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Analysis of radiotherapy optimization regimens after modified radical mastectomy

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Abstract. – OBJECTIVE: Concomitant chemo-radiotherapy after modified radical mastectomy for breast cancer is an effective means of achieving high survival rates. In this study different radiotherapy optimization regimens are compared to assess their effectiveness and toxicity rates.

PATIENTS AND METHODS: 112 patients with modified radical mastectomy participated, and were randomly assigned to one of three groups, all receiving adjuvant chemotherapy for 4-6 weeks prior to radiotherapy: group A received intensity modulated radiotherapy (radiation dose (DT) 50 Gy, 2.0 Gy/fraction, 25 times, during the course of 33-35 days); group B received concurrent radio chemotherapy and intensity modulated radiotherapy; and group C adopted concurrent radio chemotherapy and hypofractionation (DT of 42.56 Gy, 2.66Gy/fraction, 16 times, during the course of 22-24 days) with 37 cases. The occurrence of acute and chronic radiation injuries, the cancer recurrence and the survival rates were compared, and a dose volume histogram (DVH) was created.

RESULTS: The total prevalence and survival rates of Group C were significantly better than those of the other two groups ($p \leq 0.05$); in spite of the fact that the local recurrence and distant metastasis rates separately were all statistically the same ($p \geq 0.05$). Also, the total radiation injury occurrence of group C was significantly lower ($p < 0.05$); but no significant differences were found when singling out acute and chronic injury occurrences or injury severity between the three groups. The values of V5, V10, V20 and V30 increased gradually in all of the groups, and V5 and V10 in Group C were higher than those in the other two groups, but the comparison between V20 and V30 yielded no statistically significant differences.

CONCLUSIONS: Based on these results, the concurrence of hypo-fractionation radiotherapy and chemotherapy may be an effective and safe approach for cancer treatment after modified radical mastectomy, and larger studies are warranted given the convenience of the method.

Key Words:
Modified radical mastectomy, Intensity modulated radiation therapy, Hypofractionation, Recurrence rate, Survival rate, Acute and chronic radiation injury, Dose volume histogram, V5.

Introduction

Modified radical mastectomy assisted with chemo-radiotherapy is of great importance for the control of local recurrence and distant metastases, so as to improve the quality of life and the survival rates[1]. The radiotherapy is usually carried out after chemotherapy for 4 to 6 weeks, but a recent research has found that concurrent radiochemotherapy does not increase the prevalence of systemic complications[2] as previously thought. With the application of accurate intensity modulated radiation, the therapeutic effect is improved significantly, and the toxicity reduced[3]. Parameters such as V20 and V30 from the dose-volume histogram (DVH) can be used to guide the radiotherapy regimen, personalizing it[4]. A study found that the occurrence of radioactive lung injury may be more closely associated with smaller lung regions getting higher radiation doses, especially the V5 to V13[5]. At the same time, a study of cyto-dynamics showed breast cancer has a potential doubling time above average, which is an indication that the cancer is suitable for hypofractionation radiotherapy[6]. At present, hypofractionation radiotherapy is mainly applied to postoperative early breast conserving surgery[7]. However, in this study, the evidence of the benefit of a radiotherapy optimization scheme to be used also after modified radical mastectomy is provided.

Patients and Methods

Patients

112 patients admitted to our hospital from January 2012 to January 2015, and who received

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modified radical mastectomy for breast cancer were enrolled. The inclusion criteria comprised those patients suited for neoadjuvant chemo-radiation, biological treatment, and endocrine therapy; who had a Karnofsky performance score ≥ 70, and who had indications for postoperative radiotherapy without contraindications. The exclusion criteria included patients with lung function decline, intolerance to postoperative chemoradiotherapy, radiotherapy interruption, chest wall residue, supraclavicular lymph node and distant metastases, poor adherence to treatment guidelines, or incomplete follow-up data.

The Ethics Committee of our hospital approved the study and the informed consents from patients and family members were obtained. According to the hospitalization order, the patients were divided into three groups by random number table assignment. Group A, with 40 patients, received intensity modulated radiation therapy (2.0 Gy/f, 25 times, DT50Gy 33-35 days) after chemotherapy for 4-6 weeks. Group B, with 35 patients, received concurrent radio chemotherapy and intensity modulated radiation therapy. And group C, with 37 cases, received concurrent radio chemotherapy and hypofractionation (2.66 Gy/f 16 times, DT42.56 Gy, 22-24 days). The average age of Group A was 52.6 ± 12.5 years, according to the AJCC TNM staging 7 cases were in Stage I, 16 cases in Stage II, 14 cases in Stage III, and 3 patients had ipsilateral axillary lymph node metastasis. The average age of Group B members was 53.3 ± 14.1 years, with 4 cases in Stage I, 13 cases in Stage II, 18 cases in Stage III and 3 had ipsilateral axillary lymph node metastasis. The average age of Group C members was 52.9±15.3 years, with 5 cases in Stage I, 18 cases in Stage II, 14 cases in Stage III and 4 cases had ipsilateral axillary lymph node metastasis. The age, tumor staging and axillary lymph node metastasis of these three groups were comparable with differences without any statistical significance ($p > 0.05$).

