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Postmastectomy intensity modulation radiated therapy of chest wall and regional nodes

Retrospective analysis of the performance and complications up for 5 years

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Abstract

To retrospectively evaluate the performance and complications of postmastectomy intensity modulation radiated therapy (IMRT) technique.

From January 2010 to December 2014, IMRT technique was applied to 200 patients after modified radical mastectomy. The acute and late radiation toxicities have been followed up for 5 years. The treatment performance, toxicity incidence, and risk factors were investigated.

All patients included had at least 1-year of follow-up; mean follow-up was 28.5 months. Three patients had grade 3 acute radiation dermatitis; 1 patient received grade 2 acute radiation induced lung injury, while 3 patients received acute radiation esophagitis. Seven patients had edema at the end of radiotherapy. Multivariate analyses revealed that neoadjuvant chemotherapy and hypertension were the most significant risk factors for acute skin dermatitis and acute radiation induced lung injury, respectively. Trastuzumab treatment was the independent risk factor for late radiation lung injury. Internal mammary nodes irradiation might relate to acute and late radiation induced lung injury. In the follow-ups there were 125 patients that were followed up with for >2 years. The 2-year local-regional recurrence (LRR), distant metastasis (DM), and disease free survival (DFS) were 1.6%, 6.4%, and 92.80%, respectively.

Postmastectomy treatment with the IMRT technique can reduce the incidence rate of radiation toxicity by decreasing organs at risk (OARs) irradiation. Patients with risk factors for radiation toxicity should be strictly surveyed throughout radiotherapy.

Abbreviations: CI = conformity index, CT = computed tomography, CTVs = clinical target volumes, DFS = disease free survival, DM = distant metastasis, DVHs = dose-volume histograms, ECG = electrocardiograph, HI = homogeneity index, IMNs = internal mammary nodes, IMRT = intensity modulation radiated therapy, LRR = local-regional recurrence, MRM = modified radical mastectomy, OARs = organs at risk, PMRT = postmastectomy radiation therapy, PR = progesterone receptor, PTVs = planning target volumes, RTOG = Radiation Therapy Oncology Group.

Keywords: breast cancer, IMRT, normal tissue toxicity, PMRT, risk factors

1. Introduction

Breast cancer is the most commonly diagnosed cancer in women.[1] For early-stage disease, postmastectomy radiation therapy (PMRT) is a very mature technology. It can reduce the local recurrence rate and increase overall survival in patients.[2,3] With the coming era of accurate radiotherapy, intensity modulation radiated therapy (IMRT) can improve the coverage of the target volume and reduce non-uniformity distribution. Most importantly, IMRT can minimize the exposure of normal tissues to radiation and reduce complications of radiotherapy. Ma et al[4] recently reported the dosimetrical feasibility of the IMRT technique for treating chest wall and regional nodes as a whole planning target volume (PTV) after modified radical mastectomy (MRM). The data for the toxicity of IMRT after mastectomy, especially of late radiation toxicity, are very rare.

The IMRT technique was applied to treat breast cancer patients after MRM from January 2010 in our cancer center. We retrospectively analyze the performance and complications of this technique.

2. Methods

2.1. Patient information

Breast cancer patients, after MRM with a node-positive lymph and/or tumor size >5 cm, were involved in our study from January 2010 to December 2014. The exclusion criteria were as follows: distant metastases at diagnosis; male breast cancer patients; history of other malignancies; and severe deficiencies in clinical data or follow-up data. A total of 200 patients were eligible in our retrospective analysis. All patients provided written informed consent. The study was performed according to a protocol approved by the Huazhong University of Science and Technology Institutional Ethics Committee.

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2.2. Surgery and adjuvant therapy

All patients had undergone MRM, sentinel lymph node biopsy, and/or axillary lymph node dissection. When needed, adjuvant chemotherapy, endocrine therapy, and trastuzumab treatment followed based on National Comprehensive Cancer Network (NCCN).

2.3. Radiotherapy

The patient was placed supine and fixed on a breast tilt board with both arms fully abducted and externally rotated. The head was turned to the contralateral. Several transparent hoses full of computed tomography (CT) contrast agents were used to mark the caudal and lateral target region, the cranial border of chest skin and the mastectomy scar. The caudal line was 1 cm below the contralateral inframammary fold; the lateral line was the mid-axillary line; and the cranial line of chest skin was the caudal border of the clavicle head. A daily 5-mm bolus was placed on the chest wall under the thermoplastic sheet. A planning CT scan at 5-mm intervals from mid-neck to diaphragm was obtained for each patient using a CT simulator (Brilliance CT BigBore, Philips, the Netherlands). The scanned images were uploaded to the Pinnacle system and then the target region was designed.

