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Internal Mammary Lymph Node Irradiation after Breast Conservation Surgery: Radiation Pneumonitis versus Dose-Volume Histogram Parameters

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Purpose: To evaluate the association between radiation pneumonitis and dose-volume histogram parameters and to provide practical guidelines to prevent radiation pneumonitis following radiotherapy administered for breast cancer including internal mammary lymph nodes.
Materials and Methods: Twenty patients with early breast cancer who underwent a partial mastectomy were involved in this study. The entire breast, supraclavicular lymph nodes, and internal mammary lymph nodes were irradiated with a dose of 50.4 Gy in 28 fractions. Radiation pneumonitis was assessed by both radiological pulmonary change (RPC) and by evaluation of symptomatic radiation pneumonitis. Dose-volume histogram parameters were compared between patients with grade <2 RPC and those with grade ≥ 2 RPC. The parameters were the mean lung dose, V10 (percent lung volume receiving equal to and more than 10 Gy), V20, V30, V40, and normal tissue complication probability (NTCP).
Results: Of the 20 patients, 9 (45%) developed grade 2 RPC and 11 (55%) did not develop RPC (grade 0). Only one patient developed grade 1 symptomatic radiation pneumonitis. Univariate analysis showed that among the dose-volume histogram parameters, NTCP was significantly different between the two RPC grade groups ($p<0.05$). Fisher's exact test indicated that an NTCP value of 45% was appropriate as an RPC threshold level.
Conclusion: This study shows that NTCP can be used as a predictor of RPC after radiotherapy of the internal mammary lymph nodes in breast cancer. Clinically, it indicates that an RPC is likely to develop when the NTCP is greater than 45%.

Key Words: Breast cancer, Internal mammary lymph node, Radiation pneumonitis, Radiotherapy

Introduction

The inclusion of internal mammary lymph nodes (IMNs) in radiotherapy for breast cancer is still a controversial issue in either breast conservation or total mastectomy cases.[1,2] Since there is no conclusive data supporting IMN radiotherapy, and the practice of treating IMN is culture-driven rather than evidence-based.[3] Breast conservation surgery patients require more sophisticated treatment techniques for radiotherapy including IMNs; several radiotherapy field alignments and match-ups on the intact breast make the procedure more complicated, and greater lung and heart volumes may be irradiated.[4~6] This technical difficulty also limits IMN irradiation.

Development of computed tomography (CT) simulators and introduction of three-dimensional conformal radiotherapy allow more accurate delivery of radiation treatment for patients with breast cancer including IMNs, and can facilitate more quantitative dose distributions for target volumes and critical organs using dose-volume histogram (DVH) analysis.[5,6] However, it is difficult to interpret DVHs generated from

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three-dimensional plans, and so only some parts of the information are often used in clinical practice. DVH parameters such as mean lung dose (MLD), V20 (percent lung volume receiving equal to and more than 20 Gy), V30, and normal tissue complication probability (NTCP) are commonly used.[7,8)]

In one multi-center study,[8)] a large number of data were analyzed for the association between the incidence of radiation pneumonitis and DVH parameters. However, breast cancer patients made up only a small proportion of the population (59 out of the 540 patients), and only MLD was examined for correlation with the incidence of radiation pneumonitis. Although recent studies indicate the possibility of radiation pneumonitis prediction for breast cancer patients, their concerns focus on NTCP models that predict the incidence of radiation pneumonitis.[9～11)] Overall analysis to determine which DVH parameters are associated with radiation pneumonitis after breast cancer radiotherapy including IMNs has not been done yet.

The primary aim of this study was to evaluate the association between radiation pneumonitis after radiotherapy including IMNs and DVH parameters. Although the assessment of radiation pneumonitis was done retrospectively by both radiological findings and clinical manifestations, statistical analysis focused on radiological pulmonary change (RPC) rather than symptomatic radiation pneumonitis (SRP) because of the rare incidence of SRP in breast cancer patients. The DVH parameters evaluated were MLD, V10, V20, V30, V40, and NTCP. The other aim was to use our findings to provide practical guidelines to prevent RPC in radiotherapy for breast cancer including IMNs.

