in longitudinal (dorsoventral) direction is negative; favors rear (back) is positive.

Setup error monitoring characteristics

Setup error is calculated by displacement in X-, Y-, Z-axis direction of isocenter after Syngo operating system accepts registration conditions. Through registration of treatment and planning image before treatment and during radiotherapy, it will obtain displacement value in three-dimensional direction is three-dimensional coordinate offset error in origin of offset positioning isocenter, which is used to assess accuracy of patient is treatment positioning.

Online correction

After image registration, it can calculate displacement error of isocenter positioning in horizontal direction (X-axis), vertical direction (Y-axis), longitudinal direction (Z-axis) by Syngo operating system. Displacement error in X-, Y-, Z-axis is within limited range of error, therapy can thus be performed. This study decides to re-adjust patient's position or adjust treatment couch position to correct errors based on osseous manual registration. After correcting errors, re-verify patients setup errors. Treatment can only be implemented within the allowable error range. If re-setup or movement of treatment couch still fails to achieve effect of correcting errors or setup errors become larger, re-setup fixation, positioning, re-fabrication of plan and implementation of new treatment plan are needed.

CTV expansion calculation

Through image-guided verification of setup error for postoperative breast cancer patients before and during treatment, graded setup errors generated in different registration modes differ. According to concept expressed by Stroom et al. [15]: (a) Grouped systematic error (Σ) is defined as standard deviation of individual systematic error ($\bar{x}$) of all patients. Mean value of all graded error of each patient is defined as individual systematic error ($\bar{x}$); (b) Grouped random error (σ) is defined as standard deviation of individual random error (s) of all patients. The standard deviation of all graded errors of each patient is defined as individual random error (s). According to $M_1 = 2.5\Sigma + 0.7\sigma$ formula of CTV-PTV extended value proposed by van Herk [17], about prescription dose of 90% of group patients at 100% CTV wrapping reaches 95%. CTV-PTV extended formula takes into account the impact of systematic error and random error on dose, so a lot of people recognize extended value obtained by this formula. According to extended formula of organs at risk put forward by McKenzie et al. [12], PRV extended value $M_2 = 1.5\Sigma \pm 0.5\sigma$ calculates extended value of organs at risk. This study calculates extended value of displacement error of two registration modes in three-dimensional direction through extended formula, and then proposes appropriate CTV extended value and extended value of organs at risk as a reference.

Statistical methods

The SPSS13.0 software for statistical analysis, setup errors consist of systematic error and random error. Systematic error and random error are respectively represented by mean value and standard deviation. Displacement error of two registration modes in horizontal direction (X-axis), vertical direction (Y-axis) and longitudinal direction (Z-axis) are represented by setup data mean ± standard deviation ($\bar{x}$ ± s), to be analyzed with single sample *t*-test; and paired sample t-test is adopted for comparison of two sets of data errors, $p < 0.05$, difference is considered to be statistically significant.

Results

Image effect of two registration modes

All patients apply large aperture CT of CTVision system to be scanned to get positioning image, which is transmitted to On centra Master Plan system for delineation and plan design of target and organs at risk. Then ten cases of postoperative breast cancer patients' IMRT plans are send to CTVision system, and they can be performed image-guided for 3 consecutive days at the first treatment and once weekly thereafter, so that a total of 80 images are obtained. Each image obtains displacement error in three-dimensional direction through two registration modes. Patient setup to image-guided verification usually takes 6-10 minutes, including patients' treatment position fixed, treatment couch rotated 180° to large aperture CT to be scanned, and images (including graphics of target and organs at risk and CTV, PTV isodose curve used to evaluate registration effect) send to Syngo operating system platform. The scanned image shows clear osseous anatomical structure, breast tissue, lung tissue, and lymph drainage area. Osseous manual registration and skin tag registration is simple and error of isocenter can be calculated after acceptation of registration conditions.

Data analysis result of two registration modes

Ten cases of postoperative breast cancer patients received a total of 80 times of CT scan verification, then 160 groups of setup error data under two registration modes were obtained. In fractionated irradiation, all patients received a total of 83 times of image guidance to verify patient's setup errors. Wherein, depending on osseous manual registration mode, if it exceeds 5 mm in any direction of horizontal, vertical, longitudinal direction, correcting setup errors through re-set or moving treatment couch would be done. Although 3 out of 83 times setup failed, but by re-positioning or moving treatment couch, error is smaller than the previous setup error, so setup error less than5mm is met in all directions.