For each patient, the clinical target volumes (CTVs) were defined to consist of the ipsilateral chest wall, the mastectomy scar, and the supra/infra-clavicular region. Treatment of internal mammary nodes (IMNs) was strongly considered when a primary tumor was located in the inner quadrant of the breast. Each CTV of the chest wall and regional lymph nodes was delineated according to the guide of the Radiation Therapy Oncology Group (RTOG).[5] The CTV was expanded 0.5 cm to become a planning target volumes (PTVs), except the anterior border was still 2 mm below the skin surface. The cranial line was located in the caudal to the cricoid cartilage, and the posterior line was in the rib-pleural interface. If IMNs irradiation was not included, the medial border of the PTV was usually at the medial edge of the sternal-rib junction, while the IMNs were included in the target. Expansions of 5 mm for the radius of internal mammary vessels were made to form the PTV in consideration of cardiac tolerance. An entire PTV, including both chest wall and regional nodes, was formed.

The organs at risk (OARs) surrounding the targets, including bilateral lungs, heart, esophagus, contralateral breast, and spinal cord, were also contoured. The heart was defined as from its apex to the junction of great vessels with myocardium. In addition, the healthy tissue was defined as the patient's volume covered by the CT scan minus the envelope of the PTV to account for the spillage of prescription dose. For dosimetric analysis, the following indices extracted from dose-volume histograms (DVHs) were used: Dmax, Dmin, Dmean, and $V_{110\%}$ for PTV; dose homogeneity index (HI) and conformity index (CI) for PTV: HI and CI were calculated according to definition proposed by the International Commission on Radiation Units and Measurements (ICRU)[6] and expressed as follows:

$\mathrm{HI} = D_{2\%} - D_{98\%}/D_{50\%} \times 100\%$ and CI = precription isodose volume/target volume, lower HI and CI correlate with a more homogeneous target dose and better conformity, respectively.

For each patient, a multiple beams integrated plan was always used. A simplified IMRT plan was generated using Pinnacle treatment planning software (version 9.2: Pinnacle Royal Dutch Philips Electronics Ltd, Dutch). All plans were optimized to cover the whole PTVs and spare surrounding normal tissues as much as possible. The angles of the sectors covered by multiple beams are shown in Fig. 1. For the purpose of improving skin dose and avoiding the calculation errors of a dose built-up area, a daily 5 mm bolus was placed on the chest wall of each patient. For dosimetric analysis, dose-volume histograms (DVHs) were used. Then, 95% of a PTV received 50 Gy in 25 fractions. V110% of PTV $\leq$5%; V40 of the spinal cord $\leq$1%; V20 of the ipsilateral lung $\leq$30% to 35% and the total lung $\leq$20%; Dmean of the heart $\leq$10 Gy and V30 $\leq$10% for left breast cancer patients; and Dmean of the heart $\leq$6 Gy and V30 $\leq$0 Gy. Priority was high for the PTV, heart and lung constraints relative to other structures. Optimization proceeded with these settings until no further improvement was seen. A linear accelerator (Varian UNIQUE-SN2236: Lake Forest, CA) was carried out to finish the radiotherapy.

2.4. Follow-up and statistical methods

Each patient was regularly followed up by the treating physician once a week during radiotherapy and 1 month after irradiation,

