Correlation between intensity modulated radiotherapy and bone marrow suppression in breast cancer

Q. WANG[1], T. YE[1], H.-L. CHEN[1], X.-G. ZHANG[1], L.-Z. ZHANG[2]

[1]Department of Radiotherapy, Xuzhou Cancer Hospital, Xuzhou, Jiangsu, China
[2]Department of Radiotherapy, Affiliated Hospital of Xuzhou Medical College, Xuzhou, Jiangsu, China

Abstract. – OBJECTIVE: To study the correlation factors of bone marrow suppression in breast cancer radiotherapy and find out the method to guide the target area, dose limitation for breast cancer to reduce the risk of bone marrow suppression.

PATIENTS AND METHODS: 72 cases of breast cancer patients were collected through retrospective, clinical control study. For patients with Grade 0-3, bone marrow suppression in the course of radiotherapy, the dose-volume parameters (V5, V10, V20, V30, V50, D20, D40, D60, D80, D100, Min, Max, Dmean) of the chest and rib of each patient were collected and analyzed from multiple points including tumor stage, age, lesion location, surgical approach, chemotherapy regimen and the number of cycles, bone dose-volume parameters.

RESULTS: The relative parameters of the rib in the middle and severe bone marrow suppression group were significantly higher than those in the mild bone marrow depression group and the p values of V5, V10, V20, V30, Dmean, D40, D60, D80, D100 were less than 0.05. The difference of V50 in the two groups was statistically significant (p <0.05). For chemotherapy regimens containing doxorubicin, epirubicin, cyclophosphamide, the differences between bone marrow suppression group and non-bone marrow suppression were statistically significant (p =0.002).

CONCLUSIONS: The dose-volume parameters of the rib radiation is one of the main factors causing the suppression of bone marrow in radiotherapy, and the volume of the 50Gy irradiation is also a contribution to the bone marrow. For patients accepted chemotherapy with doxorubicin, epirubicin, cyclophosphamide before radiotherapy, bone marrow suppression is more likely to occur during radiotherapy. After radical mastectomy or the volume of thoracic rib is increased because of the small breast, the occurrence of bone marrow suppression is increased. The effects of radiation on the bone marrow suppression were small, while its effect on the ribs was more evident, especially on the ribs V20 and Dmean and the difference was statically significant.

Key words:
Breast cancer, Intensity modulated radiation therapy, Bone marrow suppression.

Introduction

Breast cancer has become the highest occurrence rate among all women's cancers, according to the latest report from the 2012 cancer registry. The world has about 1,400,000 new breast cancer patients and 450,000 deaths every year, which is a serious threat to women's physical and mental health[1]. In China, the incidence of breast cancer is increasing rapidly by 3% every year. Also the incidence age of breast cancer is 10-15 years younger than those of the western country. The standard treatment for breast cancer is surgery, chemotherapy, radiotherapy and endocrine therapy. The survival rate is high, and the 10-year survival rate of the patients has reached more than 80%. Postoperative radiotherapy can effectively prevent recurrence and prolong the survival time of patients[2]. But during the period of chemotherapy, the occurrence of bone marrow suppression is higher. Flat bone is the main hematopoietic site for adult. For patients with breast cancer, part of the ribs and sternum are in the irradiation area and the irradiation dose-volume parameter in radiotherapy is one of the main factors leading to bone marrow suppression. Combined with multiperiod chemotherapy before radiotherapy, bone marrow proliferation activity is significantly lower. The radiotherapy undoubtedly makes it more critical. It affects the treatment process because of severe bone marrow proliferation inhibition, thereby affecting the overall efficacy. So, it is very important to analyze and search for the related factors of bone marrow suppression in breast cancer patients to reduce the prevalence of bone

Corresponding Author: Qiang Wang, MD; e-mail: jsxzzlz@126.com

marrow suppression and to improve the quality of life, which has important clinical application value and prospect. There are very few reports available on the correlation. In this study, we compared pros and cons for breast cancer postoperative modulated radiotherapy and conformal radiotherapy, with the expectations that it can provide a reference for treatment after radiotherapy for breast cancer patients.

