Observational Study

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) 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 dosimetric 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 >5cm, 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.
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).

The CTV was expanded 0.5 cm to become a planning target volumes (PTVs), except the anterior skin and the mastectomy scar. The caudal line was turned to the contralateral. Several transparent hoses full of contrast agents were used to mark the target region when needed. The heart 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 V10% for PTV; dose homogeneity index (HI) and conformity index (CI) for PTV: 

\[ HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \times 100\% \]

\[ CI = \frac{\text{prescription isodose volume}}{\text{target volume}} \]

Each CTV was expanded 0.5 mm 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 V10% for PTV; dose homogeneity index (HI) and conformity index (CI) for PTV: 

\[ HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \times 100\% \]

\[ CI = \frac{\text{prescription isodose volume}}{\text{target volume}} \]

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 ≤ 5%; V40 of the spinal cord ≤ 1%; V20 of the ipsilateral lung ≤ 30% to 35%; and the total lung ≤ 20%; Dmean of the heart ≤ 10 Gy and V30 ≤ 10% for left breast cancer patients; and Dmean of the heart ≤ 6 Gy and V30 ≤ 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.
Table 1
Clinical characteristics of patients.

| Characteristic | Cases (%) | Contents |
|---------------|-----------|----------|
| Age | Histological grade |
| <50 y | 117 (58.5) | I |
| ≥50 y | 83 (41.5) | II |
| Menopausal status | 62 (31) |
| Premenopausal | 121 (60.5) | Unknown |
| Postmenopausal | 79 (39.5) | Receptor status |
| Diabetes | Yes | 134 (67) |
| No | 19 (9.5) | PR positive |
| Hypertension | Yes | 74 (37) |
| No | 66 (33) | ER positive |
| Cardiovascular disease | Yes | 33 (16.5) |
| Postmenopausal | 99 (49.5) | No |

ER=estrogen receptor, HER-2=human epidermal growth 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.[1]

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 ≤.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±5.16       |
|        | Dmean (Gy) | 51.38±1.09       |
|        | V10%      | 2.23±2.57        |
|        | HI        | 0.12±0.01        |
|        | CI        | 1.0±0.98         |
| Ipsilateral lung | V5 | 59.80±0.0% |
|        | V20       | 32.24±5.95       |
| Contralateral lung | Dmax (Gy) | 40.61±4.45 |
| Lung   | V5        | 33.02±7.96       |
|        | V20       | 16.39±2.03       |
| Heart  | V5        | 44.91±2.169      |
|        | V10       | 19.95±1.644      |
|        | V20       | 8.28±6.355       |
|        | V30       | 3.99±5.56        |
|        | Dmax (Gy) | 6.99±5.01        |
| Breast cancer (left) | V5 | 55.49±21.69 |
| Contralateral breast | V5 | 2.45±0.8% |
|        | Dmax (Gy) | 1.07±0.3         |
| Eosophagus | V5 | 10.65±2.43 |
|        | Dmax (Gy) | 40.61±4.45       |
| Heart  | V10       | 25.88±6.82       |
|        | V20       | 13.43±5.05       |
|        | V30       | 6.79±1.60        |
| Spinal cord | V5 | 3.9±0.121 |
|        | Dmax (Gy) | 22.34±6.37       |

O=conformity index, Dmax=maximum dose, Dmean=mean dose, HI=homogeneity index, OARs=organs at risk, PTV=planning target volume, V%V=percent volume of PTV receiving % of prescription dose.
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 leukoplaalia on the chest wall after radiotherapy, while another patient showed precordial discom- fort 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 ($P = 0.025$). Those who developed hypertension ($P = 0.024$) and received IMNs irradiation ($P = 0.034$) are more susceptible to suffer acute radiation induced lung injury. Trastuzumab treatment ($P = 0.018$) 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 ($P > 0.15$) in univariate analysis. The results showed that as independent risk factors, neoadjuvant chemotherapy (odds ratio [OR] = 5.37, $P = 0.026$) and hypertension

| 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 |
| Arm edema | 193 (86.5%) | 4 (2%) | 2 (1%) | 1 (0.5%) |

