

The metastasis of the internal mammary lymph node-a neglected strategic high point of radiotherapy for breast cancer

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Abstract

Background : To investigate the metastatic rate of internal mammary lymph nodes (IMNs) and to provide recommendations on target volume delineation of IMNs for adjuvant radiotherapy of breast cancer patients.

Methods : We retrospectively analyzed 114 breast cancer patients treated only by surgery without adjuvant radiotherapy who developed local and/or regional lymph node recurrence/metastasis in our institute from January 2015 to January 2019, and patients with widely lung or pleural metastases were excluded. We first analyzed the recurrence rate of the chest wall, the metastatic rate of internal mammary/anterior mediastinal, ipsilateral axillary and supraclavicular lymph nodes, and then investigated distribution of the IMNs.

Results : Among all of these 114 patients, the recurrence rate of chest wall, the metastatic rate of IMNs, the IMNs/anterior mediastinal lymph nodes, the ipsilateral axillary lymph nodes, and the ipsilateral supraclavicular lymph nodes were 43%, 37.7%, 59.6%, 12.3% and 22.8%, respectively. The metastatic IMNs were mainly located from the first to the second intercostal space. However, metastatic lymph nodes could also be observed above the upper edge of the first rib.

Conclusions : The metastatic rate is high in the IMNs and irradiation of the internal mammary lymphatic chain is indispensable. It is suggested that the upper bound of the internal mammary lymphatic chain should be up to the subclavian vein with 5 mm margin, thus connecting to the caudal border of supraclavicular CTV(Clinical Target Volume)in breast cancer patients with high risk of recurrence.

Background

Breast cancer is the most common malignant tumor in women, and postoperative adjuvant radiotherapy is an important treatment[1, 2]. Based on the results of the following two clinical trials—MA.20 and EORTC 22922/10925[3, 4], the 2016 National Comprehensive Cancer Network’s NCCN’s guidelines strongly recommend irradiation of IMNs to patients with 1–3 axillary lymph nodes (ALNs) positive (category 2A) after both mastectomy and lumpectomy[5], in addition to irradiation of chest wall and supraclavicular lymph nodes in postoperative adjuvant radiotherapy. Controversies persist regarding recommendation of IMNs irradiation in all patients with ALNs metastases[6]: opponents believe that the recurrence rate of IMNs is low, which is about 2% to 5%, and irradiation of IMNs increases the cardiac and pulmonary toxicity. Although, like the axilla, the internal mammary lymphatic chain is the first echelon nodal drainage site in breast cancer[7, 8], the importance of its treatment has long been debated. The metastatic rate of IMNs was 33% after the extended mastectomy of breast cancer in the 1970s[9, 10]. So there is a big difference between clinical and pathologic findings. To explain this contradiction, we analyzed 114 breast cancer patients treated only by surgery without adjuvant radiotherapy who developed local recurrence and regional lymph node metastases in our institute from January 2015 to January 2019 retrospectively, to investigate the metastatic probability and to provide recommendations on target volume delineation of IMNs for adjuvant radiotherapy of breast cancer patients surgically treated.

Methods

Ranging from 31 to 77 years old (median age 45 years old) of the onset age, these 114 patients did not undergo postoperative adjuvant radiotherapy, exclusive of patients with widely lung or pleural metastases. In light of recent data, the diagnosis and treatment of IMNs involvement has become an important topic in the management of breast cancer. The diagnosis of internal mammary/anterior mediastinal lymph node metastasis was according to clinical symptoms, signs and imaging modalities (mainly enhanced CT of chest). Under normal circumstances, the diameter of IMNs on the enhanced CT is 2mm–5mm, and lymph nodes whose diameter was more than 6mm can be diagnosed as metastases, and the anterior mediastinal lymph nodes whose diameter were more than 10mm can be diagnosed as metastases[11]. The appearance of positron emission tomography/computed tomography (PET/CT) improved the detection of positive lymph nodes[12].