Chemo-radiotherapy Regimen

All patients received Cytoxan, Adriamycin, and 5-fluorouracil (CAF), Cytoxan, methotrexate, and 5-fluorouracil (CMF), Paclitaxel and Docetaxel (PD) or Paclitaxel and Adriamycin (PA) chemotherapy regimens for 4 to 6 weeks. Additionally, the patients with positive estrogen (ER) or progesterone (PR) receptors took 20 mg/d of tamoxifen orally, or adopted a hormonal therapy with sequential oral aromatase inhibitors. Radiotherapy was provided with Elekta Precise linear accelerator 6MV-X by the same radiotherapy and nursing team.

Preparation before radiotherapy: the patients were kept in a supine position and fastened on the special breast bracket; the fixed parameters were adjusted appropriately to parallel thorax with the bed surface. Ipsilateral upper extremities were raised to reduce the irradiated lung volume, with anatomic marks and coordinate parameters completed by fixed positioning technology and successive scanning application of 16-layer Spiral CT (layer thickness of 5 mm under normal respiration), ranging from the whole neck to lower edge of liver. Before scanning, the lower edge of the rib, the center line of body, a 2 cm position of inframammary fold of unaffected side, the center line of the armpit, the surgical cicatrix, and the entrance of drainage were all marked by an artifact-free lead wire, then the imaging information was transferred to Elekta Precise treatment planning system through the local area network.

Radiotherapy regimen: the target volume delineation was strictly based on the guidelines of the Radiation Therapy Oncology Group (RTOG) target volume delineation after modified radical mastectomy, including the chest wall, clavicle lymph node area and ipsilateral axillary lymph node area, with irradiation excluding the internal mammary nodes. The surface of the chest wall was raised to 20~30 Gy by a 0.5cm-thickness equivalent layer during the process of irradiation, and the final dose reached the preset value.

Index Observation

The follow-up period until January of 2016 lasted a median time of 36.0 months, and the local recurrence and distant metastatic rates, the overall survival rate, and the acute and chronic radiation injury occurrence rates were compared, to obtain the parameters of V5, V10, V20 and V30 from the dose-volume histogram (DVH). Local recurrence was defined as ipsilateral chest wall recurrence or ipsilateral supraclavicular, axillary and internal mammary lymph node recurrence. Acute and chronic radiation injury referred to the RTOG graded standard: level 0 for no reaction, level I for slight reaction, level II for moderate and tolerable reaction, and level IV for serious complications. Acute injury covered bone marrow suppression, skin ulcers, gastrointestinal symptoms and so on, and chronic injury included radiation-induced pulmonary injury, brachial plexus injury, myocardial ischemia, etc. The definition of V5 is the percentage of the total lung volume that received an exposure dose of 5 Gy.

Table I. Comparisons of cancer recurrence and survival rates [cases (%)].

Groups	Cases	Local recurrence	Distant metastasis	Overall recurrence rate	Overall survival rate
Group A	40	12 (30.0)	5 (12.5)	17 (42.5)	26 (65.0)
Group B	35	7 (20.0)	3 (8.6)	10 (28.6)	27 (77.1)
Group C	37	4 (10.8)	2 (5.4)	6 (16.2)	33 (89.2)
χ^2		4.346	1.219	6.409	6.313
p		0.114	0.544	**0.041**	**0.043**

Note: Group A received intensity modulated radiation therapy after chemotherapy for 4-6 weeks; Group B received concurrent radio-chemotherapy and intensity modulated radiation therapy; and Group C had concurrent radio-chemotherapy and hypo fractionation.

Table II. Comparison of acute and chronic injury prevalences.

Groups	Cases	0-I	II	III-IV	Acute injury	Chronic injury	Total incidence
Group A	40	2 (5.0)	8 (20.0)	10 (25.0)	7 (17.5)	13 (32.5)	20 (50.0)
Group B	35	3 (8.6)	7 (20.0)	5 (14.3)	6 (17.1)	9 (25.7)	15 (42.9)
Group C	37	3 (8.1)	3 (8.1)	2 (5.4)	3 (8.1)	5 (13.5)	8 (21.6)
χ^2		3.448			1.724	3.859	6.973
p		0.486			0.422	0.145	**0.031**

Statistical Analysis

The SPSS19.0 software was used for statistical analysis. Briefly, the quantitative data were represented by average± standard deviation and the comparison among groups was analyzed by single factor ANOVA. The qualitative data was represented by case number or (%), and the comparison among groups was done using the χ^2-test. Ranked data were analyzed adopting the method of rank sum test. A $p < 0.05$ meant a found difference was statistically significant.