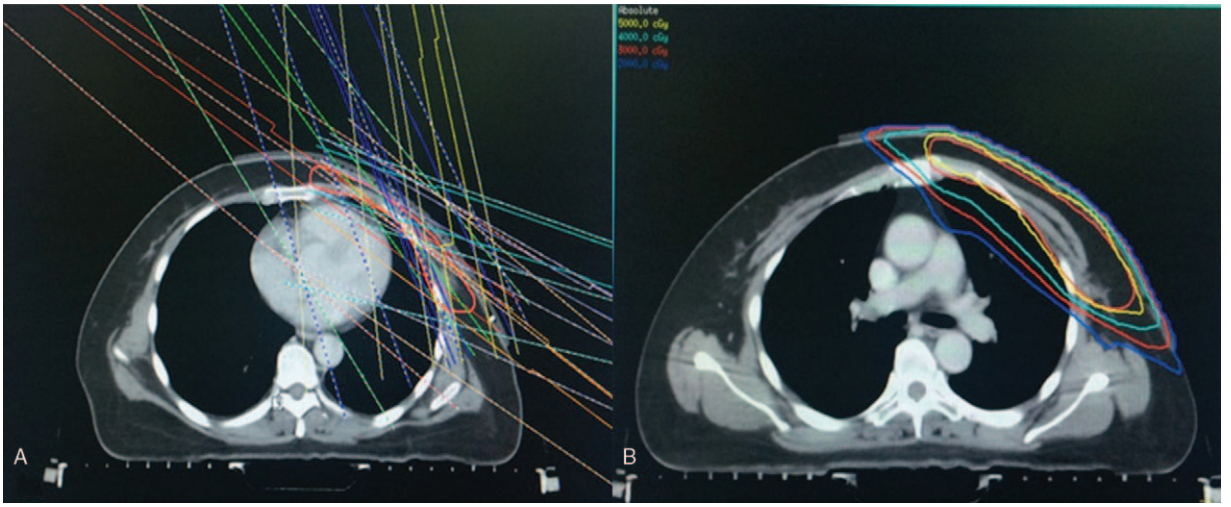

Figure 1. A 8-beam integrated plan designed for a patient with left breast cancer: (A) beam angles (45°, 105°, 115°, 125°, 302°, 320°, 335°, and 350°) for target region; (B) dose distribution.

Table 1

Clinical characteristics of patients.

Characteristic	Cases (%)	Contents	Cases (%)
Age		Histological grade	
<50 y	117 (58.5)	I	6 (3)
≥50 y	83 (41.5)	II	86 (43)
Menopausal status		III	62 (31)
Premenopausal	121 (60.5)	Unknown	46 (23)
Postmenopausal	79 (39.5)	Receptor status	
Diabetes		ER positive	134 (67)
Yes	12 (6)	ER negative	66 (33)
No	188 (94)	PR positive	126 (63)
Hypertension		PR negative	74 (37)
Yes	19 (9.5)	Her-2 positive	62 (31)
No	181 (90.5)	Her-2 negative	123 (61.5)
Cardiovascular disease		Her-2 unkown	15 (7.5)
		TNBC	27 (13.5)
Yes	6 (3)	Systemic treatment	
No	194 (97)	Chemotherapy	196 (98)
T stage		Endocrine therapy	134 (67)
T1	62 (31)	Chemotherapy method	
T2	102 (51)	Neoadjuvant chemotherapy	25 (12.5)
T3	27 (13.5)	Adjuvant chemotherapy	196 (98)
T4	7 (3.5)	Trastuzumab	41 (20.5)
TX	2 (1)	Internal mammary	
N stage		Yes	101 (50.5)
N0	33 (16.5)	No	99 (49.5)
N1	60 (30)		
N2	63 (31.5)		
N3	44 (22)		

ER = estrogen receptor, HER-2 = human epidermalgrowth factor receptor-2, TNBC = triple negative breast cancer, PR = progesterone receptor.

once a month from 1 month to 1 year after irradiation, and once every 3 months from 1 year after irradiation to date. The major observations included: early and late toxicity of radiation lung injury and radiation dermatitis, radiation esophagitis, radiation bronchitis, arm edema, and cardiotoxicity. The grading of AEs was performed according to the US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Early radiation toxicity was defined as occurring in 90 days as referred to the RTOG while late radiation occurred after 90 days.[7]

In this study, statistical analyses were performed by SPSS 16.0 (SPSS, Chicago, IL) software. Differences between the groups of patients with or without radiation toxicity were analyzed for statistical significance by using the logistic regression analysis. Variables with $P < .15$ at univariate analysis were used as input variables for multivariate logistic regression analysis to determine independent factors. P values of $\leq .05$ were considered statistically significant.

3. Results

3.1. Clinical features

Between January 2010 and December 2014, 200 patients were enrolled into the study. The follow-up time was 12 to 60 months, while the median follow-up time was 28.5 months. Patients (median age of 47 [28–69]) received radiotherapy, neoadjuvant and adjuvant chemotherapy, endocrine therapy, and trastuzumab therapy according to disease characteristics. There were 101 patients in which the tumor was in the inner quadrant and received IMN irradiation; other patients only received the chest wall and supra/infraclavicular region irradiation. The clinical features and treatments of all the patients are shown in Table 1.