Materials and Methods

1. Patient information and simulation

Twenty patients with early breast cancer who underwent partial mastectomy received radiotherapy including IMNs between January 2005 and December 2006. All patients were women, and their median age was 48 years (range; 28～76 years). Eight patients were treated for right breast and 12 patients for left breast tumors. Patients received IMN radiotherapy due to the inner location of the tumors. All except one patient finished chemotherapy before initiation of radiotherapy, and one patient received concurrent chemotherapy during radiotherapy. None of the patients had a smoking history or underlying lung disease. For the simulation, patients were immobilized with a customized styrofoam immobilization device. The ipsilateral arm was elevated above the head. CT scans were carried out using a CT-simulator (GE Medical Systems, Milwaukee, WI). Acquired CT images with 5 mm spacing were transferred to a treatment planning system (Pinnacle,[3] Philips Medical System, Andover, MA) and radiotherapy was planned.

2. Radiotherapy planning and radiotherapy techniques

For radiotherapy planning, the breast and IMNs were depicted as target volumes, and the heart and ipsilateral lung were also depicted as critical organs on CT images for each patient. The ipsilateral entire breast, supraclavicle lymph nodes, and IMNs were the target volumes. The irradiated region was divided into a supraclavicle lymph node field and breast fields. supraclavicle lymph node and breast fields were designed not to overlap each other. In the supraclavicle lymph node field, the beam center was located on the lower field edge and only the upper jaws were open to match the upper breast field edge. The gantry angle was rotated 10～15 degrees contra-laterally to avoid organs such as the spinal cord or esophagus located in the central area of the body.

For radiotherapy techniques for irradiating the breast and IMNs, we used the partially wide tangential field (PWT) technique in 17 patients and the photon-electron mixed field (PEM) technique in 3 patients (Fig. 1). In the PWT technique, radiotherapy fields were composed of tangential fields large enough to include IMNs as well as the breast. Only IMNs located on the first three intercostal spaces were included as lower IMNs were shielded with a block used to protect the lung and heart. In the PEM technique, photon tangential fields were designed to include the breast only and another electron field was set to include IMNs. A photon beam delivered 19.8 Gy and an electron beam delivered 30.6 Gy to the IMNs field. For these two techniques, 50.4 Gy of 28 fractions was prescribed to a depth of 3 cm for the supraclavicle lymph node field and to isocenter for breast fields.

