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Original Article

IMRT versus 3D-CRT for post-mastectomy irradiation of chest wall and regional nodes: a population-based cmparison of normal lung dose and radiation pneumonitis

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Abstract: Objective: Conventional post-mastectomy radiation therapy (PMRT) is often delivered with traditional field borders. We conducted a population-based study comparing the dose-volume of ipsilateral lung and acute lung injury in breast cancer patients undergoing PMRT using linac intensity-modulated radiation therapy (IMRT) and conventional 3D-CRT techniques. Methods: In this study, 169 breast cancer patients who completed PMRT at our institution were included for analysis. 78 patients received inverse planning IMRT treatment (IMRT group), and 91 patients received conventional 3D-CRT treatment (3D-CRT group). All patients received a total dose of 50 Gy in 25 fractions to the chest wall and supra/infraclavicular region as an integrated volume. The percentage volume of ipsilateral lung receiving 5 Gy (V5), 10 Gy (V10), 20 Gy (V20), and 30 Gy (V30) extracted from dose-volume histograms (DVHs) were collected and compared between treatment groups. The acute lung injury was followed up regularly. Results: The V5 of ipsilateral lung was significantly lower (P = 0.001) in the 3D-CRT group (52% ± 7%) than in the IMRT group (65% ± 9%). The V10 was similar for both groups (41% ± 7% vs. 44% ± 4%). The V20 was significantly higher (P < 0.001) in the 3D-CRT group (32% ± 6%) than in the IMRT group (29% ± 2%), also, the V30 was significantly higher (P < 0.001) in the 3D-CRT group (22% ± 5%) than in the IMRT group (21% ± 2%). After treatment, 21/91 (23.1%) patients in 3D-CRT group were diagnosed with radiation pneumonitis (RP) with Grade ≥ 2. 5/78 (6.4%) patients in IMRT group were diagnosed with RP (Grade ≥ 2). Incidence of RP has no significant difference between the two groups (P = 0.223). Conclusions: Our analysis demonstrated that our IMRT treatment could reduce V20 and V30, but increase the volume of low dose irradiation of ipsilateral lung (V5), compared to 3D-CRT treatment. This study demonstrates that both 3D-CRT and IMRT techniques are feasible for PMRT.

Keywords: Lung, post-mastectomy, IMRT, radiation pneumonitis

Introduction

Breast cancer (BC) is the most frequent female cancer worldwide. The new cases of BC accounted for 23% of all female cancers, the incidence rates of BC varies dramatically across the globe, which is higher in more developed regions. Although the utilization of breast conserving surgery (BCS) for early-stage disease has increased rapidly in last decade in mainland China, modified radical mastectomy (MRM) remains the most-accepted surgical modality in operable breast cancer (BC) [1]. In the recent ten to twenty years, there is a substantial progress in the diagnosis and treatment of breast cancer. A rapid development of various curative options has led to the improvement of treatment outcomes [2].

Radiotherapy is an essential part of breast cancer treatment. In clinical practice, different radiotherapy strategies are performed in patients with breast cancer [3]. Conventional post-mastectomy radiation therapy (PMRT) is often delivered with traditional field borders for chest wall and regional nodes.

Recently, research focus on whether post-mastectomy radiation therapy (PMRT) to the chest wall and regional lymph nodes should be standard for BC patients [4]. Qiao *et al* indicated that postoperative radiotherapy confers better rates of overall survival (OS), local control (LC), and disease-free survival (DFS) in patients with T1 to T2 breast cancer with one to three positive nodes after modified radical mastectomy [5]. Three randomized clinical trials have shown that a disease-free and overall survival advantage is conferred by the addition of chest wall and regional lymph node irradiation in women with positive axillary lymph nodes after MRM [6-8].

Although chest wall and regional nodes delineation techniques have been discussed with available contouring guidelines [9-11], computed tomography (CT)-based planning to treat chest wall and nodal regions as a whole PTV has not yet been adopted into routine practice. In this research, we conduct a population-based dosimetric study comparing the dose-volume of ipsilateral lung and acute toxicity in patients undergoing PMRT using linac IMRT versus conventional 3D-CRT technique.