| 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 | 0.751 | 0.33 | 0.046 | 0.906 | 0.999 |
| ≥40 y | 0.025 | 0.829 | 0.663 | 0.587 | 0.17 |
| Neoadjuvant chemotherapy | 0.865 | 0.217 | 0.488 | 0.703 | 0.999 |
| No | 0.728 | 0.523 | 0.195 | 0.636 | 0.071 |
| Yes | 0.787 | 0.024 | 0.101 | 0.383 | 0.691 |
| Hypertension | 0.138 | 0.564 | 0.419 | 0.217 | 0.241 |
| No | 0.776 | 0.318 | 0.462 | 0.229 | 0.076 |
| Yes | 0.669 | 0.137 | 0.057 | 0.018 | 0.211 |
| Diabetes | 0.825 | 0.034 | 0.644 | 0.066 | 0.5 |
| No | 0.776 | 0.318 | 0.462 | 0.229 | 0.076 |
| Yes | 0.669 | 0.137 | 0.057 | 0.018 | 0.211 |
| Endocrine therapy | 0.825 | 0.034 | 0.644 | 0.066 | 0.5 |
| No | 0.776 | 0.318 | 0.462 | 0.229 | 0.076 |
| Yes | 0.669 | 0.137 | 0.057 | 0.018 | 0.211 |
| Trastuzumab | 0.825 | 0.034 | 0.644 | 0.066 | 0.5 |
| No | 0.776 | 0.318 | 0.462 | 0.229 | 0.076 |
| Yes | 0.669 | 0.137 | 0.057 | 0.018 | 0.211 |
| Internal mammary radiotherapy | 0.825 | 0.034 | 0.644 | 0.066 | 0.5 |
| No | 0.776 | 0.318 | 0.462 | 0.229 | 0.076 |
| Yes | 0.669 | 0.137 | 0.057 | 0.018 | 0.211 |
late 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.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
[2] Clarke M, Collins R, Darby S, et al. Early Breast Cancer Trialsists’ Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005;366:2087–106.
[3] McGale P, Taylor C, Correa C, et al. Early Breast Cancer Trialsists’ Collaborative Group (EBCTCG) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127–35.
[4] Ma J, Li J, Xie J, et al. Post mastectomy linac IMRT irradiation of chest wall and regional nodes: dosimetry data and acute toxicities. Radiat Oncol 2013;8:81.
[5] Available at: https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx. Accessed August 20, 2017.
[6] ICRU. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT): contents. J ICRU 2010;10:NP.
[7] Cancer therapy evaluation program; 2011. Available at: http://ctep.cancer.gov/reporting/ctc.html. Accessed August 20, 2017.
[8] Goddu SM, Chaudhari S, Mamalui-Hunter M, et al. Helical tomotherapy planning for left-sided breast cancer patients with positive lymph nodes: comparison to conventional multiport breast technique. Int J Radiat Oncol Biol Phys 2009;73:1243–51.
[9] Wright JL, Takita C, Reis IM, et al. Racial variations in radiation-induced skin toxicity severity: data from a prospective cohort receiving postmastectomy radiation. Int J Radiat Oncol Biol Phys 2014;90:335–45.
[10] Graham PH, Plant N, Graham JI, et al. A paired, double-blind, randomized comparison of a moisturizing durable barrier cream to 10% glycerine cream in the prophylactic management of postmastectomy irradiation skin care: trans Tasman Radiation Oncology Group (TROG) 04.01. Int J Radiat Oncol Biol Phys 2013;86:45–50.
[11] Spierer MM, Hong LX, Wagman RT, et al. Postmastectomy CT-based electron beam radiotherapy: dosimetry, efficacy, and toxicity in 118 patients. Int J Radiat Oncol Biol Phys 2004;60:1182–9.
[12] Marks LB, Clough R, Fan M, et al. Radiation (RT)-induced pneumonitis following tangential breast/chestwall irradiation. Int J Radiat Oncol Biol Phys 2000;48:294–5.
[13] Wennberg B, Gagliardi G, Sundbom L, et al. Early response of lung in breast cancer irradiation: radiologic density changes measured by CT and symptomatic radiation pneumonitis. Int J Radiat Oncol Biol Phys 2002;52:1196–206.
[14] Belkaćem Y, Gilgorov J, Ozsahin M, et al. Concurrent trastuzumab with adjuvant radiotherapy in HER2-positive breast cancer patients: acute toxicity analyses from the French multicentric study. Ann Oncol 2008;19:1110–6.
[15] Caussa L, Kirova YM, Gault N, et al. The acute skin and heart toxicity of a concurrent association of trastuzumab and locoregional breast radiotherapy including internal mammary chain: a single-institution study. Eur J Cancer 2011;47:65–73.
[16] Shah C, Vicini FA. Breast cancer-related arm lymphedema: incidence rates, diagnostic techniques, optimal management and risk reduction strategies. Int J Radiat Oncol Biol Phys 2011;81:907–14.
[17] Hinrichs CS, Watroba NL, Rezaishiraz H, et al. Lymphedema secondary to postmastectomy radiation: Incidence and risk factors. Ann Surg Oncol 2004;11:573–80.
[18] Vujaskovic Z, Feng QF, Rababani ZN, et al. Assessment of the protective effect of amifostine on radiation-induced pulmonary toxicity. Exp Lung Res 2002;28:577–90.
[19] Ozturk B, Egehan M, Ataçevi S. Pentoxifylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: a double-blind randomize trial. Int J Radiat Oncol Biol Phys 2004;58:213–9.
[20] Taghian AG, Assaad S, Kuter I, et al. Increased risk of radiation pneumonitis in breast cancer patients treated by concomitant taxol and radiation therapy. Int J Radiat Oncol Biol Phys 1999;45(Suppl):316.
[21] Lind PA, Marks LB, Hardenbergh PH, et al. Technical factors associated with radiation pneumonitis after local and regional radiation therapy for breast cancer. Int J Radiat Oncol Biol Phys 2002;52:137–43.
[22] Matzinger O, Heinsoeth I, Poortmans P, et al. Technical factors associated with radiation pneumonitis after local and regional radiation therapy for breast cancer. Acta Oncol 2010;49:24–34.