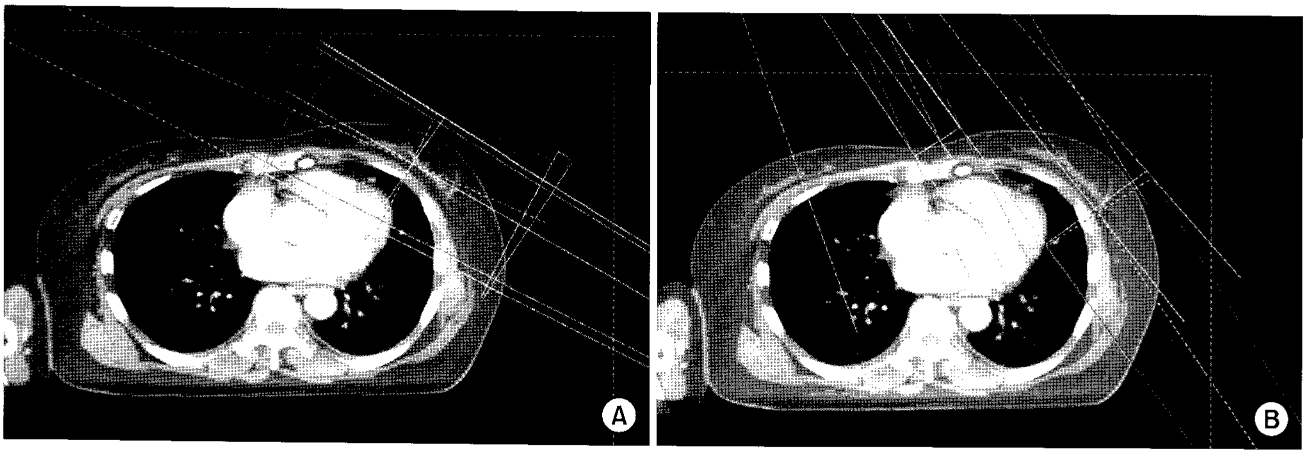

Fig. 1. Radiotherapy techniques for breast cancer including internal mammary lymph nodes (IMNs) (A) partially wide tangential field (PWT) technique, and (B) photon-electron mixed field (PEM) technique.

3. Evaluation of radiation pneumonitis

About three months after radiation treatment, the occurrence of radiation pneumonitis was assessed. The assessment included RPC as well as SRP. CT and chest X-ray images were examined for RPC, and RPC was ultimately diagnosed on the basis of change on the chest X-ray. Since CT was not the routine, CT images for follow-up were not provided for every patient. Cases in which RPC was only seen in the supraclavicle lymph node field were not counted as having RPC. RPC was graded according to the modified Arriagada classification,[12] i.e. grade 0=normal, 1=uncertain, 2=linear streaky, 3=dense diffuse opacification, and 4=dense uniform opacification. RPC findings were performed by a radiologist first. Final diagnosis was done by a radiologist together with a radiation oncologist. Cases with grade 1 (uncertain) were reclassified either as grade 0 or grade 2, as in a recent study for RPC.[13] Diagnosis of SRP was based on the RTOG/EORTC late lung morbidity scoring criteria.[14]

4. DVH parameters and statistical analysis

DVH parameters were calculated from DVHs and dose distributions on each CT image. DVH parameters analyzed in this study were MLD, V10, V20, V30, V40, and NTCP. NTCP was calculated using a Lyman-Kutcher-Burman model[15] and the coefficients n, m, and TD50 for the lung were 0.87, 0.18, and 24.5 Gy, respectively.[16]

Univariate logistic regression analysis was used to investigate correlation between RPC and DVH parameters. For this analysis, patients with different RPC were classified into two groups, one with grade <2 and the other with grade ≥ 2. RPC threshold level for correlated parameters (in this case, only NTCP) was estimated by Fisher's exact test. All statistical analyses were carried out using SPSS for windows, release 13.0 (SPSS Inc., Chicago, IL). Differences were assumed statistically significant at the value of $p<0.05$.

Results

Nine of the 20 patients (45%) developed grade 2 RPC with and 11 patients (55%) did not develop RPC (grade 0). Only one patient who received concurrent chemotherapy during radiotherapy developed SRP (grade 1). DVH parameters for this patient were 24.3 Gy, 41%, 36%, 33%, 28%, and 60% for MLD, V10, V20, V30, V40, and NTCP, respectively.

Mean values and standard deviations of MLD for RPC were 21.0±1.4 Gy (range, 18.2~23.0 Gy) for the group with grade <2 RPC and 22.9±3.2 Gy (range, 19.7~29.9 Gy) for the group with grade ≥2 RPC. Values for V10, V20, V30, V40, and NTCP were 43.0±15.0% (range, 22~54%), 34.5±10.0% (range, 19~41%), 30.4±9.0% (range, 18~37%), 23.5±8.0% (range, 12~28%), and 30.7±10.5% (range, 13~44%) for the group with grade <2 RPC, respectively, and 52.8±14.0% (range, 27~59%), 45.2±7.7% (range, 25~42%), 40.3±5.7% (range, 23~38%), 32.1±4.1% (range, 18~32%), and 51.2±21.8% (range, 20~90%) for the group with grade ≥2 RPC,