Displacement error analysis of data of all images with osseous manual registration mode and skin tag tumor bed area registration mode in X-, Y-, Z-axis direction is shown in Tables 2 and 3, of which displacement error in three directions is represented by mean ($\bar{x}$) ± standard deviation (s). Displacement errors of 80 sets of data with osseous manual registration in X-, Y-, Z-direction, X-direction: ≤ 3mm accounts for 81.2%, < 5 mm accounts for 91.3%; Y-direction: ≤ 3 mm accounts for 78.8%, < 5 mm accounts for 96.3%; Z-direction: ≤ 3 mm accounts for 98.8%, < 5 mm accounts for 100%; Displacement errors of 80 sets of data with skin tag tumor bed area registration in X-, Y-, Z-direction, X-direction: ≤ 3 mm accounts for 36.3%, ≤ 5 mm accounts for 61.3%; Y-direction: ≤ 3 mm accounts for 50%, ≤ 5 mm accounts for 76.3%; Z-direction: ≤ 3 mm accounts for 80%, ≤ 5 mm accounts for 93.8%.

Comparison of different groups of displacement error data

Comparison of two registration modes of osseous manual registration and skin tag tumor bed area registration

Ten cases of postoperative breast cancer patients received 80 times of image-guided verification. Displacement error of treatment CT image and planning CT image under osseous manual registration and skin tag tumor bed area registration in X-, Y-, Z-axis direction on Syngo operating system platform, are compared, and the analysis of two differences is as shown in Table 4.

Table 2. The result of displacement error of each patient
in the X-, Y- and Z-direction of osseous manual registration

No.	**Osseous manual registration mode ($\bar{x}$ ± s), mm**		
	X-axis	**Y-axis**	**Z-axis**
01	2.0 ± 2.1	2.1 ± 1.9	0.6 ± 1.2
02	-0.4 ± 1.3	1.3 ± 1.0	0.4 ± 1.2
03	-0.6 ± 1.5	0.6 ± 1.9	-0.4 ± 0.9
04	0.8 ± 2.3	-2.5 ± 1.5	0.1 ± 1.2
05	0.6 ± 1.5	-1.9 ± 0.6	0.8 ± 0.7
06	-0.8 ± 1.0	0.9 ± 2.2	0.8 ± 1.7
07	-0.3 ± 1.5	-2.4 ± 1.4	1.0 ± 0.9
08	1.8 ± 3.8	2.3 ± 3.2	1.1 ± 1.1
09	4.4 ± 0.5	3.5 ± 0.9	1.1 ± 1.1
10	-0.9 ± 1.9	1.3 ± 1.0	1.0 ± 0.5

Table 3. The result of displacement error of each patient
in the X-, Y- and Z-direction of skin marking registration

No.	**Skin tag tumor bed area registration mode displacement error ($\bar{x}$ ± s), mm**		
	X-axis	**Y-axis**	**Z-axis**
01	5.8 ± 1.8	3.6 ± 2.6	0.5 ± 1.6
02	-6.3 ± 2.4	-0.6 ± 4.4	2.1 ± 1.2
03	1.6 ± 2.8	-3.4 ± 1.7	1.8 ± 1.8
04	0.5 ± 2.1	-4.1 ± 2.4	0.5 ± 1.8
05	-7.8 ± 1.8	-0.9 ± 4.3	2.8 ± 1.3
06	5.0 ± 1.5	1.4 ± 3.4	0.4 ± 1.6
07	-5.5 ± 1.3	-5.1 ± 2.1	4.9 ± 1.4
08	-4.0 ± 3.9	2.1 ± 4.1	2.8 ± 1.3
09	2.8 ± 3.5	2.5 ± 3.9	0.8 ± 1.6
10	-5.5 ± 6.1	1.9 ± 4.5	2.9 ± 2.2

Table 4. The comparison of displacement error
in the X-, Y-, Z-direction of two types of registration

Direction	**Osseous manual registration**	**Skin tag tumor bed area registration**	**Paired sample *t*-test**	
	Displacement error ($\bar{x}$ ± s), mm		***t*-value**	***p*-value**
X	0.7 ± 2.4	-1.3 ± 5.6	3.16	0.002
Y	0.5 ± 2.6	-0.3 ± 4.4	1.83	0.071
Z	0.7 ± 1.1	1.9 ± 2.0	5.50	0.001

