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# Chest wall recurrence location and the lower-bound target of preventive radiotherapy after transverse incision in modified radical mastectomy

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**ABSTRACT.** We investigated the relationship between the lower-bound target of preventive radiation to the chest wall after modified radical mastectomy with a transverse incision and preoperative breast carcinoma characteristics to provide a basis for reducing radiation injury to neighboring tissues and individualizing preventive chest wall radiation targets. We analyzed the relationship between clinical stage, pathology, diseased region, condition of vessel tumor embolus, sex hormone levels, HER-2 expression levels, receipt of chemotherapy, and the distance of local chest wall recurrence under the edge of the transverse incision in 112 patients with local chest wall recurrence after radical mastectomy. There were 64 cases (57.1%) with local chest wall recurrence within 3 cm below the transverse incision fringe, 31 cases (27.7%) within 3-5 cm, 14 cases (12.5%) within 5-7 cm, and 3 cases (2.7%) exceeded 7 cm. There were statistically significant correlations between the distance from the focus of the chest wall recurrence to the inferior margin of the transverse incision and the T stage, HER-2

 

expression levels, and receipt of chemotherapy. For more than 97% of patients undergoing radical mastectomy with a transverse incision, the distance of local chest wall recurrence under the edge of the transverse incision was less than 7 cm. To accomplish individualized treatment in defining radiotherapy targets, we should pay attention to T stage, HER-2 expression levels, and the receipt of chemotherapy when determining the lower-bound location of the target for preventive chest wall radiation after modified radical mastectomy with a transverse incision.

**Keywords:** Transverse incision; Modified radical mastectomy; Chest wall local recurrence; Lower-bound radiotherapy target

## INTRODUCTION

It is common practice to perform preventive chest wall radiation for breast cancer patients eligible for radiotherapy. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed that the disease recurrence rates in local and regional lymph nodes in a non-radiotherapy group and radiotherapy group after radical mastectomy or modified radical mastectomy were 6.7% and 19.6%, respectively. Radiotherapy could reduce the recurrence rate in local and regional lymph nodes by two-thirds (Early Breast Cancer Trialists' Collaborative Group, 2000). For patients undergoing modified radical mastectomy, the location of the lower-bound target of preventive radiotherapy is now set to be 2 cm from the contralateral breast ruffle inferior margin. With 2 cm from the contralateral breast ruffle inferior margin as the lower-bound limit of the field, we have found in clinical practice that in addition to many normal lung tissues, the radiation field in patients with right-sided breast cancer also includes normal hepatic tissue, and the radiation field in patients with left-sided breast cancer also includes a portion of the intestinal canal. Therefore, while radiotherapy brings much benefit to patients, radiation injuries in the irradiation field also have some impact on patients' health. This study aimed to provide a reference for determining the lower-bound target of preventive radiotherapy after modified radical mastectomy with a transverse incision, so as to reduce radiotherapy injury to surrounding normal tissues. We analyzed the relationship between tumor features and distance of local recurrence locations in the chest wall below the incision scar in 112 patients with local chest wall recurrence after modified radical mastectomy with a transverse incision.

## MATERIAL AND METHODS

### General materials

We collected complete data of patients with local chest wall recurrence who underwent modified radical mastectomy with transverse incision in the Fourth Hospital of Hebei Medical University from August 1995 to July 2009. All patients were female; the age at recurrence was 34-68 years, and the median age was 53 years. Clinical TNM stages (2007 American Joint Committee on Cancer Stage) were T2 in 15 cases, T3 in 65 cases, T4 in 32 cases, N0 in 29 cases, N1 in 64 cases, N2 in 16 cases, and N3 in 3 cases. There were 13 cases of preoperative primary tumor located in the upper inner quadrant, 53 cases in the upper outer quadrant, 13 cases in the lower inner quadrant, 21 cases in the lower outer quadrant, and 12 cases in the

center of the breast. There were 77 cases of infiltrating duct carcinoma and 35 cases of infiltrating lobular carcinoma; postoperative pathology detected vascular tumor embolus in 16 cases. There were 30 (26.8%) patients with estrogen receptor-positive tumors, 37 (33.0%) patients with positive progesterone receptor-positive tumors, 30 (26.8%) patients with double positive tumors, and 15 (13.4%) patients with double negative tumors. With regard to human epidermal growth factor (HER-2), 32 patients had (-) expression, 30 cases had (+) expression, 29 cases had (++) expression, and 21 cases had (+++) or higher expression. Eighty-four cases received preoperative/postoperative chemotherapy, and 28 cases did not; no patients received radiotherapy.