Methods

Patient eligibility

Eligibility criteria of BC patients included: (1) age ≥ 18 years with operable breast cancer involving axillary lymph nodes, but without evidence of distant metastasis (negative results on chest CT scans, abdomen and pelvis US); (2) resection of all gross disease by MRM with level I to II axillary dissection; (3) negative surgical margins; (4) Eastern Cooperative Oncology Group performance score of 0-1; (5) completion of adjuvant chemotherapy; and (6) no previous thoracic RT. Patients with serious comorbid diseases, such as chronic obstructive pulmonary disease, connective tissue disease, postoperative wound infections, and delayed wound healing, etc., that would have negatively affected their tolerance to radiation-induced skin or lung toxicity were not eligible. Patients with synchronous bilateral breast cancers were eligible.

This study was approved by the ethnic Committee of Shanghai Medical College, Fudan University. All the patients provided written informed consent.

Study design

There were two parts in this study. The first part was to compare the dose-volume of ipsilateral lung in patients using linac IMRT versus conventional technique (dosimetric study). And the second part was to compare the incidence of radiation pneumonitis following PMRT with inverse-planned IMRT and conventional technique (clinical study).

Treatments

A non-contrast CT-simulation was performed in the supine position on a commercially available breast tilt board (Med-Tech 350) with the ipsilateral arm up and head turned to the contralateral side. Radio-opaque wires were used to mark the mastectomy scar and the clinical boundaries. A planning CT scan at 5-mm intervals from mid-neck to diaphragm was obtained for each patient using an AcQsim CT simulator (Philips Medical Systems). The 3D-CRT and IMRT plans were generated using Pinnacle treatment planning software (version 8.0). All treatments were delivered with 6-MV photon using an Electa linear accelerator. The prescribed total dose was 50 Gy in 25 fractions.

IMRT

The clinical target volume (CTV) was defined to consist of ipsilateral chest wall, mastectomy scar and supra/infraclavicular region for each patient. Each CTV was delineated according to the breast cancer atlas for radiation therapy planning consensus definitions of the Radiation Therapy Oncology Group (RTOG) (available at: http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx). The chest wall CTV was expanded 1 cm to become chest wall planning target volume (PTV), except that anterior, posterior and cranial borders were unchanged. This modification was made mainly to account for build-up region or spare underling normal lung from high dose radiation [12, 13]. Generally, expansions of 5 mm to CTV for supra/infraclavicular nodes was made to form the PTV for supra/infraclavicular nodes. The PTV for supra/infraclavicular nodes would match the PTV for chest wall. As a result, a whole PTV including both chest wall and regional nodes formed. The organs at risk (OAR) surrounding the targets, including bilateral lungs,

Table 1. Patient characteristics and demographics of patients with 3D-CRT or IMRT treatments

	Total	3D-CRT	IMRT	*P*-value
No of patients	169	91	78	
Unilateral	169	91	78	
Mean age (years)	49.2	48.2	50.4	0.902
Mean BMI kg/m^2	23.37	23.43	23.30	0.165
Active smoking	0	0	0	
Neo-adjuvant chemotherapy	21	7	14	0.104
Adjuvant chemotherapy	163	83	59	0.425
Mean follow-up (months)	27	27.1	26.9	

Table 2. Summary of DVH-based analysis for planning target volume of patients with 3D-CRT or IMRT treatments

Parameters	3D-CRT	IMRT	*P* value
Dnear-max (Gy)	54.58 ± 0.92	54.67 ± 0.86	0.515
Dnear-min (Gy)	47.52 ± 0.61	47.48 ± 0.56	0.738
Dmean (Gy)	51.63 ± 0.58	51.59 ± 0.42	0.614
V95%	98% ± 2%	98% ± 1%	0.998
V110%	2% ± 2%	2% ± 1%	1.000
Homogeneity index (HI)	0.13 ± 0.01	0.13 ± 0.02	1.000
Conformity index (CI)	1.41 ± 0.05	1.42 ± 0.03	0.125

Data are shown as mean ± SD.

heart, contralateral breast, ipsilateral humeral head, spinal cord, and esophagus, were contoured as well.