Statistics shows that in comparison of osseous manual registration and skin tag tumor bed area registration, there are differences in X-, Y-, Z-axis error, of which displacement error in X-axis direction, Z-axis direction is with statistically significant difference ($p < 0.01$), displacement error in Y-axis direction is not statistically significant ($p = 0.071$), but p-value is close to 0.05, statistically significant in trend difference. Displacement error in X-, Y-, Z-axis generated in osseous registration is significantly less than displacement error mean in X-, Y-, Z-axis direction generated in skin tag tumor bed area registration.

Comparison of two registration modes for modified radical mastectomy and breast conserving surgery patients

Mastectomy patients retain chest wall, pectoralis major and/or pectoralis minor muscle, with differences from chest anatomy with breast tumor resection. Therefore, this study also compares two registration modes for two surgical methods in three-dimension direction. Displacement error of modified radical mastectomy patients under osseous manual registration and skin tag tumor bed area registration in X-, Y-, Z-axis directions is compared and difference significance of the two is analyzed as shown in Table 5.

Table 5. Comparison of displacement error in the X-, Y-, Z-direction of two types of registration with modified radical surgery

Direction	**Osseous manual registration**	**Skin tag tumor bed area registration**	**Paired sample *t*-test**	
	Displacement error ($\bar{x}$ ± s), mm		***t*-value**	***p*-value**
X	0.2 ± 1.8	-0.9 ± 5.5	1.54	0.130
Y	-0.3 ± 2.3	-1.3 ± 4.2	2.20	0.032
Z	0.5 ± 1.2	1.8 ± 2.1	-4.96	0.002

Displacement error of breast conserving surgery patients under osseous manual registration and skin tag tumor bed area registration mode in X-, Y-, Z-axis directions is compared and difference significance of the two is analyzed as shown in Table 6. Compare differences of two registration modes from modified radical mastectomy patients and breast conserving surgery patients, displacement error mean in X-, Y-, Z-axis direction generated in osseous registration is significantly less than that in X-, Y-, Z-axis direction generated in skin tag tumor bed area registration. Displacement error mean of modified radical mastectomy in three directions is smaller than that of breast conserving surgery. By comparing the above methods, seen from maximized overlap of verification image and planning image, we believe that error range ability of skin tag tumor bed area registration is relatively large, and that osseous manual registration is better than skin tag tumor bed area registration.

Table 6. Comparison of displacement error in the X-, Y-, Z-direction of two types of registration with breast-conserving surgery

Direction	**Osseous manual registration**	**Skin tag tumor bed area registration**	**Paired sample *t*-test**	
	Displacement error (x ± s), mm		***t*-value**	***p*-value**
X	1.8 ± 3.2	-2.3 ± 5.7	3.57	0.002
Y	2.3 ± 2.1	-2.2 ± 4.0	0.19	0.852
Z	1.1 ± 0.9	2.1 ± 1.9	-2.44	0.023

Extended value of CTV and PRV

According to definition of systemic error and random error and data in Table 2 and Table 3, mean value ($\bar{x}$) and standard deviation (s) of displacement error generated in two registration modes of large aperture CT scan image and planning image is shown. PTV is generated based on calculation results of CTV extended formula, namely CTV extended value $M_1 = 2.5\Sigma + 0.7\sigma$ and PRV extended value of organs at risk $M_2 = 1.5\Sigma + 0.5\sigma$. Wherein, Σ is grouped systematic error, expressed by standard deviation of mean value ($\bar{x}$) of all graded error of all patients. σ is grouped random error, expressed by standard deviation (s) of all graded error of all patients. All setup errors are a set of grouped systemic error and random error.

Extended value is obtained by extended formula calculation. CTV external expansion of osseous manual registration modes is 4.79 mm in X direction, 5.81 mm in Y direction, and 1.46 mm in Z direction. PRV external expansion is 2.62 mm in X-direction, 3.13 mm in Y-direction, and 0.80 mm in Z-direction, it is shown in Table 7. CTV external expansion of skin tag tumor bed registration is 13.31 mm in X-direction, 8.39 mm in Y-direction, and 3.84 mm in Z-direction. PRV external expansion is 7.28 mm in X-direction, 4.50 mm in Y-direction, and 2.04 mm in Z-direction, it is shown in Table 8.