Regarding the morphology of focal recurrence in the chest wall, foci were located in the local incision scar and the surface of peripheral skin, with a few located subcutaneously. The site of incision scars usually appeared as a nodular mass, while peripheral foci usually appeared punctate and popular. The foci diameters ranged from 0.2 cm to 0.4 cm.

## Method of measurement of patients' posture and parameters

Patients laid down on radiotherapy vacuum pads, with upper limbs in the radiotherapy posture (abduct, elevate, and fix).

We measured the distance of the recurrence focus in the chest wall below the incision and transverse incision, as well as the distance from the transverse incision to 2 cm from the ruffle in the lower edge of the breast. The incision scar center was used as a reference, and a straight steel ruler was used as a measurement tool; measurement values were accurate to 0.1 cm.

## Statistical methods

We analyzed patient conditions, such as distance of local recurrence in the chest wall below the postoperative incision scar, clinical stage, type of tumor pathology, diseased region, condition of canalis haemalis tumor embolus, hormone levels, HER-2 expression, the presence of triple negative disease, and receipt of chemotherapy. All conditions were analyzed using the SPSS11.5 statistical software. The Student *t*-test and Spearman correlation analysis were used for statistical analysis.

# RESULTS

There were 64 cases with local recurrence foci located within 3 cm of the inferior margin of the transverse incision, 31 cases (27.7%) located within 3-5 cm, 14 cases (12.5%) located within 5-7 cm, and 3 cases (2.7%) located greater than 7 cm from the inferior margin of the transverse incision. The 3 cases whose local recurrence exceeded 7 cm from the transverse incision also presented with nodules in the chest wall and operation incision. The clinical stage of 2 patients was T3N1M0, while the other was T4N1M0; 1 patient was HER-$2^{++}$, 2 patients were HER-$2^{+++}$, and 3 patients received no chemotherapy.

The distance from the transverse incision to 2 cm from the inferior margin of the contralateral breast was 6.5-17 cm; the median value was 12.4 cm, and the average value was 11.75 cm. The distance from 7 cm below the transverse incision to 2 cm below the contralateral breast plica was -0.5-10 cm; the median value was 5.4 cm, and the average value was 4.75 cm. The distance from the most distal focus to 2 cm below the contralateral breast plica was > 6 cm for the 3 patients whose local recurrence foci exceeded 7 cm from

the incision.

There were significant correlations between the distance from the local recurrence focus to the inferior margin of the operation incision and T stage of the primary tumor, expression level of HER-2, and receipt of preoperative/postoperative chemotherapy ($P < 0.05$; Table 1). There was a correlation with T stage of the tumor, and the correlation coefficient was $R = 0.352$ ($P = 0.000$). There was also a correlation with HER-2 expression level, and the correlation coefficient was $R = 0.23$ ($P = 0.015$; Figure 1). There was no statistically significant association between N stage, tumor pathology type, lesion site, the condition of vessel tumor embolus, hormone levels, triple negative disease, and the distance of the chest wall local recurrence below the postoperative incisional scar ($P > 0.05$; Table 2).

**Table 1.** Relationship between T stage, HER-2 expression level, chemotherapy status, and chest wall local recurrence distance below the incision scar.

| Factor | | Distance range from recurrence focus to incision | | | | $\chi^2$ | P |
|---|---|---|---|---|---|---|---|
| | | 0-3 cm | 35 cm | 5-7 cm | >7 cm | | |
| Stage | N | | | | | | |
| T2 | 15 | 12 (80%) | 3 (20%) | 0 | 0 | | |
| T3 | 65 | 42 (64.6%) | 15 (23.1%) | 6 (9.2%) | 2 (3.1%) | | |
| T4 | 32 | 10 (31.3%) | 13 (40.6%) | 8 (25%) | 1 (3.1%) | 15.41 | 0.017 |
| HEr-2 | | | | | | | |
| - | 32 | 23 (71.9%) | 8 (25%) | 1 (3.1%) | 0 | | |
| + | 30 | 16 (53.3%) | 12 (40%) | 2 (6.7%) | 0 | | |
| ++ | 29 | 14 (48.3%) | 8 (27.6%) | 6 (20.7%) | 1 (3.4%) | | |
| +++ | 21 | 11 (52.4%) | 3 (14.3%) | 5 (23.8%) | 2 (9.5%) | 17.03 | 0.048 |
| Chemotherapy | | | | | | | |
| Yes | 84 | 48 (51.7%) | 26 (31%) | 10 (11.9%) | 0 | | |
| No | 28 | 16 (51.7%) | 5 (17.9%) | 4 (14.3%) | 3 (10.7%) | 10.4 | 0.015 |