3.2. Dosimetry data

All IMRT plans were approved by treating physicians. The number of beams was 7 to 8. Plans were assessed based on dose-volume of lung, heart, and spinal cord. All V110% of PTV were ≤5%; the HI and CI of PTV were 0.12 ± 0.01 and 1.37 ± 0.18. Dmean of the heart dose was 6.99 ± 3.01 Gy, and the data were 9.30 ± 1.21 Gy when the tumor was on the left side. The V20 of the total lung was 16.39 ± 2.93% and of the ipsilateral lung was 32.24 ± 2.95%; the V5 and Dmean of the contralateral breast were 2.45 ± 0.8% and 1.07 ± 0.3 Gy; the Dmean and Dmax of the esophagus were 10.65 ± 2.43 Gy and 40.61 ± 4.45 Gy (Table 2).

3.3. Radiation toxicity

All patients completed radiotherapy as planned. The minimum follow-up time was 1 year, while the longest follow-up period was 5 years; among them there were 125 patients who had been followed up with for >2 years. Table 3 lists the incidence of radiation toxicity. Three patients (1.5%) had grade 3 acute radiation dermatitis and no grade 4 reaction occurred. One patient (1%) developed grade 2 acute radiation induced lung injury, while 3 patients (1.5%) had acute radiation esophagitis. There were 27 cases of patients having arm edema, of which 20 cases had arm edema right after MRM and no change occurred

Table 2

Summary of DVH-based analysis for OARs and healthy tissue.

Target	Parameters	Value (mean ± SD)
PTV	Dmin (Gy)	47.71 ± 7.98
	Dmax (Gy)	57.29 ± 1.56
	Dmean (Gy)	51.38 ± 1.09
	$V_{110\%}$	2.23% ± 2.57
	HI	0.12 ± 0.01
	CI	1.37 ± 0.18
Ipsilateral lung	V5	59.80% ± 5.00%
	V20	32.24% ± 2.95%
	Dmean (Gy)	16.59 ± 1.42
Contralateral lung	V5	4.76% ± 7.92%
	Dmean (Gy)	1.20 ± 0.51
Lung	V5	33.02% ± 7.96%
	V20	16.39% ± 2.93%
	Dmean (Gy)	9.59 ± 2.01
Heart	V5	44.91% ± 21.69%
	V10	19.95% ± 11.64%
	V20	8.28% ± 6.55%
	V30	3.99% ± 3.56%
	Dmean (Gy)	6.99 ± 3.01
Breast cancer (left)	V5	55.49% ± 21.69%
Contralateral breast	V5	2.45% ± 0.8%
	Dmean (Gy)	1.07 ± 0.3
Esophagus	Dmean (Gy)	10.65 ± 2.43
	Dmax (Gy)	40.61 ± 4.45
Heart	V10	25.88% ± 6.82%
	V20	13.43% ± 3.05%
	V30	6.79% ± 1.60%
	Dmean (Gy)	9.30 ± 1.21
Spinal cord	Dmax (Gy)	22.34 ± 8.37

CI = conformity index, Dmax = maximum dose, Dmean = mean dose, HI = homogeneity index, OARs = organs at risk, PTV = planning target volume, Vx% = percent volume of PTV receiving x% of prescription dose.

Table 3

Incidence of radiation toxicity.

	0	Grade 1	Grade 2	Grade 3	Grade 4
Acute skin dermatitis	0	58 (29%)	139 (69.5%)	3 (1.5%)	0
Acute radiation pneumonitis	83 (42%)	114 (57%)	2 (1%)	0	0
Acute radiation esophagitis	179 (89.5%)	18 (9%)	3 (1.5%)	0	0
Late radiation lung injury	82 (41%)	118 (59%)	0	0	0
	No	**Mild**	**Moderate**	**Severe**	
Arm edema	193 (86.5%)	4 (2%)	2 (1%)	1 (0.5%)	

during radiotherapy. The remaining 7 patients had edema at the end of radiotherapy, and, of them, 4 patients had mild edema, 2 patients had moderate edema (1 patient went from mild edema that aggravated to moderate edema after radiotherapy, another patient had edema during axillary relapse), and 1 patient had severe edema (moderate edema aggravated after MRM). In addition, 1 patient got leukoplakia on the chest wall after radiotherapy, while another patient showed precordial discomfort after mild activity at the ending of radiotherapy. The discomfort subsided without medication, and myocardial ischemia was observed on an electrocardiograph (ECG). The tumor was on the right breast of this patient and she received trastuzumab treatment. She did not receive any special treatment because a normal ultrasonic cardiogram was observed. She successfully finished radiotherapy and trastuzumab treatment. No ECG abnormalities and precordial discomfort were observed from then on.