Table 7. The external expansion and displacement error in the X, Y and Z direction of osseous manual registration

	Osseous manual registration, mm		
	X-axis	**Y-axis**	**Z-axis**
Mean value, ($\bar{x}$)	0.70	0.50	0.70
Standard deviation, (s)	2.40	2.60	1.10
Grouped systematic error, (Σ)	1.66	2.11	0.49
Grouped random error, (σ)	0.92	0.77	0.33
CTV extended value, (M)	4.79	5.81	1.46
PRV extended value, (PRV)	2.62	3.13	0.80

Table 8. The external expansion and displacement error in the X, Y and Z direction of skin marking registration

	Osseous manual registration, mm		
	X-axis	**Y-axis**	**Z-axis**
Mean value, ($\bar{x}$)	-1.30	-0.30	1.90
Standard deviation, (s)	5.60	4.40	2.00
Grouped systematic error, (Σ)	5.04	3.06	1.45
Grouped random error, (σ)	1.46	1.05	0.30
CTV extended value, (M)	13.31	8.39	3.84
PRV extended value, (PRV)	7.28	4.50	2.04

With displacement error in three-dimensional direction generated in osseous manual registration mode, it is calculated that CTV extended values are within threshold of CTV external expansion under intensity modulated radiation therapy. Results show that it is safe and reasonable for postoperative breast cancer patients receive precise radiotherapy with breast bracket joint thermoplastic molding. Extended value of displacement error in Z-axis direction according to osseous registration mode is 1.46 mm, significantly less than 5 mm extended value required in the plan. Extended value of displacement error with skin tag tumor bed area registration is relatively large, with horizontal direction beyond 1 cm. Analysis of possible causes is above: (1) Skin receives heterogeneous pulling of the arm, causing displacement in skin surface homemade marker and positioning skin marker; (2) The patient's chest is fixed with breast thermoplastic phantom, which may cause distortion of skin tags on the skin, resulting in poor overlap of homemade marker registration; (3) Breast cancer irradiation region has tissue edema or skin wrinkles due to deteriorated skin elasticity. Based on significant difference comparison of displacement error in three-dimensional direction between two registration modes, variability of displacement error of osseous manual registration is significantly lower than that of displacement error of skin tag tumor bed area registration; CTV external expansion with displacement error of osseous manual registration in three-dimensional direction is recommended for CTV external expansion in this study. Stability of skin tag tumor bed area registration is subjected to many factors.

Discussion

Systematic errors of precise radiotherapy equipment and daily setup errors may cause difference of planned dose from actual dose. Kasabašić et al. [7] studied daily setup errors of 35 patients could cause PTV conformal index to fall 3% or above. Results show that reducing daily setup errors of radiotherapy patients is essential. Clinical study found that 3-5% dose change can lower efficiency of tumor radiotherapy and increase incidence of normal tissue complications [4]. Based on correlation research of impact of setup error on dose of target and organs at risk, deviation of irradiation dose may decrease treatment effects and increase damage to organs at risk. Setup errors affect dose of irradiation field edge, and appropriate CTV external expansion can guarantee 95% of prescription dose of clinical target volume. Harron et al. [5] reported simulation of impact of setup error and rotation error on dose of 10 cases of breast cancer patients with On centra Master Plan system. The study found that for 10 mm displacement in horizontal direction, then prescription dose of breast CTV whose dose is less than 95% increases by 8.2% in volume, and for 10 mm displacement in horizontal direction, 90% of patients CTV received 107% of prescription dose increases by 2.6% in volume. Furthermore, less than 5 mm error in vertical direction or rotation angle no more than 2° will not affect DVH parameters, but setup errors over 5 mm or rotation error over 2° may result in large changes in dosimeter for a few patients, in creating large dose of hot or cold spot area. Domestically, Zhang et al. [23] studied 95% of breast volume of IMRT plan after breast conserving surgery, which received 99.8% of prescription dose, more even than 98.3% target dose distribution of IMRT plan after reference of error. In this study, 95% of prescription dose of 10 cases of postoperative breast cancer patients after intensity modulated radiotherapy is covered 98.1% PTV. The results meet the requirements set by the plan. Studies have shown that impact of setup errors on dose of breast cancer IMRT plan is worthy of further discussion.