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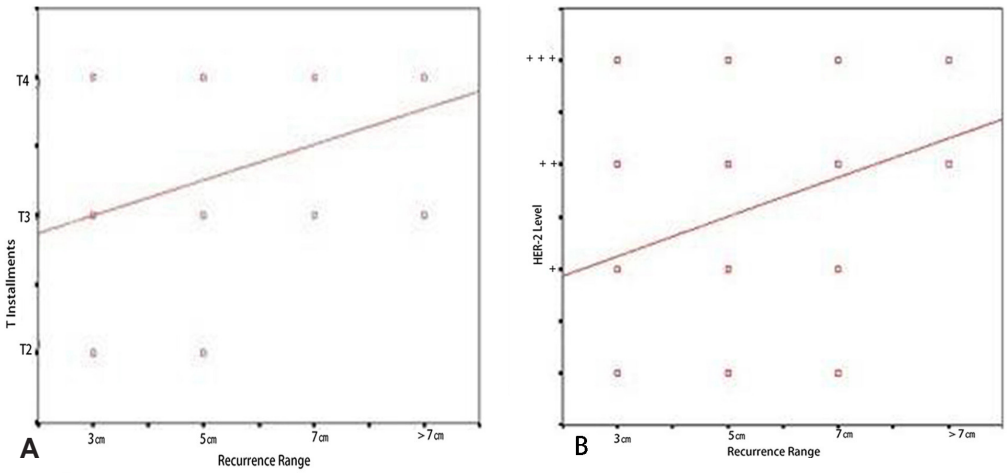


**Figure 1.** Relationships between the distance from the local recurrence focus to the inferior margin of the operation incision and T stage of the primary tumor and HER-2 expression level ($P < 0.05$) (A: T installment $R = 0.352$, $P = 0.000$; B: HER- 2, $R = 0.23$, $P = 0.015$).

**Table 2.** Relationship between N stage, tumor pathology type, diseased region, the condition of canalis haemalis tumor embolus, hormone levels, presence of triple negative disease, and chest wall local recurrence distance below incisional scar

| Factor | | Distance range from recurrence focus to incision | | | | $\chi^2$ | P |
|---|---|---|---|---|---|---|---|
| | | 0-3 cm | 3-5 cm | 5-7 cm | >7 cm | | |
| N | n | | | | | | |
| N0 | 29 | 22 (75.9%) | 5 (17.2%) | 2 (6.9%) | 0 | | |
| N1 | 64 | 27 (42.2%) | 23 (35.9%) | 11 (17.2%) | 3 (4.7%) | | |
| N2 | 16 | 13 (81.3%) | 2 (12.5%) | 1 (6.2%) | 0 (0%) | | |
| N3 | 3 | 2 (66.7%) | 1 (33.3%) | 0 (0%) | 0 (0%) | 15.02 | 0.09 |
| Pathology type | | | | | | | |
| Duct carcinoma | 77 | 47 (61.0%) | 22 (28.6%) | 6 (7.8%) | 2 (2.6%) | | |
| Lobular carcinoma | 35 | 17 (48.6%) | 9 (25.6%) | 8 (22.9%) | 1 (2.9%) | 5.1 | 0.17 |
| Diseased region | | | | | | | |
| Upper inner quadrant | 13 | 8 (61.5%) | 3 (23.1%) | 1 (7.7%) | 1 (7.7%) | | |
| Upper outer quadrant | 53 | 34 (64.2%) | 12 (22.6%) | 6 (11.3%) | 1 (1.9%) | | |
| Lower inner quadrant | 13 | 7 (58.3%) | 4 (30.8%) | 2 (15.4%) | 0 | | |
| Lower outer quadrant | 21 | 10 (47.6%) | 8 (38.1%) | 3 (14.3%) | 0 | | |
| Central region | 12 | 5 (41.7%) | 4 (33.3%) | 2 (16.7%) | 1 (8.3%) | 7.25 | 0.84 |
| Vessel tumor embolus | | | | | | | |
| Yes | 16 | 10 (62.5%) | 2 (12.5%) | 3 (18.8%) | 1 (6.2%) | | |
| No | 96 | 54 (56.3%) | 29 (30.2%) | 11 (11.4%) | 2 (2.1%) | 3.12 | 0.37 |
| Hormone expression | | | | | | | |
| E(-) P(-) | 15 | 7 (46.7%) | 4 (26.7%) | 3 (20%) | 1 (6.6%) | | |
| E(+) P(+) | 30 | 19 (63.3%) | 8 (26.7%) | 2 (6.7%) | 1 (3.3%) | | |
| E(-) P(+) | 37 | 27 (73.0%) | 7 (18.9%) | 3 (8.1%) | 0 | | |
| E(+) P(-) | 30 | 11 (36.7%) | 12 (40%) | 6 (20%) | 1 (3.3%) | 12.4 | 0.19 |
| Triple negative | | | | | | | |
| Yes | 11 | 6 (54.5%) | 4 (36.4%) | 1 (9.1%) | 0 | | |
| No | 101 | 58 (57.4%) | 27 (26.7%) | 13 (48.6%) | 3 (48.6%) | 0.79 | 0.85 |