3D-CRT

Two tangential semi-opposed beams (to avoid divergence), physical wedges (usually 15° or 30°), and a multileaf collimator were used for 3D-CRT. The beam angles, wedge angles, and beam weighting (usually minimal) were chosen to optimize coverage of the PTV, while minimizing exposure to the ipsilateral lung, heart and contralateral breast. Gantry angles ranged from 42° to 55° for the medial fields and from 224° to 232° for the lateral fields for patients treated on the right side, and from 305° to 322° for the medial fields and from 133° to 147° for the lateral fields for patients treated on the left side. The fields extended 2 cm anteriorly of the chest to provide coverage of the "flash" region. The supra/infraclavicular region was designed with separate anterior mixed photon-electron beams.

Dosimetric analysis

For treatment plan evaluation and dosimetric analysis, the following PTV statistics were obtained from dose-volume histograms (DVHs): 1) Dnear-max, Dnear-min and Dmean: Dnear-max is defined to be the dose to the 2% of the PTV (D2%), Dnear-min is the dose to the 98% of the PTV (D98%), and Dmean is the mean dose of the PTV; 2) V95% and V110%: percent volume receiving greater than 95% to 110% of prescribed dose; 3) Dose homogeneity index (HI) and conformity index (CI): HI and CI were calculated according to definition proposed by the International Commission on Radiation Units and Measurements (ICRU), lower HI and CI correlate with a more homogeneous target dose and better conformity, respectively. For evaluation of OAR, the following PTV statistics were used: contralateral lung (V5 and D_{mean}); left-sided heart lesion (V5, V10, V20, V30, D_{mean}); spinal cord (D_{max}); ipsilateral humeral head (D_{mean}); and esophagus ($D_{near\text{-}max}$ and D_{mean}).

Clinical study

To ensure accurate delivery of each plan, orthogonal megavoltage electronic portal images were captured once before the first treatment and per week thereafter, and compared with reference digitally reconstructed radiographs (DRRs) to verify patient position. Each patient was regularly followed up by the treating physician once a week during radiotherapy and after irradiation. Radiation pneumonitis (RP) was assessed within 6 months. If patients have symptoms such as fever (usually low grade) and cough after radiation therapy, CT scan was performed for pneumonitis diagnosis. A clear demarcation conforming to the irradiation port is needed to confirm the diagnosis.

Statistical analysis

T-test was used to compare the numerical difference of dosage between the 3D-CRT and IMRT groups. Chi-square test was used to examine the difference of incidence between

Table 3. Summary of DVH-based analysis of ipsilateral lung of patients with 3D-CRT or IMRT treatments

	3D-CRT	IMRT	*P* value
V5	52% ± 7%	65% ± 9%	0.001
V10	41% ± 7%	44% ± 4%	0.052
V20	32% ± 6%	29% ± 2%	< 0.001
V30	22% ± 5%	21% ± 2%	< 0.001

Data are shown as mean ± SD.

the two groups. A *P*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 169 breast cancer patients who completed PMRT at our institution were included for analysis. The IMRT group had 78 patients, and the 3D-CRT group had 91 patients. Patient characteristics in the two groups were shown in **Table 1**. All our patients are unilateral, and none of them are active smokers. There is no significant difference in the mean age and mean body mass index (BMI) of patients between IMRT and 3D-CRT groups (*P*-values are 0.902 and 0.165, respective, by T-test). Neo-adjuvant chemotherapy had been administered in 14/78 (17.9%) of the flaps in IMRT group, and in 7/91 (7.7%) of the flaps in 3D-CRT group. Adjuvant chemotherapy had been administered in 59/78 (75.6%) of the flaps in IMRT group, and in 83/91 (91.2%) of the flaps in 3D-CRT group. By Chi-square test, there is no significant different difference in number of patients administered neo-adjuvant chemotherapy or adjuvant-chemotherapy between IMRT and 3D-CRT groups.