3.4. Univariate analysis of risk factors of radiation toxicity

In terms of the influencing factors for acute skin dermatitis, univariate analyses showed that there were significant differences between patients with and without neoadjuvant chemotherapy ($P = .025$). Those who developed hypertension ($P = .024$) and received IMNs irradiation ($P = .034$) are more susceptible to suffer acute radiation induced lung injury. Trastuzumab treatment ($P = .018$) meant a greater chance of late radiation lung injury (Table 4).

3.5. Multivariate analysis of risk factors of radiation toxicity

The logistic regression was used to analyze the risk factors that were considered significant ($P > .15$) in univariate analysis. The results showed that as independent risk factors, neoadjuvant chemotherapy (odds ratio [OR] = 5.37, $P = .026$) and hypertension

Table 4

Results of univariate analysis of risk factors of radiation toxicity.

	Acute skin dermatitis	Acute radiation lung injury	Acute radiation esophagitis	Late radiation lung injury	Arm edema
Age	0.289	**0.052**	0.458	0.265	0.237
<40 y					
≥40 y					
Neoadjuvant chemotherapy	**0.025**	0.829	0.663	0.587	0.17
No					
Yes					
Adjuvant chemotherapy					
Anthracyclines	0.751	0.33	0.946	0.906	0.999
Taxanes	1	**0.12**	0.59	0.68	0.391
Anthracyclines+Taxanes	0.865	0.217	0.488	0.703	0.999
Menopausal status	0.728	0.523	0.195	0.636	**0.071**
Premenopausal					
Postmenopausal					
Hypertension	0.787	**0.024**	**0.101**	0.383	0.691
No					
Yes					
Diabetes	**0.138**	0.564	0.419	0.217	0.241
No					
Yes					
Endocrine therapy	0.776	0.318	0.462	0.229	**0.076**
No					
Yes					
Trastuzumab	0.669	**0.137**	**0.057**	**0.018**	0.211
No					
Yes					
Internal mammary radiotherapy	0.825	**0.034**	0.644	**0.066**	0.5
No					
Yes					

Table 5

Results of multivariate analysis of risk factors of radiation toxicity.

	P	OR
Acute skin dermatitis		
Neoadjuvant chemotherapy	**.026**	5.37
Diabetes	.145	4.707
Acute radiation lung injury		
Age	.221	1.528
Hypertension	**.039**	3.914
Trastuzumab	.161	1.71
Internal mammary radiotherapy	.055	1.77
Acute radiation esophagitis		
Hypertension	.114	2.183
Trastuzumab	.063	0.485
Late radiation lung injury		
Trastuzumab	**.019**	2.549
Internal mammary radiotherapy	.074	1.692
Arm edema		
Menopausal status	.09	2.025
Endocrine therapy	.103	0.502

OR = odds ratio.

(OR = 3.914, $P = .039$) can induce acute skin dermatitis and acute radiation induced lung injury, respectively. Trastuzumab treatment (OR = 2.549, $P = .019$) was an independent risk factor of late radiation induced lung injury. Patients receiving IMNs irradiation were more likely to get acute (OR = 1.77, $P = .055$) and late (OR = 1.692, $P = .074$) radiation induced lung injury (Table 5). The reason that the both *P* values were greater than .05 may be limited patients involved in the study.

3.6. Efficacy of IMRT technique

Because the follow-up time was not long enough, only 125 cases were followed up to 2 years. Two-year local-regional recurrence (LRR), distant metastasis (DM), and disease free survival (DFS) were 1.6%, 6.4%, and 92.80%, respectively. Of these, 2 cases recurred. One was a chest wall recurrence with distant metastasis, and another case was right axillary lymph node recurrence. Distant metastasis was observed in 8 patients (6.4%) and 6 patients died. In sum, 5.1% of the 125 patients died because of breast cancer.