Patients and Methods

Patients

72 patients with breast cancer treated in our hospital were selected for research. All patients were diagnosed with breast cancer by pathological examination. All patients were female, aged between 29-68 years old, average (49.7±8.9) years old, 47 cases of left side and 25 cases of right side. 23 cases were treated with breast conserving surgery, and 49 cases were treated with radical mastectomy. All patients underwent postoperative chemotherapy. The blood test was normal before radiotherapy. There was no significant difference in the general data of patients (p <0.05), which was comparable. All patients received intensity modulated radiation therapy.

Methods

CT scan: The patients were positioned according to CT simulator guide. Patients were laid down in supine positioning in bed with hands placing in the superior frontal. A fine wire was used to mark breast contour as a reference and breast bracket omentum was used to fix the affected side breast, center marked with plumbum points. CT simulation scan was conducted under quiet breathing state with thickness of 5 mm. The scanning ranged from the cricothyroid membrane margin to the first lumbar vertebra, which includes full of contralateral breast and all nearby organs such as liver, lung, heart and other. After scanning, the images of the body surface were marked and images were transmitted to the Varian treatment planning system.

Delineation of target area: The area of the clavicle and chest wall was selected as the target area. The Inner, outer, upper and lower boundaries of chest wall were parastern, axillary midline, lower margin of clavicular head and 2 cm lower than breast (wire circle mark for reference). Clinical target volume (CTV) will include the whole breast, chest wall or clavicle according to the condition of the disease. Plan target volume (PTV) will be 5 mm outer than CTV three-dimensionally. It was narrowed down to 3 mm under the skin in the external to protect the skin. While outlining the whole lung, contralateral breast, chest and rib was included as a study parameter to compare after the completion of the plan. It was made sure that endangering of vital organ should be limited. The treatment plan was 95%PTV50Gy/2Gy/25F.

Treatment: All patients were treated with 6MV X-ray intensity modulated radiotherapy. 4 fields were treated with radiotherapy. Setting the dose limiting conditions for normal organs and planning targets, the dose of the radiation in the planned target area should not exceed 105% of the prescription dose and the dose of the ipsilateral lung is lower than that of the prescription dose. The dose of the heart is less than 30Gy. A total of radiation dose was 50Gy, 1 times a week, sustaining for 5 weeks, 25 times in total. The blood was tested every week, recording the related parameters.

Efficacy evaluation: Patient's age, the location of the disease, T staging, M staging and N staging of tumour, chemotherapy regimen and chemotherapy cycles were recorded. PTV, the parameters of the contralateral breast, the whole lung, the chest and the affected side four organs were recorded in the DVH, including V5, V10, V20, V30, V40, Min, Max, D mean, D20, D40, D60, D80, D100. The blood toxicity reactions were observed regularly on routine basis. The grading standards were according to radiation therapy oncology group (RTOG) acute radiation injury grade.

Grade 0: white blood cells $\geq 4.0 \times 10^9$/L. Level 1: white blood cell is greater than or equal to 3.0×10^9/L-4.0×10^9/L; Grade 2: white blood cell $\geq 3.0 \times 10^9$/L -4.0×10^9/L. Level 3: white blood cell $\geq 1.0 \times 10^9$/L-2.0×10^9/L. Level 4: white blood cell $< 1.0 \times 10^9$/L. We defined the level of hematologic toxicity in patients with 1-4 levels as a bone marrow depression group and 0 levels of hematologic toxicity as a non-bone marrow depression group so as to analyze the relevant factors of the bone marrow suppression. At the same time, we defined the patients with 0-1 level of hematological toxicity as mild bone marrow depression group. The patients with grade 2-4 were defined as moderate and severe bone marrow suppression group.

Statistical Analysis

Data was analyzed with SPSS18.0 (SPSS Inc., Chicago, IL, USA). Measurement and count data were compared with the *t*-test and X^2 test. The *p* values less than 0.05 means was considered as statistically significant.