Plan evaluation

According to the planning target volume of treatment (**Table 2**), there was no statistically significant difference for all the parameters between the IMRT and 3D-CRT groups. We compared the percentage volumes of ipsilateral lung receiving 5 Gy (V5), 10 Gy (V10), 20 Gy (V20), and 30 Gy (V30) in IMRT and 3D-CRT groups. As shown in **Table 3**, the V5 of ipsilateral lung was lower in the 3D-CRT group (52% ± 7%) than in the IMRT group (65% ± 9%), and their difference was statistically significant (P = 0.001). Difference of V10 was not significant between the two groups (41% ± 7% *vs.* 44% ± 4%, P = 0.052). However, the V20 was higher in the 3D-CRT group (32% ± 6%) than in the IMRT group (29% ± 2%), and there was a statistical significance (P = 0.001). Similarly, the V30 was higher in the 3D-CRT group (22% ± 5%) than in the IMRT group (21% ± 2%), and there was a statistical significance as well (P = 0.001).

Organ at risk (OAR) was also evaluated between IMRT and 3D-CRT plans. As shown in **Table 4**, the V5 of contralateral lung was significantly lower (P = 0.022) in the 3D-CRT group (14% ± 7%) than in the IMRT group (12% ± 4%). However, difference of Dmean (Gy) at contralateral lung were not significant between the two groups. The V5 and V10 of heart (left-sided lesions) were significantly lower (both P < 0.001) in the 3D-CRT group than in the IMRT group. Interestingly, at higher dosages, difference of V20 and V30 of heart OAR were insignificant between 3D-CRT and IMRT groups. For other organs such as spinal cord, ipsilateral humeral head, and esophagus, dosage difference between IMRT and 3D-CRT groups were insignificant.

Side effects

When patients finished the radiation therapy, radiation pneumonitis (RP) was diagnosed within 6 months after treatment. 21/91 (23.1%) patients in 3D CRT group were diagnosed with radiation pneumonitis (RP) with Grade ≥ 2. 5/78 (6.4%) patients in IMRT group were diagnosed with RP (Grade ≥ 2). Incidence of RP has no significant difference between the two groups (P = 0.223). Furthermore, there were 13/91 (14.3%) patients who developed moist desquamation in the 3D-CRT group, while there were 3/78 (3.8%) patients who developed moist desquamation in the IMRT group. Incidence of moist desquamation cases in the 3D-CRT group was significantly higher than in the IMRT group (P = 0.021). The median time of moist desquamation was 6 weeks after treatment, and mostly occurred within 1-2 weeks. The sites of moist desquamation frequently occurred in anterior axillary fold and in chest wall. Both groups had no severe radiation pneumonitis. No other severe acute toxicities were observed.

Discussion

With the development of economy and changing of life style, cancers have been a severe

Table 4. Summary of DVH-based analysis for organ at risk (OAR) evaluation of patients with 3D-CRT or IMRT treatments

Organ	Parameters	3D-CRT	IMRT	*P* value
Contralateral lung	V5	12% ± 4%	14% ± 7%	0.022
	Dmean (Gy)	2.19 ± 1.03	2.25 ± 1.43	0.752
Heart (left-sided lesions)	V5	45% ± 16%	56% ± 14%	< 0.001
	V10	26% ± 9%	31% ± 8%	< 0.001
	V20	15% ± 7%	14% ± 6%	0.325
	V30	6% ± 5%	7% ± 3%	0.125
	Dmean (Gy)	9.32 ± 1.14	8.71 ± 1.51	0.003
Spinal cord	Dmax (Gy)	36.10 ± 4.93	37.25 ± 6.43	0.191
Ipsilateral humeral head	Dmean (Gy)	23.98 ± 6.26	25.15 ± 5.70	0.209
Esophagus	Dnear-max (Gy)	40.29 ± 9.16	42.17 ± 7.54	0.151
	Dmean (Gy)	10.14 ± 2.19	10.27 ± 1.52	0.660

Data are shown as mean ± SD.

burden of society in China [14]. The improvement of overall survival remains the ultimate goal for anti-cancer treatment, an adjuvant and primary radiation aims to improve overall survival by treating tumor and area at risk with local regional therapy. In BC treatment, PMRT could reduce the risk of local-regional failure (LRF), with its potential physical and psychologic morbidity, as well as a reduction in the risks of distant relapse and death [15]. In addition, PMRT for local advanced and lymph node positive breast cancer has been studied in large randomized trials [6, 16], these research indicated that PMRT definitely improve local regional control and overall survival [17].