4. Discussion

The conventional PMRT technique always compromises the target coverage and dose homogeneity. For example, there could be a hot spot as long as tangential photon beams scatter at the supraclavicular. A cold spot could be formed once there was more adipose tissue under the junction of the tangential photon beams and the internal mammary field. Our results showed that IMRT technique applied to patients under PMRT can result in good conformity and homogeneity for the target field while maintaining similar doses to OARs as conventional techniques.[8]

The study also showed an advantage for both early and late normal tissue toxicities. The incidence rate of grade 3 acute radiation dermatitis was 1.5% (3 cases) compared with 8.2% (9 cases) in a prospective study observed by Wright et al.[9] Other studies showed the incidence rates were as high as 31.3% and 50.8%, respectively.[10,11] The incidence rate of acute radiation induced lung injury treated with the conventional PMRT was 2.6% (16 cases), reported by Marks et al.[12] In the observation of Wennberg et al[13] in 121 cases, 4% (5 cases) had a diagnosis of acute radiation induced lung injury. In our study, the incidence rate of grade 2 was 1% (2 cases), which is an obvious decrease. In addition, the incidence rate of grade 2 acute radiation esophagitis was 1.5%, lower than the results of conventional research after PMRT. The studies conducted by Belkacémi et al[14] and Caussa et al[15] showed that the rates of ≥grade 2 acute radiation esophagitis were 12% (16 cases) and 5% (4 cases), respectively. Furthermore, arm edema is a common late toxicity. Recently, Shah and Vicini[16] found that PMRT could easily induce arm edema in their retrospective research, and the incidence rate was from 58% to 65%. In another retrospective study,[17] the incidence of arm edema was 27%, excluding the patients who developed arm edema before radiotherapy. Our results showed 13.5%, and most of them were mild arm edema. The incidence rate was much lower than conventional radiotherapy. A reasonable explanation could be that IMRT offers a better conformity index (CI) and homogeneity index (HI), which can avoid radiation to level 1 axillary lymph nodes and surrounding blood vessels. Breast cancer patients always survive for a long time, and arm edema can bring out much worse physical and psychological effects. In other words, the IMRT technique can improve the quality of life of patients. As for assessing heart radiation toxicity, we have insufficient data because of the short follow-up time, and more data needs to be followed up before we proceed to further analysis. For the patient who appeared to have myocardial ischemia on ECG, we thought it was related to trastuzumab treatment rather than related to the radiotherapy.

We also conducted an analysis of risk factors for radiation toxicities of breast cancer patients. Some studies[18–20] reported age, chemotherapy drugs, and doses were risk factors for acute radiation lung injury. Lind et al[13,21] found short-term postradiotherapy lung density changes and symptomatic radiation pneumonitis (RP) were associated with radiotherapy techniques. Matzinger et al[22] initiated research to compare the incidence of acute radiation lung injury between IMNs plus supraclavicular region irradiation and IMNs irradiation only. The incidence was 4.3% and 1.3%, respectively. Our research showed that IMNs irradiation might relate to acute and late radiation induced lung injury. In our study 98.3% of the patients received supraclavicular region irradiation. Therefore, the incidence of radiation lung injury increased when IMNs were involved in irradiation. We also found that patients received neoadjuvant chemotherapy presented more serious acute skin dermatitis during treatment. Patients received neoadjuvant chemotherapy always had less adjuvant chemotherapy and this means shorter spare time from surgery to radiotherapy. Longer time from surgery to radiotherapy may decrease the serious acute skin dermatitis incidence rate. Our study showed that hypertension was an independent risk factor for acute radiation lung injury. The reason for that is still unknown; further studies should be performed. It is still worth noting that the radiation dose on the lung needs to be strictly given if patients had hypertension for a long time, especially for those who needed IMNs irradiation simultaneously. Our study also discovered that trastuzumab treatment was an independent factor for late radiation induced lung injury. No similar results are reported. However, having longer follow-up times and more patients could offer us better results.

5. Conclusion

In summary, the postmastectomy treatment with the IMRT technique can reduce the incidence rate of radiation toxicity by

improving target region coverage and decreasing OAR irradiation. Patients with risk factors for radiation toxicity should be strictly surveyed throughout the radiotherapy. Breast cancer is a chronic and systemic disease; the quality of life plays a more important role in the treatment now that survival rates keep rising. Postmastectomy IMRT technique has shown its advantages concerning radiation toxicity, and it can be considered for application in clinical work.

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