Results

Clinical characteristics of all patients

From these female patients that shown in table 1, we can see that most of the tumor locations are lateral quadrant, with a rate of 82.5%; the molecular subtype of Her2 negative(HR+), Her2 positive(HR+/-) and TNBC (triple negative breast cancer) are 30.7%, 34.2%, and 35.1% respectively; and the rate of tumor staging that under stage IIIA is 71.9%.

Clinical characteristics of patients with chest wall recurrence and regional lymph nodes metastases

The characteristics of chest wall recurrence and regional lymph node metastasis are shown in Table 2: we have analyzed 114 breast cancer patients with chest wall recurrence and regional lymph node metastases retrospectively, including 49 cases with chest wall recurrence, accounting for 43% of all patients; 43 cases with IMNs metastases only, with a metastatic rate of 37.7%, and 68 cases with IMNs/anterior mediastinal lymph node metastases, with a metastatic rate of 59.6%; there were 14 cases with ipsilateral ALNs recurrence, accounting for 12.3% of all patients and there were 26 cases with ipsilateral supraclavicular lymph node recurrence, accounting for 22.8% of all patients. It can be seen from Table 3 that the metastatic rate of IMNs/anterior mediastinal lymph nodes(we called extensive internal mammary lymph node) is more than 40%, regardless of tumor location, molecular subtype and tumor staging.

Distribution of the metastatic internal mammary/anterior mediastinal lymph nodes

Table 4 illustrates the locations of the metastatic IMNs. Of the 43 patients, 45.4% were in the first intercostal space, 36.4% were in the second intercostal space, 9.1% were in the third intercostal space, and 2.3% were in the fourth intercostal space. IMNs were mainly located in the first to the second intercostal space(Fig.1 A-B), and the anterior mediastinal lymph nodes were mainly distributed in the 3A and 6 region (Fig.1 C-D). Moreover, metastatic lymph nodes could also be observed above the upper edge of the first rib(Fig.1 E-F), with a metastatic rate of 7%.

Discussion

The 2016 NCCN guidelines strongly recommended irradiation of IMNs for postoperative adjuvant radiotherapy to patients with 1–3 positive ALNs after both mastectomy and lumpectomy (category 2A) [5]. Changes in the guidelines did not eliminate the controversies of irradiation of internal mammary lymphatic chain. The reason was probably that the recurrence rate was only 2% according to clinical reports[13], and the irradiation dose of cardiopulmonary was increased by irradiation of the internal mammary lymphatic chain[14, 15]. We studied 114 patients of local and/or regional lymph node recurrence without adjuvant radiotherapy retrospectively. The recurrence rates of chest wall, supraclavicular and axillary lymph nodes were 43%, 22.8%, and 12.3%, respectively, consistent with the literatures[16]. However, the recurrence rate of IMNs was 37.7%, only secondary to that of chest wall, and the recurrence rate was higher than that of the supraclavicular region according to our study. So the recurrence rate of IMNs was underestimated probably. The reason is perhaps that IMNs are small, whose diameter are usually between 2mm to 5mm. The routine imaging examinations easily miss IMNs for it is usually 6mm in diameter even if it metastases, unless the huge mass is formed in the very late stage. In addition, the recurrence of IMNs rarely exists isolatedly, often combining with systemic metastases such as liver, lung and so on[17]. And there is no obvious clinical symptoms when the recurrence of IMNs occurs, so the physicians usually concentrate their attentions on other recurrence/metastases. We retrospectively analyzed 114 breast cancer patients treated only by surgery without adjuvant radiotherapy who developed local and/or regional lymph node recurrence/metastases, and found that the recurrence rate of IMNs is very high, which is consistent with the pathologic results of the extended mastectomy[10, 18]. It answers the clinical problems which have confused us for many years, and also suggests the necessity of irradiation of the internal mammary lymphatic chain. There is no reason to exclude IMNs which had a higher recurrence rate from the target volume, now that the supraclavicular lymph nodes need to be irradiated.