Results

Local Recurrence, Distant Metastatic Rate, Overall Recurrence, and Overall Survival Rate

The overall recurrence and survival rates of Group C were clearly better than those of the other two groups, and the differences were statistically significant ($p < 0.05$). On the other hand, the local recurrence and distant metastasis rates of these three groups were not significantly different ($p > 0.05$) (Table I).

Acute and Chronic Injury Prevalence Rate

The total radiation injury prevalence rate of group C was lower than that of other two groups, and the difference was statistically significant ($p < 0.05$); even if the separate acute and chronic injury prevalence rates of these three groups showed no statistically significant differences ($p > 0.05$) (Table II).

Comparison of Parameters V5, V10, V20 and V30 of Affected Lung

In three groups, the values of V5, V10, V20 and V30 increased gradually. The values of V5 and V10 in Group C were higher than those of the other two groups, but the comparison between V20 and V30 yielded no statistically significant differences (Table III).

Discussion

Radiotherapy regimen after modified radical mastectomy can decrease local and regional recurrence rate significantly, especially for the patients with more than 4 axillary lymph node metastases and a TNM above T3[8,9]. Combined chemotherapy and endocrine therapy can minimize the distant metastasis rate[10]. Treatment timing is very important, and postoperative concurrent radiochemotherapy has been shown to be safe and effective; in addition, the combination of hypofractionation of the radiotherapy regimen can shorten the radiotherapy time and radiation exposed area[11]. This study concluded that Group C had overall better results: the total recurrence and total

Table III. Comparison of dose volume histogram parameters V5, V10, V20 and V30 of affected lung (%).

Groups	V5	V10	V20	V30
Group A	20.2 ±12.4	38.4±9.3	52.3±17.7	65.6±16.0
Group B	18.9±10.3	35.7±9.5	50.2±17.6	63.3±16.3
Group C	**36.7±8.3**	**42.5±12.3**	51.7±18.4	60.4±16.5
F	8.624	6.547	2.324	0.657

survival rates of Group C were better, and the total radiation injury prevalence rate was lower than in the other two groups. And while the values of V5, V10, V20 and V30 increased gradually in the three groups, the values of V5 and V10 in Group C were higher than those in the other two groups. Although the study might get some negative results due to small sample size and short time of follow-up, it still explained that the combination of hypofractionation and concurrent radiochemotherapy after modified radical mastectomy is of certain application value for prognosis improvement and radiation damage reduction.

Clinical practice shows that single dose of 2.6-4 Gy is safe for breast radiotherapy[12]. A research[13] conducted to compare three different kinds of hypo fractionation regimens after modified radical mastectomy in 300 patients found the short protocols were all equally effective therapeutically, and there were no significant differences in their toxicity. Hypofractionation regimens can provide an effective and safe treatment being more convenient for patients and less demanding of hospital resources, and freeing up time for chemo- and endocrine therapies. Studies[14,15] have found that the volume of the lung being irradiated is associated with the occurrence of radioactive pneumonitis and with its severity. One of the studies[14] conducted indicated that for the patients with non-small cell lung cancer who received concurrent chemo-radiotherapy, the occurrence of Level 3 radioactive pneumonitits or above is closely related to V5 with a critical value of 42%. Yet, another work[17] analyzed the lung dosimetric parameters of patients who received helical tomotherapy to demonstrate that V5 was related to the occurrence of Level 2 or higher radioactive pneumonitits, with a V5 critical vale of 65%. On our hands, the average value of V5 was 36.7% and the average value of V10 was 42.5%. The critical values of V5 were different, but this illustrates that V5 is an important reference index to evaluate the radioactive injury of different radiotherapy regimens.

The control of exposure parameters can reduce the incidence of radioactive injury, however in our study there still were some patients with radioactive injury; the reason why this happened may be due to the result of low-dose radiation to a large area, the so-called low-dose sensitization[18] which is harder to avoid. Intensity modulated radiation therapy technology tends to disperse the exposure dose leading to the minimum of the V20 and V30 limits, and the result is the inevitable increase in low-dose exposure areas of healthy tissues[19].

Conclusions

Increasing the radiotherapy dose of hypofractionation by single time and reducing the radiotherapy area may become a safe and effective irradiation regimen after modified radical mastectomy.

Conflicts of interest

The authors declare no conflicts of interest.

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