The conventional PMRT treatment generally includes two opposed tangential photon beams for chest wall, and separate anterior fields for regional nodes with mixed photon-electron beams. This treatment has several disadvantages. First, the tissue between the chest wall and supraclavicular region +/- IMN may be under or overdosed. Because of the junction or overlap between the tangents and anterior fields, conventional PMRT potentially increases normal tissues toxicities or reduces tumor control probability. Although there were several studies reported to address the junction issue between chest wall and supraclavicular region [18, 19], it's difficult to eliminate the overlap between chest wall and IMN with geometric matching method. Second, the use of mixed beams for regional nodes may be associated with inhomogeneous dose distribution. In addition, the maximum depth of supra/infraclavicular region varied with patients' anatomy [20] and body mass index (BMI) [21] routine use of mean depth did not optimally cover intended targets for every patient, and might also result in overdose to some normal tissues in a portion of patients.

There is little doubt that PMRT substantially reduces the risk of LRF. Wu *et al* indicated that PMRT can improve survival in breast cancer patients aged 35 years or younger with four or more positive nodes [22]. A retrospective analysis performed by Orecchia *et al* demonstrated that post-mastectomy radiotherapy reduces recurrence and mortality of breast cancer [23]. Although chest wall and regional nodes delineation techniques have been discussed with available contouring guidelines [9-11], computed tomography (CT)-based planning to treat chest wall and nodal regions as a whole PTV has not yet been adopted into routine practice. It was reported that radiation of SC fields using prescriptions of radiation dose to empiric depths often leads to suboptimal coverage of targeted volumes, unnecessary degrees of dose in homogeneity, or both [21]. Optimized CT-based treatment plan generates appropriate target coverage and dose homogeneity. However, the biggest concern of IMRT treatment is the dose-volume of ipsilateral lung. We conducted a population-based study comparing the dose-volume of ipsilateral lung and acute lung injury in patients undergoing PMRT using a linac IMRT technique versus conventional technique. We found that the V5 of ipsilateral lung was lower in the 3D-CRT group than in the IMRT group. However, the V20 and V30 were significantly higher in the 3D-CRT group than in the IMRT group (P < 0.001). These findings demonstrated that IMRT reduce the high dose of the ipsilateral lung, only increasing the V5.

Radiation pneumonitis (RP) is the most common side effect following PMRT. In contrast to 3D-CRT plan, distinct dosimetric parameters should be considered in IMRT planning. In our study, the incidence of ≥ 2 Grade RP is 15.9% in patients receiving PMRT. The incidence of RP varies widely among reports because of differences in radiation techniques, evaluation of symptoms, and method of reporting. For patients treated with 3D-CRT, the volume of lung receiving 20 Gy has consistently been found to predict the risk of symptomatic RP. The frequency of symptomatic RP was reportedly 1-7% after local and regional nodes were treated to a total dose of 45-50 Gy with conventional techniques [24-26]. In the current study, number of RP cases had no statistical significance between 3D-CRT and IMRT group. For other side reactions and OAR evaluations, we observed that in V5 and V10, IMRT induced significantly higher percentage volumes of contralateral lung and heart compared to 3D-CRT, indicating IMRT technique may cause more heart lesions at low dosage range.

Our study demonstrated that IMRT reduce the high dose of the ipsilateral lung. There is no statistical difference in the incidence of radiation pneumonitis after treatment. This study demonstrates that both 3-DCRT and IMRT techniques are feasible for PMRT.

Disclosure of conflict of interest

None.

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