As we known, IMNs mainly receive lymphatic drainage from the medial and central parts of breast, and also from chest wall. The output tube is connected to the supraclavicular lymph nodes and also leads to the anterior mediastinal lymph nodes, and enters the vein via the thoracic duct or the right lymphatic duct finally. We found that the metastasis of the anterior mediastinal lymph node is not uncommon. The anterior mediastinum is a stenotic region between the sternum, pericardium and the mediastinal pleura. In the anatomical basis, the anterior mediastinal lymph nodes include the parasternal group and the anterior mediastinum group, while the parasternal group is IMN in breast cancer. The anterior mediastinum, which mainly receives lymphatic drainage from the adjacent pleura, is not a region of high-risk lymph node

metastasis even in lung cancer, unless the pleural involvement or the reflux of enlarged mediastinal lymph node is formed.

Traditionally, the definition of the internal mammary lymphatic chain is between the first to the third intercostal space[19], but metastatic lymph nodes could also be observed above the upper edge of the first rib. We know that the internal mammary artery originates from the lower wall of the first segment of the subclavian artery, down from the 1–2cm lateral side of the sternal, and are divided into two branches of the superior epigastric artery and the musculophrenic artery until the sixth intercostal space. The internal mammary artery has two veins which accompanied with it. Therefore, when designing the target volume of the internal mammary region, it is suggested that the upper bound of the internal mammary lymphatic chain should be up to the subclavian vein with 5 mm margin, thus connecting to the caudal border of supraclavicular CTV in breast cancer patients with high risk of recurrence. Anatomically, the anterior mediastinal metastatic lymph nodes should be derived from the internal mammary lymphatic chain, excluding widely lung or pleural metastases. Based on the above reasons, we proposed an important concept: extensive internal mammary lymph node region. The extensive internal mammary lymph node region mainly refers to the internal mammary lymphatic chain and the anterior mediastinal lymph node region (mainly 3A and 6 regions). As we know, the metastatic IMNs are usually small to be easily missed by routine imaging examinations, but the metastatic anterior mediastinal lymph nodes are usually larger and easier to be identified on enhanced CT images. Therefore, the inclusion of the anterior mediastinum lymph node in the extensive internal mammary lymph node region can reduce the underestimation of the probability of clinically internal mammary lymph node metastasis probably. Our results suggest that the metastatic rate of the anterior mediastinal lymph node is 50.9%. If IMN region and anterior mediastinum are included, the recurrence rate of the extensive internal mammary lymph node is 59.6%. So we think that irradiation of the internal mammary lymphatic chain is an indispensable part of adjuvant radiotherapy for breast cancer patients surgically treated which is consistent with the NCCN guidelines[5].

Veronesi. et al[20] performed a follow-up of 737 patients who had not undergone adjuvant radiotherapy and systemic therapy after radical mastectomy for thirty years. The prognosis of patients with IMNs metastases was similar with that of the ALNs metastases. The 10-year disease-free survival was 59.6% and 62.4%, respectively. And both of IMNs and ALNs metastases having the worst prognosis, the 10-year disease-free survival was 37.3%. Once IMNs recurred, according to the poor prognosis of the follow-up of 6,000 breast cancer patients, IMN metastasis may indicate distant metastasis[17]. In 2009, Heuts et al[21] reported that in a follow-up of 764 patients for 46 months, the prognosis of patients with IMN metastasis, almost similar to that of the ALN metastasis, was improved due to the correct understanding of IMN metastasis. In our retrospective study, 36 patients had both IMNs metastases and distant metastases, because the output tube of IMN is located in the supraclavicular and anterior mediastinum region, and it enters the superior vena cava through the left and right jugular veins finally, thus resulting in widely systemic metastases. We also found that the metastatic rate of the extensive internal mammary lymph node is more than 41.2%, regardless of the tumor location, molecular subtype or tumor staging of breast cancer. IMNs can not be removed in radical surgery or modified radical mastectomy due to the abandon

of extended radical resection, so active irradiation of the internal mammary lymphatic chain may reduce the metastasis and recurrence of IMN, and improve the prognosis of breast cancer patients, but positive systemic therapy still play an important role in breast cancer patients.