Results

Comparison of clinical data from two different groups of patients

The blood routine test was checked and recorded weekly during radiotherapy. Firstly, we defined white blood cells $4.0x10^9$/L as the standard to divide bone marrow depression group and non-bone marrow suppression group to analyze the relevant parameters. Patients with white blood cells $3\text{-}4.0x10^9$/L were for level I of bone marrow suppression. The clinical treatment is generally not required special treatment and tolerate radiotherapy can also be accepted. Patients with white blood cells $<3.0x10^9$/L were defined as Level II, III of bone marrow suppression often which needed to deal with, otherwise it can affect the treatment and be even life-threatening. The white blood cells count $3.0x10^9$/L was taken as standard for grouping patients with mild bone marrow suppression group and moderate to severe bone marrow suppression group to analyze the relevant parameters (Table I).

Further, patients were divided into two groups according to whether WBC $>4.0x10^9$/L or not.

Table I. Clinical data of the two groups of patients (unit: person).

	WBC 4.0 X10⁹/L		WBC 3.0 X 10⁹/L	
	Non bone marrow suppression group (Level 0)	Bone marrow suppression group (Level 1-4)	Mild bone marrow suppression group (Level 0-1)	Moderate to Severe bone marrow suppression group (Level 2-4)
Patients	21	51	52	20
Age	51.52±7.3	49.04±9.5	48.8±7.38.6	52.0±9.6
Tumor position				
Left side	12 (64.8%)	34 (68%)	33 (63.5%)	13 (68.4%)
Right side	9 (35.2%)	16 (32%)	19 (36.5%)	6 (31.6%)
Operation mode				
Radical operation	14 (66.7%)	35 (68.6%)	35 (67.3%)	14 (70%)
conserving surgery	7 (33.3%)	16 (31.4%)	17 (32.7%)	6 (30%)
Clinical stage				
T1	7 (33.3%)	19 (37.3%)	20 (38.5%)	6 (30%)
T2	12 (57.1%)	28 (54.9%)	29 (55.8%)	11 (55%)
T3	2 (9.5%)	4 (7.8%)	3 (5.8%)	3 (15%)
T4	0	0	0	0
N0	1 (4.8%)	9 (17.6%)	4 (7.7%)	6 (30%)
N1	8 (38.1%)	15 (29.4%)	20 (38.5%)	3 (15%)
N2	5 (23.8%)	16 (21.4%)	16 (30.8%)	5 (25%)
N3	7 (33.3%)	11 (21.6%)	12 (23.1%)	6 (30%)
M0	21 (100%)	51 (100%)	52 (100%)	20 (100%)
M1	0	0	0	0
Chemotherapy regimen	13 (61.9%)	17 (33.3%)	27 (51.9%)	3 (15%)
A (doxorubicin)	10 (47.6%)	40 (78.4%)	35 (67.3%)	15 (75%)
C (cyclophosphamide)	4 (23.8%)	27 (52.9%)	18 (34.6%)	13 (65%)
E (epirubicin)	13 (61.9%)	32 (62.7%)	30 (57.7%)	15 (755)
T (paclitaxel class)				
Chemotherapy cycle	15 (81%)	35 (71.4%)	38 (77.6%)	12 (65%)
≤6 cycle	4 (19%)	14 (28.6%)	11 (22.4%)	7 (35%)
>6 cycle	863.1±307.9	619.3±303.4	799.7±298.9	473.1±234.3
Breast irradiation volume	133.1±23.1	124.2±33.8	123.6±36.1	129.9±24.3
Volume of the rib	52.5±4.2	46.9±8.5	47.9±7.1	48.5±9.6
Volume of the sternum	185.8±26.1	170.3±20.5	124.8±25.9	174.3±17.1
Volume of the sternum and rib				

Table II. Comparison of parameters of affected side of rib in the bone marrow suppression group and the non-bone marrow suppression group (WBC 4.0 X10^9/L group).