E = estrogen receptor; P = progesterone receptor

## DISCUSSION

Local recurrence is one of the main reasons for treatment failure after radical mastectomy. Currently, the local recurrence rate after breast cancer surgery, as reported by both foreign and domestic reports, ranges from 4.0% to 32.05%. The chest wall is the most common site of recurrence, and accounts for 50.0-94.0% of all local recurrences (Brewster et al., 2007; Paepke et al., 2007; Dinh et al., 2008; Fodor et al., 2008; Pennery, 2008). There are multiple factors resulting in postoperative chest wall recurrence of breast cancer, which may be related to local infiltration of the primary focus and lymph node metastatic focus, postoperative cancer cell residue, generalized dissemination of cancer cells to local tissues, and possibly operation type (Herrinton et al., 2005). Numerous clinical studies have demonstrated that radiotherapy can significantly reduce local recurrence rates after radical mastectomy; thus, preventive chest wall radiation is especially important for patients with a radiotherapy indication after radical mastectomy.

The design of radiotherapy targets after breast cancer operations depend on the patients' condition of disease development and operation type. Compared with a traditional longitudinal incision operation, a transverse incision has the following advantages: axillary fossa exposure is clear; the scavenge of axillary lymph nodes is thorough; skin tension is reduced; necrosis rate of the skin flap is low; the incision heals well; the effect on upper limb function is minimal; the incision is relatively concealed; it can reduce psychological effects caused

by unilateral breast defects; and so on. Now it has become the main operation method for modified radical mastectomy. For breast cancer patients receiving preventive postoperative radiotherapy, whether the radiation field can completely involve the recurrence site around the primary tumor in the target region is an important factor influencing local tumor recurrence. Currently, conformality after modified radical mastectomy or emphasis of the radiotherapy target range primarily continue to use the target range of conventional radiotherapy, i.e. the ipsilateral chest wall and supraclavicular/infraclavicular region. In addition, the axillary fossa and/or internal mammary lymph drainage area are irradiated when there is an indication. In traditional radiotherapy, the lower-bound target of the radiation field almost meets the requirement of involving the operation scar after a breast cancer operation with a longitudinal incision, and this has achieved good preventive and local effect. However, in clinical practice, in addition to many normal lung tissues, the radiation field of patients with right-sided breast cancer also includes some normal hepatic tissue, and the radiation field of patients with left-sided breast cancer also includes a part of the intestinal canal. Because of the fact that transverse incision is the main operation method now, breast cancer patients receive preventive postoperative radiotherapy. There have been no reports as to whether there is the need to adjust the lower-bound target of traditional chest wall radiotherapy to reduce unnecessary injury to neighboring organs. Through investigating the focus location of 112 patients with chest wall recurrence after radical mastectomy with a transverse incision, we found in this study that all the recurrence foci grew upwards and downwards, with the operation scar in the center. The lower-bound location of postoperative local recurrence in the chest wall in over 97% of patients was located within 7 cm of the inferior margin of the operation scar, while the distance between the 7 cm and 2 cm levels of the contralateral breast plica was -0.5-10 cm, the median value was 5.4 cm, and the average value was 4.75 cm. The distance between the most distal focus and the 2 cm level of the contralateral breast plica was more than 6 cm for the 3 patients whose recurrence focus exceeded 6 cm. According to this, we think it is of significance to use the center of the transverse incision scar as a reference and to make appropriate adjustments to the lower-bound location of preventive radiotherapy to the chest wall after radical mastectomy with a transverse incision.