Compared with conventional breast cancer radiotherapy, image-guided radiotherapy improves treatment precision and dose distribution homogeneity in postoperative treatment of breast cancer. While applying CT image-guided to verify setup error during treatment, if the error is large, we shall improve treatment precision by re-setup or moving treatment couch to correct errors. Isocenter displacement change due to different registration modes and various parts of tumor matching area may be different. So the key is to apply registration modes and matching area more appropriate for cancer treatment to reduce setup errors, and then guide precise radiotherapy. Theoretically, automatic registration is result of maximized registration area of CT image and planning CT image in concept of image registration. But in fact, automatic registration is only maximized registration area, which cannot reach precise requirement of our registration part. Therefore, when automatic registration does not meet the requirements, manual registration should be performed. Manual registration needs to be considered patients' tumor location, clinical features, registration area anatomical structure and other characteristics, so that obtained setup error is accurate and reliable. There exist individual differences in manual registration. In domestic study, individual differences of osseous registration and grayscale registration setup errors adopted by different doctors are studied [10]. Therefore, for manual registration, the same physicist and experienced physicians are required to jointly determine registration area and mode. In addition, the quality of CT image also determines registration results and required time. Because of a certain activity between osseous registration is approximate to rigid structure and breast, prone to breast deformation and certain unconformity with volume change, so in osseous registration, manual fine-tuning is needed by giving of consideration to breast area PTV. Large aperture CT of CTVision image-guided radiation therapy system in this study is with high-resolution for soft tissue and clear picture, which effectively improves registration effect and time. For skin tag tumor bed area registration, thanks to homemade marker with good development, tumor bed area registration effect is good, which can effectively guarantee PTV matching area of tumor bed area, simple and practicable. Abroad, Baroni et al. [1] reported, several developing markers are posted to breast radiotherapy area, developing mark position error is displayed through real-time monitoring of breast area, patient's breast tissue changes are verified, impact of setup error on dosimetry is assessed, which can potentially improve therapeutic precision.

IMRT target delineation after modified radical mastectomy includes chest wall and supraclavicular lymph node. Due to irregular shape, it is subjected to the impact of setup. Chest wall target is vulnerable to volatility and volume changes of breast tissue during treatment, while IMRT technology requires a higher setup accuracy to perform. In research on breast radiotherapy, there are also some gaps at home and abroad in setup error data. In this study, fractioned setup error results of postoperative breast cancer patients are analyzed. The results of this study show that, when displacement over 3 mm and 5 mm occurs in any direction, osseous manual registration is superior to skin tag registration regardless of variation degree of error, or actual percentage of limited 3 mm or 5 mm of actual error. In domestic literature report, average setup errors in X-, Y-, Z-axis of image-guided radiotherapy for breast cancer is less than 5 mm [21]. Xu et al. [20] reported setup errors of IMRT of patients with modified radical mastectomy, and average error is 1.27 ± 0.88 mm in horizontal direction, 2.01 ± 1.32 mm in vertical direction and 2.44 ± 2.17 mm in longitudinal direction. The results of the study are similar to setup error results of above studies in three-dimensional direction.

Setup errors are subjected to various factors. Setup errors of breast conserving surgery patients are mainly affected by breast shape, changes in breast volume, and changes in arm abduction, difference in arm abduction muscle contraction and chest wall muscles contraction, which may influence displacement change of breast and chest wall. For modified radical mastectomy patients, displacement error caused by female breast change can be excluded, but there exist external forces pulling the chest wall, surgical scar shrinkage, different degrees of tension during treatment, nervousness caused by discomfort, which cause changes in the chest wall. In addition, accuracy of radiotherapy equipment, setup technical level of different technical personnel, and patients' degree of adaptability to setup, etc. cause setup errors. This paper focuses on patients with breast cancer bracket joint thermoplastic molding to verify setup errors of patients, with unnecessary setup errors minimized, such as errors caused by setup technology of different technicians and different image registration operating force by different physicists. By appointment of every image-guided verification 1 day in advance, the same technician and physicist are coordinated for image-guided verification. There exist some differences between results of this study and setup errors result of image-guided radiotherapy of foreign studies on breast conserving surgery patients, which may be because breast is an organ with large move ability and there exists difference in breast size of European, American and Asian race. Tsuchiya et al. [16] study confirms consistent advantage of IMRT for Asian women with breast conserving surgery and IMRT for western patients with breast conserving surgery. But volume of Asian patients' breast is 50% of that of Western patients, with inconsistent breast sports and shift baseline. In further study, it is confirmed that dose in homogeneity of breast tissue is related to breast volume, and dose distribution is more uniform in IMRT target.