DVH parameter of affected side ribs	Bone marrow suppression group (n=51)	Non-bone marrow suppression group (n=21)	*t*-value	*p*-value
V5	54.4±9.9	51.8±6.6	-1.09	0.279
V10	50.9±6.1	40.9±5.4	-0.749	0.457
V20	34.6±7.6	33.5±5.2	-0.601	0.550
V30	30.0±4.6	30.4±5.3	-0.327	0.744
V40	26.8±4.2	26.6±4.1	0.207	0.836
V50	17.8±4.8	18±5.1	-0.097	0.923
Min[1]	44.8±9.2	28.7±13.1	-0.78	0.435
Max[2]	5660±280	5771±443	1.279	0.205
Dmean[3]	1847±272	1811±224	-0.529	0.598
D20	4801±409	4755±677	-0.353	0.725
D40	1292±684	1194±536	-0.582	0.562
D60	392±365	328±147	-0.779	0.439
D80	153±243	110±36	-0.795	0.429
D100	46±11	23±13	-0.910	0.366

[1]Min was for tissue volume receiving the minimum dose.
[2]Max was for tissue volume receiving the maximum dose.
[3]D mean was for the tissue volume accepting the mean dose.

The patients with WBC > 4.0x10^9/L were defined as non-bone marrow suppression group and the patients with WBC <4.0x10^9/L were divided into bone marrow suppression group (Table I).

Comparison of parameters for affected side of rib in the bone marrow suppression group and the non-bone marrow suppression group

Parameters like V5, V10, V20, V30, V40, Min, Max, Dmean, D10, D20, D40, D60, D80, D100, DVH, etc. of ribs were collected from the DVH and compared. Table II shows that the related parameters of the bone marrow depression group were significantly higher than those of the non-bone marrow suppression group, but data was not statically significant with p >0.05.

V5, V10, V20, V30, V40 were for the tissue volume accepting ≥5Gy, 10GY, 20GY and 30Gy, 40gy. D10, D20, D40, D60, D80, and D100 were for the radiation dose accepted by 10, 20, 40, 60, 80, and 100% of the tissue volume.

Comparison of DVH parameters of the sternum in the bone marrow suppression group and the non-bone marrow suppression group

Table III shows the relative parameters of the bone marrow depression group were significantly less than those of the non-bone marrow depression group. In addition, the p value for V5, V10, V20, V30, Min, Dmean, D40, D60, D80, D100 were all less than 0.05, showing significant difference.

The patients were divided into a group of bone marrow suppression and non-bone marrow suppression based on whether WBC > 4.0x10^9/L or not. And we divided them into mild bone marrow suppression group and moderate and severe bone marrow suppression group according to WBC >3.0x10^9/L or not (Table I). Parameters like V5, V10, V20, V30, V40, Min, Ma, Dmean, D10, D20, D40, D60, D80, D100, DVH, etc. of ribs and sternum were collected from the DVH and compared (Table IV). We can conclude from table IV that the relative parameters of the middle and severe bone marrow depression group were significantly higher than those of mild bone marrow suppression group, with p value of V5, V10, V20, V30, Dmean, D40, D60, D80 and D100 less than 0.05.

Comparison of the parameters of the sternum in the bone marrow depression and non-bone marrow suppression

Table V shows that the relative parameters of the middle and severe bone marrow depression group were significantly higher than those of the mild bone marrow depression group. The p value of V50 was less than 0.05, and difference was statistically significant.

Table III. Comparison of parameters of the sternum in the bone marrow suppression group and the non-bone marrow suppression group (WBC 4.0 X10^9/L group).

DVH parameter of sternum	Bone marrow suppression group (n=51)	Non-bone marrow suppression group (n=21)	*t*-value	*p*-value
V5	93.5±9.0	98.7±2.0	2.607	0.011
V10	66.4±25	84.5±17.5	3.015	0.004
V20	41.5±27.8	58.7±30	2.324	0.023
V30	24.2±20.2	36.7±26.1	2.183	0.032
V40	10.4±12	15.3±12.6	1.551	0.125
V50	2.68±6.2	2.19±2.4	-0.351	0.727
Min	319.1±218	553.9±335	3.221	0.002
Max	5132±588	5299±602	1.090	0.279
Dmean	1954±830	2501±805	2.562	0.013
D20	2851±1160	3367±973	1.793	0.077
D40	2070±1005	2654±968	2.265	0.027
D60	1544±862	2138±912	2.612	0.011
D80	1072±688	1606±788	2.866	0.005
D100	334.2±215.7	535.1±339.1	3.013	0.004