The irradiation of IMNs is problematical because it may increases cardiac dose, morbidity and mortality. There have been significant advances in radiotherapy technology, with sophisticated imaging integrated into planning systems using techniques that protect the heart with shielding or deep inspiration breath holding. This allows shaping or sculpting radiation doses to complex cancer volumes, while using modern equipment with on-board computed tomography scans with treatment times of about 5 minutes to reduce the dose to normal structures such as the heart. These advances have the potential to further increase the additional benefit of radiotherapy beyond surgery and systemic therapy, and thereby increasing survival rates.

Conclusions

In conclusion, we found that the metastatic rate is high in the IMNs and we think that irradiation of the internal mammary lymphatic chain is indispensable. It is suggested that the upper bound of the internal mammary lymphatic chain should be up to the subclavian vein with 5 mm margin, thus connecting to the caudal border of supraclavicular CTV in breast cancer patients with high risk of recurrence. Further high-quality prospective randomized trials are needed to validated this conclusion.

List Of Abbreviations

IMNs: Internal Mammary Lymph Nodes

CTV: Clinical Target Volume

NCCN: National Comprehensive Cancer Network

ALNs: Axillary Lymph Nodes

PET/CT: Positron Emission Tomography/Computed Tomography

TNBC: Triple Negative Breast Cancer

Declarations

Ethics approval and consent to participate

This study is in accordance with the Declaration of Helsinki and has been approved by the Ethics Committee of Zhongnan Hospital of Wuhan University. Due to the retrospective nature of the study, informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

YZ conceived and designed the study, and critically revised the manuscript; LL performed the research and wrote the first draft; HZ and LW collected and analyzed the data; CX and YZ participated in paper writing and revised the manuscript. All authors have read and approved the manuscript.

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Tables

Table 1

Clinical characteristics of all patients

	Number(n=)	Percent(%)
Gender		
female	114	100
Tumor location		
medial/central	20	17.5
lateral	94	82.5
Molecular subtype		
Her2 negative(HR+)	35	30.7
Her2 positive(HR+/-)	39	34.2
TNBC	40	35.1
Tumor staging		
I	16	14.0
IIA	30	26.3
IIB	36	31.6
IIIA	17	14.9
IIIB	8	7.0
IIIC	7	6.1

Table 2

Clinical characteristics of chest wall recurrence and RN^a metastasis

	Number(n=)	Percent(%)
Chest wall recurrence	49	43.0
IMNs ^b metastasis	43	37.7
Anterior mediastinal lymph node metastasis	58	50.9
IMNs/anterior mediastinal lymph node metastasis	68	59.6
Ipsilateral supraclavicular lymph node recurrence	26	22.8
Ipsilateral axillary lymph node recurrence	14	12.3

^a Regional Nodal.

^b Internal Mammary Lymph Nodes

Table 3

Clinical characteristics of IMNs/anterior mediastinal lymph nodes metastases

	IMNs/anterior mediastinal lymph node metastases (%)	No IMNs/anterior mediastinal lymph node metastases (%)
Tumor location		
medial/central	14(70%)	6(30%)
lateral	52(55.3%)	42(44.7%)
Molecular subtype		
Her2 negative(HR+)	17(48.6%)	18(51.4%)
Her2 positive(HR+/-)	21(53.8%)	18(46.2%)
TNBC	28(70%)	12(30%)
Tumor staging		
I	10(62.5%)	6(37.5%)
IIA	18(60%)	12(40%)
IIB	16(57.1%)	12(42.9%)
IIIA	7(41.2%)	10(58.8%)
IIIB	6(75%)	2(25%)
IIIC	9(60%)	6(40%)

Table 4

Anatomic distribution of IMNs metastases

Location of the metastatic IMNs	Number(n=)	Percent(%)
The upper edge of the first rib	3	7
The first intercostal space	20	45.4
The second intercostal space	16	36.4
The third intercostal space	4	9.1
The fourth intercostal space	1	2.3
The fifth intercostal space	0	0
The sixth intercostal space	0	0