In this study, 10 cases of postoperative breast cancer patients with breast bracket joint thermoplastic phantom were positioned. Setup errors were verified after 83 times of repeated positioning. Only 3 times had relatively large setup errors, which needed re-setup or movement of treatment couch to correct setup errors, with setup failure rate at 3.8%. Then 80 images-guided CT images and planning image are compared, with respectively using osseous manual registration and skin tag tumor bed area registration and setup error in X-, Y-, Z-axis for pair wise comparison are obtained. Displacement change of two registration modes differs, for its reason: when patient's chest is fixed with thermoplastic phantom, positioning mark on the phantom subjected to little influence of changes in respiratory movement, so relative position is relatively fixed, and therefore displacement error of osseous manual registration in Z-axis direction is not reflected. For skin tag tumor bed area registration, after homemade marker is affixed to the skin surface of tumor bed area, marker will have location change in longitudinal direction with patient's respiratory movements or weight loss. Therefore, this paper compares modified radical mastectomy patients with breast conserving surgery patients in above methods, and comparison results of modified radical mastectomy patients with above methods are consistent with results of all patients. Considering small number of cases of breast conserving surgery patients, setup error of breast conserving surgery patients cannot be fully reflected.

Spadea et al. [14] studied impact of breast and chest wall radiotherapy with thermoplastic phantom on intra-fractioned and inter-fractioned setup error. By 4DCT image monitoring, maximum average motion of outer contour of breast is 1.3 ± 1.6 mm, maximum average chest wall motion is 1.6 ± 1.9 mm, random errors in horizontal, vertical and longitudinal direction are respectively 4.0 mm, 12.0 mm, 4.5 mm, and standard deviation of systematic errors are respectively 2.7 mm, 9.8 mm, 4.1 mm. Through this fixed with thermoplastic phantom and 4DCT monitoring, displacement error in longitudinal direction of skin and chest wall of 7 cases out of 8 patients is limited within 2 mm. The results show that thermoplastic phantom fixing can effectively control impact of respiratory movement on patient's positioning. There are similar researches about the impact of respiratory movement in breast cancer radiotherapy on patient. Based on 4DCT research, displacement change in sagittal view of breast cancer radiotherapy caused by free breathing movement does not exceed 2 mm [8, 18]. Li et al. [9] applied thermoplastic molding technology in IMRT of postoperative breast conserving surgery, with setup errors in three directions respectively 2.5 ± 1.0 mm, 2.8 ± 1.1 mm, 2.6 ± 1.0 mm. Setup error of double labeling method of thermoplastic molding is smaller than that of conventional thermoplastic molding technology. In domestic relevant research, setup errors in three-dimensional direction of breast cancer patients with breast bracket, vacuum pad or breast bracket joint vacuum pad fixation are smaller than 5mminlocation verification [2, 13]. Zhang et al. [22] studied setup errors in three-dimensional direction of breast bracket joint thermoplastic molding for postoperative breast cancer patients, which are respectively 1.8 ± 0.6 mm, 1.9 ± 0.8 mm, 1.7 ± 0.5 mm. In this study, setup error of breast cancer bracket joint thermoplastic molding after breast cancer surgery is similar to that in domestic report, but different from setup error of radiotherapy fixation after breast conserving surgery in foreign reports. Considering difference of females in Western countries and Asian women in body and breast volume, setup error may be different. But in the present study, setup errors in longitudinal direction are significantly less than that those in other directions, which is consistent with results of thermoplastic molding in foreign reports. Considering that thermoplastic phantom can effectively reduce the impact of respiratory movement on displacement errors in longitudinal direction, breast bracket joint thermoplastic phantom can reduce setup errors to some extent, and radiotherapy for breast cancer patients with thermoplastic molding can effectively reduce the impact of respiratory movement.