Discussion

Breast cancer is the most common malignant tumour in female. The incidence rate of breast cancer is increasing rapidly by 3% every year in China. The main treatment method for breast cancer patients is postoperative radiotherapy and chemotherapy. The postoperative radiotherapy according to different subtypes and different stages of breast cancer can reduce the local recurrence rate of breast cancer by 23%-26% to 6%-7% and improves the overall survival rate. Because chest wall recurrence accounted for 44%-69% of all local recurrence after radical mastectomy or breast conserving surgery, most breast cancer patients need local radiotherapy[3,4]. During clinical radiotherapy, patients with bone marrow suppression occurrence has high rate. It is reported that only proximal epiphysis of spine bone, ilium, ribs, sternum, skull and long one are marrow hematopoietic at the age of 18 or so and OS planum is the main hematopoietic site in adult[5]. The ribs and sternum is irradiated inevitably during chest radiation. In the treatment of breast cancer, the chest wall and the supraclavicular region are normal irradiation area. Sternum and ribs are flat bones and participate in hematopoiesis. Sternum and ribs are flat bones and participate in hematopoiesis. The dose-volume parameter in radiotherapy is one of the main factors leading to bone marrow suppression. At present, it is believed that breast cancer is a systemic disease, and chemotherapy plays an important role in the treatment. Hematological toxicity is the most common toxic and adverse reaction in chemotherapy and it is also the major dose limiting toxicity, which may also produce images of bone marrow proliferation induced by the subsequent radiotherapy[6,7]. We divided patients into bone marrow suppression group and non-bone marrow suppression group regarding 4.0x10^9/L as the standard and analyzed the relevant parameters (Table I). There was no significant difference of the T staging, N staging and surgical treatment between bone marrow depression group and non-bone marrow suppression group. The main program of chemotherapy was CE-T, CEF-T, CAF, TP, AC-T, T (D) EC, etc. were compared with one of the four major chemotherapeutic agents to investigate which chemotherapy drugs were used in the early stage of radiotherapy had clear bone marrow inhibition effect. The four groups were those containing A (ADM), C (cyclophosphamide), E (epirubicin), T (taxol) and control (without treatment). The differences of doxorubicin, cyclophosphamide, epirubicin application in bone marrow suppression group and non-bone marrow suppression between group were statically significant (Table I). No significant differences were shown in the application of paclitaxel class between the two groups. So avoiding the use of doxorubicin, epirubicin and cyclophosphamide during chemotherapy may decrease occurrence probability of bone marrow suppression after local radiation. In addition the comparison of cycles number of chemotherapy group shows no statistically significance (Table I).

Table IV. Comparison of the parameters of the sternum in the bone marrow depression and non-bone-marrow suppression (WBC 3.0 X 109/L group).

DVH parameter of affected side ribs	Mild bone marrow suppression (n=51)	Moderate and severe bone marrow group (n=21)	*t*-value	*p*-value
V5	52.0±6.9	58.1±12.4	-2.634	0.001
V10	40.2±5.3	68.4±9.6	-2.134	0.036
V20	32.8±5.2	38.1±9.5	-3.032	0.003
V30	29.4±4.6	32.6±5.7	-2.477	0.016
V40	26.2±4.1	27.8±3.9	-1.428	0.158
V50	17.6±4.2	18.5±6.4	-0.693	0.491
Min	28.8±13.7	69.5±14.6	-2.007	0.049
Max	5710±353	5647±294	0.709	0.48
Dmean	1782±218	1980±303	-3.08	0.003
D20	4752±548	4880±323	-0.977	0.332
D40	1151±572	1556±732	-2.478	0.016
D60	321.4±146	510.8±540	-2.336	0.022
D80	104.8±33.8	235.4±378	-2.491	0.015
D100	23.5±15	81.2±173	-2.40	0.019