Table 1. Univariate Logistic Regression Analysis of Association between Radiological Pulmonary Change and Dose-Volume Histogram Parameters

Parameters	Mean value±standard deviation		p-value (for univariate analysis)
	Grade<2 RPC	Grade≥2 RPC	
MLD (Gy)	21.0±1.4	22.9±3.2	NS
V10 (%)	43.0±15.0	52.8±14.0	NS
V20 (%)	34.5±10.0	45.2±7.7	NS
V30 (%)	30.4±9.0	40.3±5.7	NS
V40 (%)	23.5±8.0	32.1±4.1	NS
NTCP (%)	30.7±10.5	51.2±21.8	0.046

RPC: radiological pulmonary change, MLD: mean lung dose, NTCP: normal tissue complication probability, NS: no significant

Table 2. Fisher's Exact Test for the Determination of Radiological Pulmonary Change Threshold Level for Normal Tissue Complication Probability

	Grade<2 RPC	Grade≥2 RPC	p-value
NTCP<45%	11	3	0.002
NTCP≥45%	0	6	

RPC: radiological pulmonary change, NTCP: normal tissue complication probability

respectively.

In the univariate analysis, only the NTCP parameter was associated with RPC (p=0.046). There were no significant associations with the other DVH parameters (Table 1).

Fisher's exact test was further carried out to determine the RPC threshold level for NTCP. Several values for NTCP were arbitrarily chosen to examine whether they would give statistical meanings for this analysis. The value of 45% for NTCP was finally chosen because it gave the best result for statistical analysis. This value was also estimated from Fig. 2, where we display patients 1 to 11 in the group with grade <2 RPC and patients 12 to 20 in the group with grade ≥ 2 RPC. To carry out this test, the group with grade <2 RPC was further divided into two groups, one with NTCP <45% (n=11) and the other with NTCP ≥45% (n=0). The group with grade ≥2 RPC was also divided into two groups, one with NTCP <45% (n=3), and the other with NTCP ≥45% (n=6). This test showed significant differences (p=0.002), indicating that there was a difference between the RPC grade

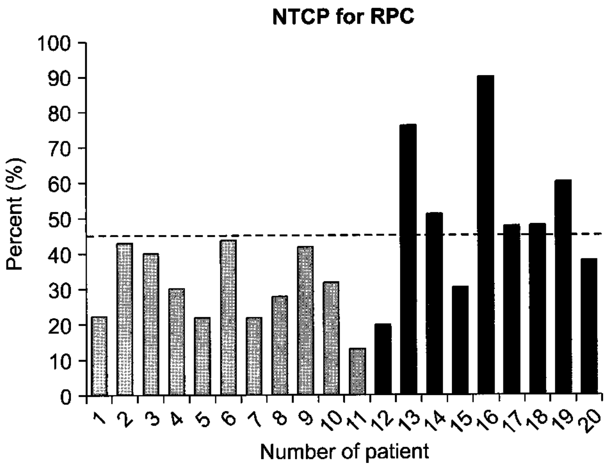

Fig. 2. Normal tissue complication probability (NTCP) for radiological pulmonary change (RPC). Patients from 1 to 11 were included in the group with grade<2 RPC and patients from 12 to 20 were included in the group with grade ≥2 RPC. The dotted line represents 45% for NTCP.

groups when the value for NTCP was set at 45% (Table 2). Among the 14 patients with NTCP values less than 45%, 3 patients developed RPC with grade 2 and 11 patients did not develop RPC (grade 0, Table 2). As a result, RPC can still develop below a value of 45% for NTCP. However, all patients with an NTCP value greater than 45% developed RPC, and so it can be predicted that RPC will develop above the value of 45% for NTCP.