For radiotherapy of postoperative breast cancer patients, radiation doses to the heart and lung need to be assessed, while deviation of radiation dose is caused by intra-fractioned and inter-fractioned setup errors. By studying appropriate external expansion of target and organs at risk, target is ensured to be irradiated by prescription dose, while radiation dose to organs at risk is not increased. In setup errors, the influence of systematic errors and random errors on dose distribution differs. Systematic errors may remain unchanged or show certain regular changes under certain measurement conditions, with repetitive and one-way, including inadequate linear accelerator equipment accuracy, CT scan data change difference, and accurate performance change of laser positioning system. Random error is caused by many factors and thus is uncertain. High-dose target caused by random errors deviates to low-dose organs at risk. When target dose is lower than prescription dose, the systematic error may cause overall target deviation. Based on CTV extended value $M_1 = 2.5\Sigma + 0.7\sigma$ proposed by Van Herk [17], in which Σ represents grouped systematic errors, and σ represents grouped random error, it indicates that control of systematic errors is more important than that of random error, and its impact on CTV external expansion is greater. CTV extended boundary is obtained through systematic errors and random errors in setup errors. Meanwhile, CTV extended value calculated by CTV expansion formula also considers impact of setup errors on dose. The resulting CTV external expansion ensures that 90% patients of 95% of prescription dose covers 100% CTV. Through setup errors of osseous manual registration, researchers conclude that CTV extended value M_1 of IMRT of breast cancer patients in three- dimensional direction is respectively: 4.79 mm, 5.81 mm, 1.46 mm. There are some studies indicate that there exists certain difference in CTV external expansion caused by setup errors of chest cancer radiotherapy [11, 18, 19]. Further analysis shows that setup errors of chest cancer may be different when different units adopt different technologies, and that there exist differences in setup extended value, which may be associated with radiotherapy equipment, systemic errors of scanned images and positioning standards of technical personnel. But extended value of chest tumor radiotherapy positioning by different research units can be used as clinical reference based on different research methods and selected tumor sites. By improving equipment performance and positioning technology of different technical personnel, CTV extended value can be reduced.

For irradiation of postoperative breast cancer patients, since radiation dose lacks accurate assessment of organs at risk, it is difficult to control setup errors, which causes radiation-induced lung injury. In recent years, left-sided breast cancer radiotherapy which may cause delayed heart damage attracts are more and more causing researchers' attention. In this study, extended value M_2 of organs at risk is obtained through osseous manual registration. But there are some differences in extended calculations of external expansion of organs at risk according to characteristics of different types of organs. Lung tissue belongs to parallel organ in radiotherapy after breast cancer surgery, so CTV extended value can be obtained without external expansion of organs at risk or with systemic error. For series or parallel small organs in breast cancer radiotherapy, such as organs at risk like heart, thyroid, when dose deviation causes excessive dose radiation, severe acute reactions or delayed heart disease may be caused. Therefore, strict external expansion is needed for plan setting. Further analysis derives that organs at risk are extended in three ways:

a) PRV extended value $M_2 = 1.5\Sigma - 0.5\sigma$, showing that defined dose of organs at risk > 60%;
b) PRV extended value $M_2 = 1.5\Sigma - 0.5\sigma$, showing that defined dose of organs at risk is between 40% and 60%, or > 60%, but random error variation range is large;
c) PRV extended value $M_2 = 1.5\Sigma + 0.5\sigma$, showing that defined dose of organs at risk < 40% or defined dose is under unknown circumstances.

External expansion of organs at risk should be decided by influence factors such as tumor site and design of treatment plan, etc.

Conclusions

This study, with CTVision image-guided radiation therapy system, by registration of treatment and planning CT images, measures setup errors, and verifies the feasibility of therapeutic body position before treatment and during radiotherapy. The results of research show that:

1) For IMRT of CTVsion image-guided breast cancer patients in X-, Y-, Z-direction, setup error of osseous manual registration is significantly smaller than that of skin tag tumor bed area registration, and osseous manual registration is more suitable for IMRT of postoperative breast cancer patients.
2) Fixation of positioning of postoperative breast cancer patients with breast bracket joint thermoplastic phantom is with relatively good repeatability and stability, and can meet requirement for accuracy of treatment plan execution. This fixation method can effectively control displacement error in longitudinal direction caused by respiratory movement.
3) To study systemic error and random error of IMRT for postoperative breast cancer patients, actual extended value of CTV and organs at risk of the unit are determined, which can guide design of treatment plan and better ensure therapeutic dose of target and protection of organs at risk.

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