The comparison of PTV of two groups setting WBC 4.0x10^9/L as the standard showed that it is significantly smaller in the bone marrow suppression group than that of the non-bone marrow suppression group. However, the comparison of mild bone marrow depression group and moderate to severe bone marrow suppression group shows significant difference. The small target area is more likely to suppress, which is associated with a greater volume of sternum or rib irradiation because of a radical mastectomy or small breast. During the comparison of the relative parameters of the rib, V5, V10, V20, V30, V40, V50, Min, Max, Dmean, D20, D40, D60, D80, D100 of the rib in the bone marrow suppression group was significantly higher than those of the non-bone marrow suppression group (p >0.05). During the comparison of the relative parameters of sternum, V5, V10, V20, V30, Min, Dmean, D40, D60, D80, D100 of the sternum in the bone marrow suppression group was smaller than those of the non-bone marrow suppression group (p <0.05) (Table II).

The small bone was accompanied with mild marrow suppression, which in turn shows that the bone marrow suppression caused by radiotherapy is small. The main reason may be related to the rib. We then compared the two groups of patients standardized with 3.0x10^9/L, and all the parameters of

Table V. Comparison of the parameters of the sternum in the bone marrow depression and non-bone-marrow suppression (WBC 3.0 X 10^9/L group).

DVH parameter of affected side ribs	Mild bone marrow suppression (n=51)	Moderate and severe bone marrow group (n=21)	*t*-value	*p*-value
V5	95.9±6.5	92.8±10.6	1.494	0.140
V10	72.6±23.9	69.4±26.1	0.489	0.626
V20	45.9±29.8	48.0±28.8	-0.268	0.790
V30	26.5±22.7	31.4±22.7	-0.822	0.414
V40	10.4±10.5	15.5±15.9	-1.588	0.117
V50	1.61±2.42	4.96±9.2	-2.442	0.017
Min	408.7±281.1	311.7±245.4	1.356	0.179
Max	5140±639	5285±448	-0.929	0.356
Dmean	2100±807	2150±989	-0.220	0.826
D20	2907±1078	3247±1241	-1.147	0.255
D40	2201±972	2342±1167	-0.520	0.605
D60	1723±872	1705±1033	0.074	0.942
D80	1249±714	1173±867	0.379	0.706
D100	415±280	333±242	1.114	0.257

the sternum of the patients in the bone marrow group were more than those in the mild inhibition group and difference was statistically significant (Tables III, IV, V). It shows that the large dose irradiation of sternum may affect bone marrow hematopoiesis. As for the parameters of the ribs, the parameters in the moderate and severe groups were significantly higher than those in the mild inhibition group, and *p* values of rib V5, V10, V20, V30, Min, Dmean, D40, D60, D100 were lower than 0.05. It shows that the large dose irradiation of ribs may affect bone marrow hematopoiesis.

Conclusions

The dose-volume parameter of the rib is one of the main factors that lead to the suppression of bone marrow suppression. The sternum volume exposure to 50Gy was also contributed to the bone marrow suppression. Chemotherapy with doxorubicin, epirubicin, cyclophosphamide before radiotherapy in patients was prone to induce bone marrow suppression. The large breast that is projected forward will reduce the exposure of the sternum and ribs. While after radical mastectomy, or small breast volume will increase the exposure volume of thoracic rib, and the occurrence of bone marrow suppression will increase. The exposure volume of sternum in the bone marrow depression group was significantly less than that of the non-one-marrow depression group, indicating that the sternum exposure has little effect on the bone marrow suppression. While the role of ribs in the middle and severe bone marrow suppression group is more obvious regarding WBC 3.0 X 10^9/L group, especially the ribs V20 and Dmean. This can be applied to our future clinical work in the treatment of breast cancer after radiotherapy to protect the rib as far as possible and control V20, and Dmean parameters so as to reduce the occurrence of bone marrow suppression and improve patient quality of life, reduce medical consumption.

Conflict of Interest:

The Authors declare that they have no conflict of interests.

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