Discussion and Conclusion

In cases of radiotherapy including IMNs in breast cancer, more sophisticated treatment techniques are needed. Recent reports detail various techniques for IMN treatment.[5,6] Pierce *et al.*[6] reported that the use of PWT was the most appropriate compromise for target coverage and normal tissue sparing when irradiating the chest wall and IMNs. Arthur *et al.*[5] generated and evaluated acceptable treatment plans for three different techniques used for IMN treatment. Based on this evaluation, they suggest that the PWT technique provides optimal coverage of the target volume, reduces coverage of normal tissue volume to an acceptable level, and is easily reproducible with a high degree of dose homogeneity throughout the target. At the same time, they also found that the PEM technique could allow lower doses than other techniques for the ipsilateral lung at dose levels above 20 Gy.

Jeong *et al.*[17] evaluated 4 different techniques in 10 patients and concluded that PWT was the most appropriate for radiotherapy including IMNs in reducing doses to the ipsilateral lung and heart and delivering the proper dose to IMNs. In the current study, we mainly used the PWT technique, but we also used the PEM technique for some patients when PWT would have delivered too much radiation to the ipsilateral lung.

Chest X-ray images or CT images may be used for the assessment of RPC. High-resolution CT images have proven to be sensitive in detecting diffuse pulmonary change after radiotherapy.[18] CT images, therefore, may be used to compare different radiotherapy techniques and the lung injuries they cause.[19] Nevertheless, chest X-ray images rather than CT images were used to assess RPC in this study, since plain radiographs have been the routine in follow-up at our institution.

SRP is an uncommon complication after irradiation in early breast cancer patients. Lingos *et al.*[20] reported that 17 women out of a total patient population of 1624 developed clinical SRP (1.0%). Their report, however, showed that when patients received a three-field technique (two tangential fields and axillary or supraclavicular field) with chemotherapy concurrently, the incidence of radiation pneumonitis was 8.8% compared with 1.3% for those who received sequential chemotherapy and radiotherapy (p=0.002). The only patient who developed SRP in this study received chemotherapy during radiotherapy. DVH parameters for this patient were 24.3 Gy, 41%, 36%, 33%, 28%, and 60% for MLD, V10, V20, V30, V40, and NTCP, respectively. Although the NTCP value was higher than our cut-off value, we think that concurrent chemotherapy might have contributed to the development of SRP in this patient. Therefore, we do not advise giving chemotherapy during radiotherapy, especially in patients who receive IMN irradiation.

In the present study, NTCP was associated with RPC. Kwa *et al.*[8] evaluated the association between radiation pneumonitis and 3-dimensional dose distribution in the lung. They reported that MLD was a useful predictor of the risk of advanced pneumonitis, but they did not perform an overall evaluation of radiation pneumonitis with other DVH parameters, and their analysis was only applied to advanced SRP (grade$\geq$2). In a review for prediction of radiation pneumonitis in lung cancer,[7] the authors evaluated associations between radiation pneumonitis risk and DVH parameters such as MLD, V20, V30, and NTCP. Most studies demonstrate an association between DVH parameters and radiation pneumonitis risk. In particular, for studies that found an association between NTCP and radiation pneumonitis risk, the average values of NTCP for radiation pneumonitis development were 19.6%[21] and 39.8%.[22] The latter value is comparable to our finding (51.2%) since NTCPs for both studies were calculated for the ipsilateral lung. However, since such evaluation depends on assumptions with regard to DVH parameters, CT contouring practices, radiation pneumonitis grade, and the timing of radiation pneumonitis assessment, any comparison between the current study and other studies for the association between radiation pneumonitis and DVH parameters needs careful consideration.

Recently, some researchers have studied NTCP models to predict the incidence of radiation pneumonitis from the lung DVH on the basis of data for breast cancer patients,[9~11] since the analysis for radiation pneumonitis may be different between breast cancer and lung cancer.[11] They tried to find the best NTCP model and include more fundamental factors that influenced the incidence of radiation pneumonitis in the model. Equivalent uniform dose or MLD was suggested factors.[9,11] However, analyses were different for various grades[11] and various end points.[9,10] Consequently, the conditions for each case should be considered before direct application of a certain NTCP model.