Figures

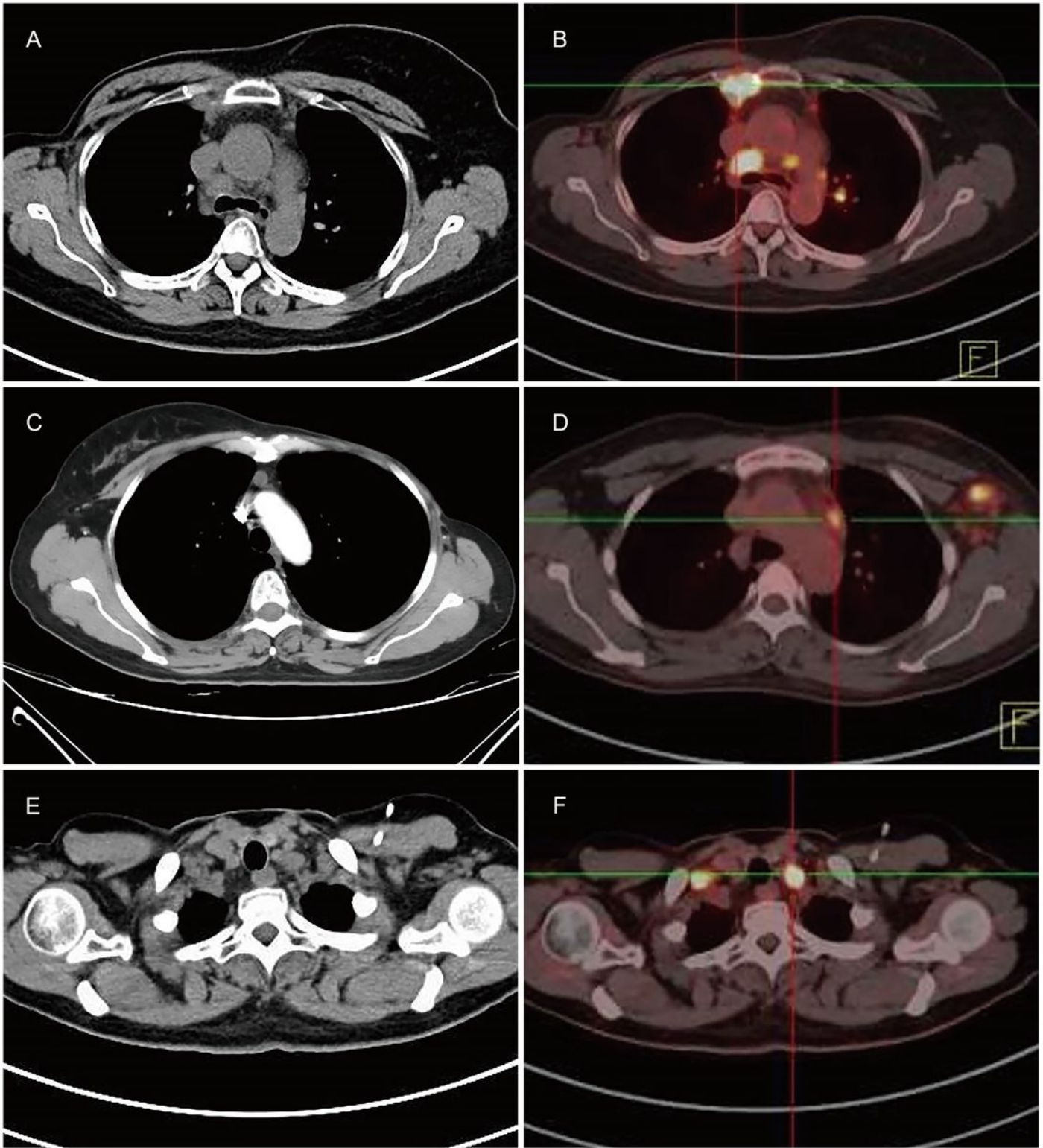


Figure 1

(A-B) the enlargement of the internal mammary lymph nodes; (C-D) the enlargement of anterior mediastinal lymph node; (E-F) metastatic lymph node that observed above the upper edge of the first rib.