Now studies on individualized targets for preventive radiotherapy of breast cancer patients mainly focus on the inner breast region and axillary fossa, while there have still been no reports on the results of the lower-bound target location of the chest wall. Our study found that there were statistically significant associations between the range from the local recurrence focus to the inferior margin of the operation incision and tumor T stage, expression level of HER-2, receipt of chemotherapy, and it was also correlated with tumor T stage and expression level of HER-2.

The T stage of breast cancer is determined through the largest diameter of the tumor and whether the tumor directly invades the chest wall and skin. Results of a multivariate analysis of prognosis in 101 patients with postoperative recurrence showed that primary tumor > 5 cm is an independent prognostic factor of survival after chest wall recurrence. In this study, the local recurrence foci of 15 T2 patients were all located within 5 cm below the operation scar; among 65 T3 patients, the local recurrence foci of 63 patients were located within 7 cm below the operation scar, and 2 cases exceeded 7 cm (3.1%). Among 32 T4 patients, the local recurrence foci of 31 patients were located within 7 cm below the operation scar, and 1 case exceeded 7 cm (3.1%). Further correlation analysis found that there was a correlation between T stage of the tumor and the distance from the local recurrence focus to the inferior margin of

the operation incision, i.e. with the progression of T stage, the location of local recurrence on the chest wall showed a trend to increase.

Chemotherapy is an important part of the comprehensive treatment of breast cancer. With regard to eradicating local subclinical foci and generalized micrometastatic foci, as well as reducing the rapid growth of micrometastatic foci after radical operations, preoperative neoadjuvant chemotherapy, postoperative adjuvant chemotherapy to prevent recurrence or metastasis, and salvage chemotherapy for recurrence and metastasis all have important significance. A study by Borner et al. (1994) showed that among patients with an interval of > 12 months from operation to recurrence, tumors were positive for both estrogen and progesterone receptors, recurrent nodules were < 4 cm, and the largest tumor diameter was < 3 cm; thus, patients could benefit from local excision and chemotherapy after radiotherapy. In this study, none of the 3 patients whose focus of local recurrence was located greater than 7 cm from the inferior margin of the operation scar received chemotherapy. Thus, it was considered that there was great significance in receiving chemotherapy to reduce the range of chest wall recurrence after a breast cancer operation.

HER-2 is a member of the family of epidermal growth factor receptors and has intracellular tyrosine kinase-like activity; thus, it can enhance cell motility and promote cell division and secretion of proteases, and thus promotes tumor invasion and metastasis. Studies have shown that a low level of HER-2 is expressed in normal breast cells, while it is overexpressed in 20-35% of breast cancers (Gong et al., 2007). Ross and Fletcher (1999) analyzed the results of 47 studies and showed that HER-2 expression status acted as an independent prognostic indicator of disease-free survival in breast cancer in about 60% studies, and the significance was not inferior to the effect of lymph node metastasis on prognosis of breast cancer. In our study, the foci of local recurrence was located within 7 cm below the operation scar for all 62 patients with negative or weakly positive (+) HEr-2 expression; for the 3 patients with a foci distance greater than 7 cm, HER-2 was strongly or overexpressed. Further correlation analysis showed that HER-2 expression levels in the tumors were correlated with the distance between the focus of local recurrence to the inferior margin of the operation incision. For example, with increasing expression of HER-2, there was a trend toward increased distance between the local recurrence and incision, which demonstrates to some degree most scholars' opinion that expression level of HER-2 is positively correlated with tumor invasion.

Local recurrence after radical mastectomy is a complicated process involving the interaction of multiple factors. With increased recognition of postoperative preventive radiotherapy, the incidence rate of local recurrence has significantly decreased. Now the concept of individualized therapy based on comprehensive treatment of breast cancer has been widely accepted by people. Radiologists should also consider how to reasonably design individualized postoperative regimens for breast cancer patients. We believe that while the use of transverse incision in radical mastectomy is gradually increasing, it is more reasonable to use the incision site as a reference to determine the lower-bound target of radiotherapy rather than using lower boundary of the contralateral breast as a reference. At the same time, the tumor size, HER-2 expression level, and chemotherapy status of patients should also be considered. This study is limited by the objective condition, such as fewer pathological types, inadequate sample size, and so on; thus, further study is still needed. We hope our study can provide the basis for research on the accurate design of lower-bound targets of preventive radiotherapy after modified radical mastectomy with transverse incision, and decrease unnecessary radiotherapy damage.

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