Our study has some limitations. First, more cases are needed and more diverse grades of radiation pneumonitis should be added for a more thorough evaluation of the relationship between DVH parameters and the incidence of radiation pneumonitis. However, it is very difficult to collect patients with serious radiation pneumonitis, in particular for SRP. It is because the incidence of SRP is rare, about 1%, after radiotherapy for breast cancer with modern radiotherapy techniques.[20] Most reports about radiation pneumonitis include thoracic tumors such as lung or esophageal cancer rather than breast cancer. Since we selected patients cautiously to prevent irradiating too much lung volume, there was no patient with SRP except one and no patient with serious RPC in the current study. RPC without symptoms improved without sequelae and did not negatively affect the patient's clinical courses. RPC without symptoms can be neglected clinically, and so we suggest that IMNs irradiation can be safely applied in the lung dose level given in this study. Second, the correlation between clinical parameters and the incidence of radiation pneumonitis was not analyzed in this study, because the study population was so small that such analysis was not appropriate.

In conclusion, the analysis of predictive factors for radiation pneumonitis has been performed that is clinically useful to prevent the development of potential lung toxicity. Although the assessment of radiation pneumonitis was done for both RPC and SRP, statistical analysis was carried out for RPC. Among DVH parameters, only NTCP could be used as a predictor of RPC after radiotherapy of IMNs in breast cancer. For a practical guideline on treatment planning for radiotherapy including IMNs in breast cancer, we suggest that RPC is likely to develop above an NTCP value of 45%.

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국문초록

유방보존술 후 내유림프절 방사선 조사: 방사선 폐렴과 체적-선량 히스토그램 변수들

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목 적: 방사선 폐렴과 체적-선량 히스토그램(dose-volume histogram, DVH) 변수들 사이의 연관성을 평가하고, 내유림프절이 포함된 유방암의 방사선치료에서 방사선 폐렴을 방지할 수 있는 실제적인 지침을 제공하고자 한다.

대상 및 방법: 부분유방절제술을 받은 초기 유방암 환자 20명이 본 연구에 포함되었다. 전체 유방, 상부쇄골림프절, 내유림프절에 총 28회 50.4 Gy가 조사되었다. 방사선 폐렴은 방사선 영상에서의 폐 변화(radiological pulmonary change; RPC)와 증상이 있는 방사선 폐렴(symptomatic radiation pneumonitis)에 의해 평가되었다. DVH 변수들은 grade<2 RPC와 grade≥2 RPC로 나누어 비교되었다. 이 때, DVH 변수들은 평균 폐 선량(mean lung dose), V10 (10 Gy 이상 받는 폐의 백분율 부피), V20, V30, V40, 그리고 정상 조직 합병증 확률(normal tissue complication probability, NTCP)이다.

결 과: 20명의 환자 중 9명(45%)에서 grade 2 RPC가 발생하였고, 11명(55%)에서는 발생하지 않았다. 1명의 환자에서 grade 1의 증상이 있는 방사선 폐렴이 발생하였다. 단변량 분석에서 DVH 변수 중, NTCP가 두 RPC grade 군 간에 유의한 차이를 보여주고 있다 ($p<0.05$). Fisher의 정확한 검증(exact test)은 NTCP값 45%가 RPC의 threshold level로서 적합함을 보여준다.

결 론: 본 연구는 NTCP가 유방암의 내유림프절 방사선치료 후 RPC 예측인자 중 한가지로 쓰일 수 있음을 보여준다. 임상적으로 이는 NTCP 45% 이상에서 RPC가 발생하기 용이함을 의미한다.

핵심용어: 유방암, 내유림프절, 방사선 폐렴, 방사선치료